# A PHASE IV STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS

PROTOCOL DATE: Version 7.0, Final 25 April 2013

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# 1. PROCEDURES IN CASE OF EMERGENCY

## Table 1: Sponsor Contact Information

| Role in Study | Name | Address and Telephone Number |
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## 2. SYNOPSIS

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| PRODUCT NAME | OXYCODONE ORAL SOLUTION |
| PROTOCOL NUMBER | 2012O004 |
| DEVELOPMENT PHASE | PHASE IV |
| PROTOCOL TITLE | A PHASE IV STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS |
| INDICATION | Moderate to severe pain |
| PRINCIPAL INVESTIGATOR | This is a multicenter study. The lead Principal Investigator will be:<br>Senthilkumar Sadhasivam, M.D.<br>Cincinnati Children's Hospital Medical Center<br>3333Burnet Avenue, MLC2001<br>Cincinnati, OH 45229 |
| PLANNED STUDY SITES | Up to 10 sites in the US. |
| OBJECTIVE | The objective of this study is to characterize the pharmacokinetics and to evaluate the safety of single and multiple doses of Oxycodone Oral Solution in pediatric and adolescent subjects for postoperative pain. |
| STUDY DESIGN | This is a Phase IV study to characterize the pharmacokinetics and to evaluate the safety of Oxycodone Oral Solution administered to pediatric and adolescent subjects for postoperative pain. It is an open-label, multicenter study conducted at up to 10 sites. Subjects will be enrolled preoperatively up to 14 days before surgery with the expectation that they will require intravenous (IV) access after the surgery for at least 24 hours and postoperative analgesia with an opiate-level medication. After dosing with Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to 17, and a dose to be determined based on pharmacokinetic (PK) modeling from the interim analyses for subjects under age 2), subjects will be carefully monitored for safety. A total of 110 pediatric and adolescent male or female subjects will be enrolled, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years. Subjects within each age group will be evenly distributed by age and gender.<br>An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 6 months to <2 years will receive will be based on PK modeling from the interim analysis.<br>An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that |

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| | the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on PK modeling from the interim analysis.<br><br>The study will consist of a Screening period within 14 days of surgery; a predose check-in (Day −1); a treatment period after surgery (Day 1, Time Zero); and an End-of-Study assessment. The total duration of the study, excluding Screening, will be approximately 1 full day.<br><br>Eligible subjects who provide assent (7 to <17 years old) and whose parent(s) or legal guardian(s) provide consent as required will have study assessments performed at Screening. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone. At this time (during Day −1), they will have a predose check-in to have eligibility confirmed.<br><br>After subjects ages 2 to <17 have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.<br><br>After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via Nurse-Controlled Analgesia (NCA). The Fentanyl will be provided by the study site pharmacy.<br><br>Subjects will undergo an End-of-Study assessment at least 24 hours after receiving the first dose of Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study.<br><br>Safety will be assessed by monitoring AEs, clinical laboratory test results, vital sign measurements, temperature, pulse oximetry, and physical examination findings.<br><br>The Faces, Legs, Activity, Crying, Consolability Scale (FLACC) will be used to measure pain prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution in subjects under age 2. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl.<br><br>Serial blood samples for PK analysis will be collected for the determination of plasma concentrations of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) prior to the first dose (within 15 minutes of dosing); 5, 15, 30, and 60 minutes after dosing; and 2, 4, 6, 8, 12, and 24 hours after dosing. For subjects under age 2, serial blood |

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| | samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 15, 30, and 60 minutes after dosing; and 2, 6, 12, and 24 hours after dosing. |
| PLANNED NUMBER OF SUBJECTS | A total of 110 subjects, including a minimum of 20 subjects under age 2, 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years, are planned for this study to ensure adequate evaluation of the safety and PK profiles of Oxycodone Oral Solution. |
| STUDY ENTRY CRITERIA | Inclusion criteria<br>A subject will be eligible for inclusion in the study if he or she meets the following criteria:<br>1. Is male or female <17 years of age at the time of dosing.<br>2. Subject 2 to <17 years of age, be in at least the 25% for weight according to the Center for Disease Control pediatric growth charts and weighs at least 28 lb at the time of dosing with study drug.<br>3. Is generally healthy as documented by medical history (except for the condition for which the procedure is being performed); physical examination (including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; 12-lead electrocardiograms; clinical laboratory assessments; and general observations. Has a negative serum pregnancy test at Screening and predose check-in for females of childbearing potential.<br>4. Is an outpatient for a surgical procedure and is expected to remain hospitalized for at least 24 hours after dosing with study drug.<br>5. Is anticipated to have postsurgical pain requiring a parenteral analgesic regimen using a short-acting opioid analgesic and is anticipated to be switched to an oral opioid for at least 1 dose (according to institution standard of care).<br>6. Has an indwelling access catheter for blood sampling.<br>7. Agrees to comply with all protocol requirements. If not old enough, the legally responsible parent(s) or legal guardian(s) must agree to comply with all protocol requirements.<br>8. Has been informed of the nature of the study and informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, in accordance with institutional review board requirements.<br>Exclusion criteria<br>A subject will be excluded from the study if he or she meets the following criteria:<br>1. Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (except for the condition for which the procedure is being performed) as determined by the clinical investigator.<br>2. Has any clinical laboratory test result outside the normal range.<br>3. Has a positive test result for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus antibody. |

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| | 4. Had a clinically significant illness, except for the condition for which the procedure is being performed, in the 28 days before dosing with study drug as determined by the clinical investigator.<br>5. Is a lactating or breastfeeding female.<br>6. Uses any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug. Use of all other prescription medications, except required pre-op medications and birth control, is prohibited within 3 days of dosing with study drug. Use of any over-the-counter medications (including herbal or dietary supplements and therapeutic doses of vitamins), except for required pre-op medications, is prohibited within 24 hours of dosing with study drug, with the exception of topical spermicide. Use of St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.<br>7. Consumes alcohol-, caffeine-, or xanthine-containing products within 48 hours before dosing and during periods when blood samples are collected.<br>8. Consumes grapefruit, grapefruit products, Seville oranges, or pomelo-containing products within 14 days of dosing. Fruit juices, with the exception of apple and grape, will be prohibited during the study.<br>9. Is a smoker or has used nicotine or nicotine-containing products within 30 days of dosing.<br>10. Has a history of alcohol or drug addiction or abuse within the last year.<br>11. Subject 2 to <17 years of age, has a positive urine test result for drugs of abuse (amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, and benzodiazepines) or alcohol at Screening (not required for subjects less than 2 years of age).<br>12. Donated blood within 28 days or plasma within 14 days of dosing or plans to donate them within 4 weeks after completing the study.<br>13. Has a history of relevant drug allergies, food allergies, or both (i.e., allergy to oxycodone, allergy to related drugs, or any significant food allergy that could interfere with the study).<br>14. Is intolerant to direct venipuncture.<br>15. Received an investigational drug within 28 days of dosing.<br>16. Has taken oxycodone or oxymorphone within the 48 hours before anticipated dosing with study drug.<br>17. Is not suitable for entry into the study in the opinion of the investigator. |
| INVESTIGATIONAL PRODUCT | Oxycodone Oral Solution provided by VistaPharm, Inc., supplied in 500-mL bottles. Oxycodone Oral Solution contains 4.5 mg of oxycodone free base per 5 mL (5 mg oxycodone HCl/5 ml) and the following inactive ingredients: poloxamer 188 NF, sodium benzoate NF, citric acid anhydrous US Pharmacopeia (USP), glycerin natural USP, sorbitol solution 70% USP, |

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| | FD&C Red #40 , raspberry flavor, and water. |
| TREATMENT REGIMEN | Each subject in the 2 to 6, 7 to 12 and 13 to <17 age groups will receive a dose of Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, and 0.07 mg/kg for ages 13 to 17) in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain medication. The first 10 subjects in each of these age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. Each subject under age 2 will receive a single dose of Oxycodone Oral Solution. The dose will be determined based on PK modeling from the interim analyses. Oxycodone Oral Solution will be administered with an oral medication syringe. |
| CRITERIA FOR EVALUATION | Pharmacokinetic endpoints:<br>• Area under the plasma concentration versus time curve from Time Zero to the last measurable concentration ($AUC_{0-t}$)<br>• Area under the plasma concentration versus time curve from Time Zero to infinity ($AUC_{0-inf}$)<br>• Ratio of $AUC_{0-t}$ to $AUC_{0-inf}$ ($AUC_{0-t}/AUC_{0-inf}$)<br>• Maximum measured plasma concentration ($C_{max}$)<br>• Time of the maximum measured plasma concentration ($T_{max}$)<br>• Apparent first-order terminal elimination rate constant ($K_{el}$)<br>• Apparent first-order terminal elimination half-life ($t_{1/2}$)<br>• Apparent clearance (CL/F)<br>• Volume of distribution (V/F)<br>Other PK parameters may be calculated if deemed necessary.<br>Safety endpoints:<br>Safety will be assessed by the monitoring and recording of AEs; clinical laboratory results (including hematology, serum chemistry, and urinalysis); vital sign measurements (systolic and diastolic blood pressures, heart rate, and respiratory rate); temperature; pulse oximetry; and physical examination findings.<br>Exploratory Study Endpoints:<br>Analgesic sparing will be the surrogate efficacy endpoint in children under age 2.The Total FLACC Score will be an exploratory endpoint in children under age 2. |
| STATISTICAL METHODS | <u>Analysis Populations</u><br>PK Population: the PK population will consist of all subjects who receive study drug and have at least 1 measureable plasma concentration.<br>Safety Population: the safety population will consist of all subjects who receive study drug.<br><u>Subject Characteristics and Disposition</u><br>For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).<br>Baseline demographic and background variables will be summarized. The |

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| | number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized.<br><br>Pharmacokinetic Analyses<br><br>Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be listed and summarized. Each subject's oxycodone plasma concentrations will be graphed by using both a normal scale y-axis and a logarithmic scale y-axis. Mean oxycodone plasma concentrations will also be graphed using scheduled elapsed sampling times for both the normal and logarithmic scale y-axis.<br><br>Pharmacokinetic parameters will be listed for each subject and summarized. Key PK parameters will be contrasted with adult values from the literature.<br><br>Other PK analyses may be performed as appropriate.<br><br>Safety Analyses<br><br>Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.<br><br>Actual values and changes from Baseline for clinical laboratory results, pulse oximetry, and vital sign measurements will be summarized at each time point using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or shift tables where appropriate. Physical examination findings will be presented in a listing. |
| SAMPLE SIZE DETERMINATION | The evaluable sample size for this study is powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for oxycodone with at least 80% power.<br><br>Because of an anticipated dropout rate of 33%, a recruited sample size of 30 subjects is considered sufficient to ensure 20 evaluable subjects to assess the PK profiles of Oxycodone Oral Solution.<br><br>While the PK analysis will require a recruited sample size of 30 subjects, the trial will enroll 110 subjects to gather adequate safety information in the pediatric/adolescent patient population. |
| STUDY AND TREATMENT DURATION | The sequence and maximum duration of the study periods will be as follows:<br><br>Screening is up to 14 days.<br><br>The total study duration for each subject is 1 full day, excluding Screening.<br><br>The maximum treatment duration for each subject is 1 full day. |

## 3. TABLE OF CONTENTS

## 3.1 List of Tables

## 4. LIST OF ABBREVIATIONS

| | |
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| AE | Adverse event |
| AUC | Area under the curve |
| $AUC_{0\text{-}inf}$ | Area under the concentration-time curve from Time Zero to infinity |
| $AUC_{0\text{-}t}$ | Area under the concentration-time curve from Time Zero to the last measurable concentration |
| $C_{max}$ | Observed maximum plasma concentration |
| CRA | Clinical research associate |
| CRF | Case report form |
| CRO | Contract Research Organization |
| CSR | Clinical study report |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |
| FLACC | Face, Legs, Activity, Cry, Consolability Scale |
| GCP | Good Clinical Practice |
| HCl | Hydrochloride |
| ICH | International Conference on Harmonisation |
| IRB | Institutional review board |
| ITT | Intention-to-Treat Population |
| IV | Intravenous |
| $K_{el}$ | Elimination rate constant |
| kg | Kilogram |
| L | Liter |
| lbs | Pounds |
| mg | Milligram |
| min | Minutes |
| mL | Milliliter |
| NCA | Nurse-Controlled Analgesia |
| PK | Pharmacokinetic |
| RPM | Revolutions per minute |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SOC | Standard of care |

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| $t_{1/2}$ | Apparent elimination half-life |
| TBV | Total blood volume |
| $T_{max}$ | Time of maximum concentration |
| USP | United States Pharmacopeia |

# 5. INTRODUCTION

## 5.1 Background and Rationale

### 5.1.1 Indication and Usage

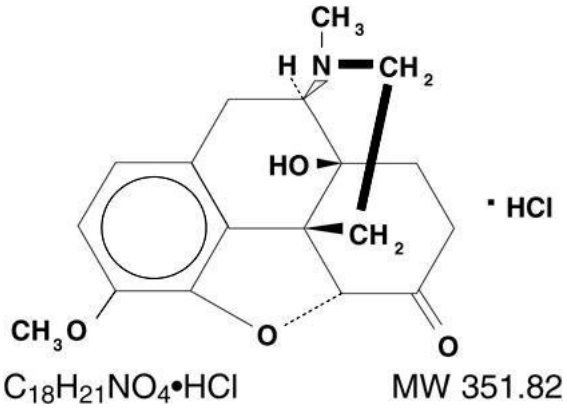
Oxycodone (4, 5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride) is a semisynthetic opioid that has been in clinical use since 1917 and approved for use in the US since 1950. Developed by VistaPharm, Inc., oxycodone hydrochloride (HCl) US Pharmacopeia (USP) oral solution, 5 mg per 5 mL, is an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate. This product was approved by the Food and Drug Administration (FDA) on January 12, 2012 (application New Drug Application 201194). In addition, Lehigh Valley Technologies, Inc. has developed Oxycodone Hydrochloride Oral Solution available as a 100 mg/5 mL (20 mg/mL) concentration which is indicated for use in opioid-tolerant patients only. This product was approved by the Food and Drug Administration (FDA) on October 20, 2010 (application New Drug Application 200535). The results of the study described with the current protocol will be utilized to meet regulatory requirements for both VistaPharm, Inc. and Lehigh Valley Technologies, Inc.

Oxycodone HCl is currently available in the US in a number of other forms and combinations. Oxycodone is a Schedule II controlled substance. The VistaPharm, Inc., oxycodone hydrochloride (HCl) (USP) oral solution, 5 mg per 5 mL, will be utilized for the purposes of this protocol.

### 5.1.2 Description

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride and has the following structural formula:




### 5.1.3 Pharmacodynamics

Oxycodone is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of oxycodone are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Additional detailed information on the pharmacodynamic properties of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

### 5.1.4 Pharmacokinetics

#### 5.1.4.1 Absorption

About 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison with a parenteral dose. This high oral bioavailability (compared to other oral opioids) is due to lower presystemic metabolism, first-pass metabolism, or both of oxycodone.

A single-dose food effect study was conducted in normal adult volunteers using the 5 mg/5 mL solution. The concurrent intake of a high fat meal was shown to enhance the extent (a 27% increase in the area under the plasma concentration versus time curve [AUC]) but not the rate of oxycodone absorption from the oral solution. In addition, food caused a delay in the time of maximum concentration ($T_{max}$) (1.25 to 2.54 hours).

#### 5.1.4.2 Distribution

Following intravenous (IV) administration, the volume of distribution for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk.

#### 5.1.4.3 Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone but not noroxycodone is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs.

#### 5.1.4.4 Elimination

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: up to 19% was reported for free oxycodone; up to 50% was reported for conjugated oxycodone; 0% was reported for free oxymorphone; no greater than 14% was reported for conjugated oxymorphone; and both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Additional detailed information on the physical, chemical, and pharmaceutical properties of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

### 5.1.5 Clinical Experience

Oxycodone hydrochloride USP oral solution has been studied in adult populations, with a focus on pharmacokinetics, safety, and tolerability. A total of 4 clinical pharmacokinetic (PK) and bioavailability studies have been conducted to support the development and labeling of oxycodone hydrochloride USP oral solution.

In addition, there are a number of published studies in the medical literature that report on the pharmacokinetics of oxycodone in clinical and nonclinical settings, in a variety of doses and routes of administration.[1-19]

### 5.1.6 Study Rationale

Despite published studies on dosing and pharmacokinetics in pediatric populations,[20-25] oxycodone has never received an official indication for use in children. Pursuant to the Pediatric Research Equity Act (21 USC 355c), the FDA has requested that VistaPharm, Inc. and Lehigh Valley Technologies, Inc. conduct a postapproval and postmarketing (Phase IV) PK and safety study in subjects < 17 years of age.

## 5.2 Summary of Potential Risks and Benefits

### 5.2.1 Potential Risks

The most frequently observed adverse events (AEs) reported with oxycodone include light headedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in subjects who can walk than in subjects who cannot walk, and some of

these adverse reactions may be alleviated if the subject lies down. Other AEs include euphoria, dysphoria, constipation, skin rash, and pruritus.

Additional detailed information on potential AEs and on specific warnings and precautions with the use of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

Given that some of the subjects will be infants and young children, the effect of multiple blood draws can be considered a potential risk or adverse situation. A published review of the safe limits of blood sample volumes in child health research suggests that existing guidelines specify limits ranging from 1% to 5% of total blood volume (TBV) over 24 hours. However, the limited available evidence that includes findings from nonrandomized studies shows a minimal risk with one-off sampling of up to 5% of TBV.[26]

For subjects 2 <17 years of age, this protocol specifies a maximum of 11 serial blood samples of 0.5 mL each for a total of 5.5 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. In addition, up to 10 mL will be allotted as discard volume for the 11 PK samples and the final laboratory testing drawn through the indwelling catheter. Existing blood draw guidelines for pediatric research suggest minimal risk is between 3% and 5% of total blood volume (TBV) over 24 hours or on a single draw and TBV is generally estimated at 75-80 mL/kg. For the smallest child permitted per protocol, 2 to <17 years of age (weight: 28 lbs or 12.7 kg), the TBV would be estimated at 952.5 ml. The maximum safe volume drawn would therefore be between 28 and 47 mL, based on minimal risk at 3-5% TBV over 24 hours. The required 10.5 mL plus up to 10 mL of discard volume, or a cumulative volume of 20.5 mL, is well under the 3-5% of TBV guideline for the smallest eligible participant using the smallest estimation of TBV. [26]

For the child less than 2 years of age, there is a maximum of 8 serial blood samples of 0.5 mL each for a total of 4.0 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. The required 9 mL is under the 3-5% of TBV guideline.

### 5.2.2 Benefits

The size of the test dose (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to 17, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2) is designed to provide adequate analgesia for moderate to severe pain in substituting for the routinely prescribed postoperative pain regimen according to the custom of the attending physician and the institutional standard of care (SOC).

No other benefit is anticipated or expected for subjects participating in this study.

## 6. OBJECTIVE

The objective of this study is to characterize the pharmacokinetics and to evaluate the safety of single and multiple doses of Oxycodone Oral Solution in pediatric and adolescent subjects.

## 7. STUDY DESIGN

### 7.1 Overall Study Design and Plan

This is a Phase IV study to characterize the pharmacokinetics and to evaluate the safety of Oxycodone Oral Solution administered to pediatric and adolescent subjects following a surgical procedure. It is an open-label, multicenter study conducted at up to 10 sites. Subjects will be enrolled preoperatively up to 14 days before surgery with the expectation that they will require IV access after the surgery for at least 24 hours and postoperative analgesia with an opiate-level medication. After dosing with Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to 17, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2), subjects will be carefully monitored for safety. A total of 110 pediatric and adolescent male or female subjects will be enrolled, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years. Subjects within each age group will be evenly distributed by age and gender.

An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects under age 2 will receive will be based on PK modeling from the interim analysis.

An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on PK modeling from the interim analysis.

The study will consist of a Screening period within 14 days of surgery; a predose check-in (Day −1); a treatment period after surgery (Day 1, Time Zero); and an End-of-Study assessment. The total duration of the study, excluding Screening, will be approximately 1 full day.

Eligible subjects who provide assent (7 to <17 years old) and whose parent(s) or legal guardian(s) provide consent as required will have study assessments performed at Screening. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone. At this time (during Day −1), they will have a predose check-in to have eligibility confirmed.

After subjects ages 2 to <17 years have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA. The Fentanyl will be provided by the study site pharmacy.

Water, Gatorade, Powerade, Pedialite, or Popsicles will be allowed for the first hour (1 hour) following dosing, but subjects must avoid fruit juice (excluding apple and grape), including fruit-containing popsicles, throughout the course of the study.

Subjects will undergo an End-of-Study assessment at least 24 hours after dosing with Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study. Subjects who discontinue the study for any reason will not be replaced.

Safety will be assessed, between time 0 and 24 hours post first study medication administration, by monitoring AEs, clinical laboratory test results, vital sign measurements, temperature, pulse oximetry, and physical examination findings.
The FLACC will be used to measure pain prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution in subjects under 2 years of age. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl.

For subjects 2 to <17 years of age, serial blood samples for PK analysis will be collected for the determination of plasma concentrations of oxycodone at the predose time point (within 15 minutes of dosing); 5, 15, 30, and 60 minutes after dosing; and 2, 4, 6, 8, 12, and 24 hours after dosing. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 15, 30, and 60 minutes after dosing; and 2, 6, 12, and 24 hours after dosing.

## 7.2 **Discussion of Study Design**

This is an open-label, nonrandomized, multicenter study designed to assess the pharmacokinetics and safety of the product oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, in pediatric and adolescent subjects <17 years of age following a surgical

procedure and expected to require postoperative opioid analgesia and to require an indwelling IV catheter for a minimum of 24 hours after being cleared for oral intake. Target enrollment will be 110 subjects, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years, to evaluate safety in the population. Subjects within each age group will be evenly distributed by age and gender. In addition, this sample size will allow for an adequate evaluable population according to published population PK studies in children[21] and unofficial FDA guidance on sample size calculations based on estimates of clearance and volume of distribution.[27] Recruitment projections are based on a review of recent reports of adolescent scoliosis surgery showing that major specialty surgical centers average 10 to 20 patients per year in this age group.[28-32]

### 7.3 Study Sites

The study will take place at up to 10 sites in the US.

### 7.4 Point of Contact

A point of contact will be identified to provide subjects with information on the study, subject rights, and whom to contact in case of study-related injury. This information will be provided in the subject information and informed assent and consent forms.

## 8. SUBJECT POPULATION

### 8.1 Selection of Study Population

#### 8.1.1 Inclusion Criteria

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1 Is male or female <17 years of age at the time of dosing.

2 Subject 2 to <17 years of age, be in at least the 25% for weight according to the Center for Disease Control pediatric growth charts and weighs at least 28 lb at the time of dosing with study drug.

3 Is generally healthy as documented by medical history (except for the condition for which the procedure is being performed); physical examination (including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; 12-lead electrocardiograms (ECGs); clinical laboratory assessments; and general observations. Has a negative serum pregnancy test at Screening and predose check-in for females of childbearing potential.

4 Is an outpatient for a surgical procedure and is expected to remain hospitalized for at least 24 hours after dosing with study drug.

5 Is anticipated to have postsurgical pain requiring a parenteral analgesic regimen by using a short-acting opioid analgesic and is anticipated to be switched to an oral opioid for at least 1 dose (according to institution standard of care).

6 Has an indwelling access catheter for blood sampling.

7 Agrees to comply with all protocol requirements. If not old enough, the legally responsible parent(s) or legal guardian(s) must agree to comply with all protocol requirements.

8 Has been informed of the nature of the study, and informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, in accordance with institutional review board requirements.

### 8.1.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets the following criteria:

1 Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (except for the condition for which the procedure is being performed) as determined by the clinical investigator.

2 Has any clinical laboratory test result outside the normal range.

3 Has a positive test result for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus antibody.

4 Has a clinically significant illness, except for the condition for which the procedure is being performed, in the 28 days before dosing with study drug as determined by the clinical investigator.

5 Is a lactating or breastfeeding female.

6 Uses any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug. Use of all other prescription medications, except required pre-op medications and birth control, is prohibited within 3 days of dosing with study drug. Use of any over-the-counter medications (including herbal or dietary supplements and therapeutic doses of vitamins), except for required pre-op medications, is prohibited within 24 hours of dosing with study drug, with the exception of topical spermicide. Use of St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.

7 Consumes alcohol-, caffeine-, or xanthine-containing products within 48 hours before dosing and during periods when blood samples are collected.

8 Consumes grapefruit, grapefruit products, Seville oranges, or pomelo-containing products within 14 days of dosing. Fruit juices, with the exception of apple and grape, will be prohibited during the study.

9 Is a smoker or has used nicotine or nicotine-containing products within 30 days of dosing.

10 Has a history of alcohol or drug addiction or abuse within the last year.

11 Subject 2 to <17 years of age, has a positive urine test result for drugs of abuse (amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, and benzodiazepines) or alcohol at Screening (not required for subjects less than 2 years of age).

12 Donated blood within 28 days or plasma within 14 days of dosing or plans to donate them within 4 weeks after completing the study.

13 Has a history of relevant drug allergies, food allergies, or both (i.e., allergy to oxycodone, allergy to related drugs, or any significant food allergy that could interfere with the study).

14 Is intolerant to direct venipuncture.

15 Received an investigational drug within 28 days of dosing.

16 Has taken oxycodone or oxymorphone within the 48 hours before anticipated dosing with study drug.

17 Is not suitable for entry into the study in the opinion of the investigator.

## 8.2 Removal of Subjects from Therapy or Assessment

All subjects are free to withdraw from participation in this study at any time for any reason and without prejudice.

The investigator may terminate a subject from the study at any time for lack of therapeutic effect that is intolerable to the subject or otherwise considered unacceptable, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or unsuitability for the study in the investigator's opinion to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate case report form (CRF). Whenever possible and reasonable, evaluations that were scheduled for study completion should be performed at the time of premature discontinuation.

Subjects who discontinue from the study will not be replaced.

# 9. STUDY TREATMENTS

## 9.1 Method of Assigning Subjects to Treatment Groups

### 9.1.1 Under Age 2

Subjects under age 2 who meet all eligibility criteria will receive a single dose of Oxycodone Oral Solution. This will be an open-label study and does not require randomization.

### 9.1.2 Ages 2 to <17

Subjects ages 2 to <17 who meet all eligibility criteria will be scheduled to receive single or multiple doses of Oxycodone Oral Solution. This will be an open-label study and does not require randomization.

## 9.2 Identification of Investigational Products

The study drug is Oxycodone Oral Solution (5 mg/5 mL) manufactured by VistaPharm (Largo, FL). Oxycodone Oral Solution is a red solution intended for oral administration.

Oxycodone Oral Solution will be supplied in 500-mL bottles. Oxycodone Oral Solution contains 4.5 mg of oxycodone free base per 5 mL (5 mg oxycodone HCl/5 ml) and the following inactive ingredients: poloxamer 188 NF, sodium benzoate NF, citric acid anhydrous USP, glycerin natural USP, sorbitol solution 70% USP, FD&C Red #40, raspberry flavor, and water.

VistaPharm will provide an adequate supply of study drug to the sites.

Ketorolac for injection (15 mg/mL or 30 mg/mL), Morphine Sulfate for injection (2 mg/mL), and Fentanyl via NCA for use as a rescue medication will be provided by the study site pharmacy. Should other rescue medication be required they will be provided by the study site pharmacy.

## 9.3 Treatment Administered

The study drug will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s).

### 9.3.1 Under Age 2

Each subject will receive a single dose of Oxycodone Oral Solution in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain medication. The dose will be determined based on PK modeling from the interim analyses. Oxycodone Oral Solution will be administered with an oral medication syringe.

### 9.3.2 Ages 2 to <17

Each subject will receive a dose of Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, and 0.07 mg/kg for ages 13 to 17) in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain

medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. Oxycodone Oral Solution will be administered with an oral medication syringe.

## 9.4 Storage

Oxycodone Oral Solution will be stored in a locked facility with restricted access. This may be a locked cabinet or room for which the number of keys is limited and in compliance with standards of the Drug Enforcement Administration for Schedule II narcotics. Chain of custody of the study drug will be followed in accordance with the individual site's standard procedures, which will be documented by the site and provided to the sponsor. The study drug will be stored at controlled room temperature between 20°C and 25°C (68°F-77°F). The sponsor will provide to the site personnel instructions for the storage and return of used and unused study drug.

## 9.5 Labeling

Each container of study drug will be labeled with study-specific information that meets all applicable regulatory requirements.

## 9.6 Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of study drug, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received study drug. The investigator will not supply study drug to any person except those named as subinvestigators on the FDA 1572, designated staff, and subjects in this study. The investigator will not dispense study drug from any sites other than those listed on the FDA 1572. Study drug may not be relabeled or reassigned for use by other subjects.

Upon completion of the study, unused supplies of study drug will be reconciled by the investigator and returned to the sponsor as directed.

## 9.7 Blinding and Unblinding Treatment Assignment

Not applicable.

## 9.8 Selection of Dose in the Study

The published literature on treatment of pediatric pain with oxycodone reports doses ranging from 0.125 to 0.2 mg/kg, up to a maximum of 15 mg, for treatment of acute musculoskeletal pain, including suspected fractures in emergency room settings, for treatment of undifferentiated abdominal pain, and for pediatric burn wound care in outpatient clinics.[33-36] A PK modeling has been conducted using the data derived from the 4 studies conducted in the adult population. Based on these population data, the test dose chosen for subjects ages 2 to 6 is 0.1 mg/kg, ages 7 to 12 is 0.08 mg/kg, ages 13 to 17 is 0.07 mg/kg, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2, given when the subjects have been cleared for oral

intake and in place of the analgesic regimen (nonoxycodone and nonoxymorphone) prescribed postoperatively for subjects by their attending physicians according to institutional SOCs. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed.

The dose for subjects under age 2 will be determined based on PK modeling from the interim analyses.

## 9.9 Selection of Timing of Dose for Each Subject

The design of the study and the timing of dosing were selected to provide the appropriate basis for assessing the PK parameters of oxycodone following administration of the first dose.

## 9.10 Treatment Compliance

All study drugs will be administered in the hospital by study personnel and recorded in the CRF. Study personnel will confirm that the subject ingests the entire dose of study drug.

The date and time of study drug administration will be recorded on the appropriate page of the CRF. If a subject does not receive the study drug, the reason for the missed dose will be recorded.

## 9.11 Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate CRF. The medication name, dose, including frequency, date, and indication for use must be recorded. Time of rescue medication will also be recorded. The medical monitor should be notified in advance of (or as soon as possible after) any instances in which prohibited therapies or rescue medications are administered. Medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the study medication may be given at the discretion of the investigator.

### 9.11.1 Permitted Therapies

Concomitant medications (with the exceptions described in Section 9.11.2) are allowed, but should be limited to only those medications considered necessary.

Nausea and vomiting are common opioid-induced AEs for which subjects do develop a tolerance. Subjects who undergo surgery requiring opioid analgesia for an extended period of time may develop these AEs. Therefore, it is expected that some subjects will need to be given an antiemetic. Any antiemetic used during treatment with study drug should be recorded as a concomitant medication.

### 9.11.2 Prohibited Therapies

Use of any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug through the end of the study is prohibited. Use of all other prescription medications, with the exception of allowable pre-op medications and birth control, is prohibited within 3 days of dosing with study drug. Use of any monoamine oxidase inhibitor is prohibited until 14 days after the final dose of study drug.

Use of any over-the-counter medications (including herbal or dietary supplements and therapeutic doses of vitamins), except for allowable pre-op medications, is prohibited within 24 hours of dosing with study drug, with the exception of topical spermicide. Use of St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.

Restrictions:

Females of childbearing potential must be practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or double-barrier method). For the purpose of this study, all females who are menstruating will be considered to be of childbearing potential unless they are biologically sterile or surgically sterile for more than 1 year.

Consumption of alcohol-, caffeine-, or xanthine-containing products within 48 hours before dosing and during periods when blood samples are collected is prohibited. Consumption of grapefruit, grapefruit products, Seville oranges, or pomelo-containing products is prohibited within 14 days of dosing with study drug. All types of fruit juices, with the exception of apple and grape, and fruit-containing popsicles will be prohibited during the study.

Subjects who smoke or use nicotine or nicotine-containing products within 30 days of Screening will be excluded from study participation.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continuation in the study at the discretion of the sponsor, investigator, medical monitor, or other authority.

## 9.12 Rescue Medication

In subjects ages 2 to <17 years, if pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

In subjects under age 2, if pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA. The Fentanyl will be provided by the study site pharmacy.

## 10. STUDY PROCEDURES

Subjects' legally responsible parent(s) or legal guardian(s) will provide written informed consent and subjects will provide written informed assent (as appropriate) before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Table 2 (Section 17) presents the schedule of events to be performed during the study.

### 10.1 Screening (Day −14 to Day −1)

Subjects must be screened within 14 days before enrollment in the study. The following procedures will be performed at Screening:

- Obtain written informed consent and assent (as appropriate).
- Review inclusion and exclusion criteria.
- Collect demographic information.
- Record medical history, including prior and current therapies (e.g. prescription and nonprescription medications).
- Perform a physical examination including weight, height, body mass index, and vital signs (blood pressure, heart rate, respiratory rate, and oral temperature).
- Perform serum pregnancy test for all females of childbearing potential.
- Perform urine drug screen (Section 11.2.2), excluding subjects < 2 years of age.
- Perform 12-lead ECG.
- Collect blood and urine samples for clinical laboratory tests (complete blood count with differential, clinical chemistry, serology, and urinalysis) (Section 11.2.2).

### 10.2 Predose Check-in (Day −1)

The predose check-in (Day −1) can be performed the same day as surgery (Day 1) at which time eligibility and prior medications will be reviewed and updated as needed. Medical history will be recorded, if it was not completed at Screening, and vital signs will be obtained. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone.

### 10.3 Open-Label Treatment (Day 1, After Surgery)

The following procedures will be performed on Day 1:

- Measure blood pressure, heart rate, and respiratory rate before dosing (within 90 minutes) with Oxycodone Oral Solution and every 15 minutes for 4 hours after

dosing, then every 2 hours until 24 hours after the first dose of Oxycodone Oral Solution.

- Measure temperature every 2 hours for 24 hours after the first dose of Oxycodone Oral Solution.
- Continuous pulse oximetry beginning as soon as possible following procedure through 8 hours after the last study dose of Oxycodone Oral Solution. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last study dose of Oxycodone Oral Solution.
- Assess pain in subjects under 2 years of age by using the FLACC prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the first dose of Oxycodone Oral Solution. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl**.**
- Record concomitant medication use.
- Assess and record AEs prior to dosing and throughout the remainder of Day 1.
- For subjects 2 to <17 years of age, collect serial blood samples for PK analysis at the predose time point (within 15 minutes of dosing); 5, 15, 30, and 60 minutes after dosing; and 2, 4, 6, 8, 12, and 24 hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the Oxycodone Oral Solution dose (within 15 minutes of dosing); 15, 30, and 60 minutes after dosing; and 2, 6, 12, and 24 hours after dosing.
- After subjects ages 2 to <17 have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care.
- After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA.

Water, Gatorade, Powerade, and Popsicles will be allowed for the first hour (1 hour) following dosing, but subjects must avoid fruit juice (excluding apple and grape), including fruit-containing popsicles, throughout the course of the study.

## 10.4 **End-of-Study/Early Discontinuation**

Subjects will undergo an End-of-Study/Early Discontinuation assessment at least 24 hours after dosing with Oxycodone Oral Solution.

The following procedures will be performed at the End-of-Study/ Early Discontinuation visit:

- Measure vital signs (blood pressure, heart rate, and respiratory rate).
- Clinical laboratory testing (complete blood count with differential and clinical chemistry).
- Record concomitant medications.
- Record AEs.

After these procedures are performed, the study staff will determine whether it is safe for the subject to be discharged from the study.

# 11. STUDY ASSESSMENTS

## 11.1 Pharmacokinetics

Blood samples for PK assessments in the subjects 2 to <17 years of age will be collected at the predose time point (within 15 minutes of the first dose of Oxycodone Oral Solution); 5, 15, 30, and 60 minutes after dosing; and 2, 4, 6, 8, 12, and 24 hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, blood samples for PK analysis will be collected prior to the Oxycodone Oral Solution dose (within 15 minutes of dosing); 15, 30, and 60 minutes after dosing; and 2, 6, 12, and 24 hours after dosing. Time Zero is the time of the first dose of Oxycodone Oral Solution.

The following PK parameters will be calculated:

- Area under the plasma concentration versus time curve from Time Zero to the last measurable concentration ($AUC_{0-t}$)
- Area under the plasma concentration versus time curve from Time Zero to infinity ($AUC_{0-inf}$)
- Ratio of $AUC_{0-t}$ to $AUC_{0-inf}$ ($AUC_{0-t}/AUC_{0-inf}$)
- Maximum measured plasma concentration ($C_{max}$)
- Time of the maximum measured plasma concentration ($T_{max}$)
- Apparent first-order terminal elimination rate constant ($K_{el}$)
- Apparent first-order terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Volume of Distribution (V/F)

Other PK parameters may be calculated if deemed necessary.

### 11.1.1 Sample Collection

Blood collection will be performed using an existing indwelling access catheter (arterial or venous noted on CRF) at the start of the study (the use of Emla at the insertion site is permitted). All catheter lines should be appropriately flushed per institutional SOC before each blood draw. The 0.5-mL blood samples will be obtained and placed into 2.0-mL K3 ethylenediamine tetra-acetic acid tubes at each blood collection time point. The labels for all biological sample collection and storage containers will contain, at a minimum, the subject's number, protocol number, collection date, and scheduled collection time (study hour).

| Study Visit/Phase | Amount Collected (mL) | Number of Samples Collected | Total Amount Collected per Subject (mL) |
|---|---|---|---|
| Screening Serum Chemistry and Hematology[a] | 2.5 mL | 1 | 2.5 mL |
| Pharmacokinetics (2 to <17 years old) or | 0.5 mL | 11 | 5.5 mL |
| Pharmacokinetics (<2 years old) | 0.5 mL | 8 | 4.0 mL |
| End of Study Serum Chemistry and Hematology | 2.5 mL | 1 | 2.5 mL |
| Grand Total | -- | -- | 14.0 – 20.5 mL[b] |

[a] Where possible, results from clinical laboratory tests performed as part of the standard of care (SOC) will be used for study purposes. A separate blood draw for the clinical laboratory test portion of this protocol will occur only if the clinical laboratory tests as part of the SOC will not be available to coincide with the approximate time scheduled by the protocol. Preoperative or intraoperative (collected before the incision) test results must be available for review by the investigator before enrolling any subject into the study. Procedures for blood draws should follow institutional SOC.

[b] The total includes up to 10-mL discard volume for all 11 pharmacokinetic and laboratory testing samples, for the 2 to <17 year olds. Total blood volume drawn for research purposes must not exceed 3% of subject's total blood volume, which is assumed to be 75 mL/kg.

### 11.1.2 Blood Volumes

Existing blood draw guidelines for pediatric research suggest minimal risk is between 3% and 5% of total blood volume (TBV) over 24 hours or on a single draw, and TBV is generally estimated at 75-80 mL/kg. For the smallest child permitted per protocol from ages 2 to <17 years (weight: 28 lbs or 12.7 kg), the TBV would be estimated at 952.5 ml. The maximum safe volume drawn would therefore be between 28 and 47 mL, based on minimal risk at 3-5% TBV over 24 hours. The required 10.5 mL plus up to 10 mL of discard volume, or a cumulative volume of 20.5 mL, is well under the 3-5% of TBV guideline for the smallest eligible participant using the smallest estimation of TBV.[26] For the child less than 2 years of age, there is a maximum of 8 serial blood samples of 0.5 mL each for a total of 4.0 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. The required 9 mL is under the 3-5% of TBV guideline.

### 11.1.3 Sample Processing

Immediately after collection, the tube will be gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction will be separated by placing the collection tube into a refrigerated centrifuge (4°C to 8°C) for 10 minutes at approximately 1500*g* or 3000 RPM. The plasma fraction will be withdrawn by pipette and placed into polypropylene freezing tubes in 2 approximately equal aliquots. All sample collection and freezing tubes will be clearly labeled in a manner that identifies the subject and the collection time. Labels will be fixed to the freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be placed into a freezer at approximately –20°C (± 10°C) or below until transfer or shipment to the bioanalytical laboratory. The time between sample collection and freezer storage should not exceed 90 minutes. The additional blood draws for the purposes of pharmacokinetic assessment in this study do not pose more than a minor risk to the subjects.

### 11.1.4 Transport of Samples

The clinic staff will inventory the samples that are to be shipped to the bioanalytical laboratory. Each shipment will contain a complete set of samples. The second set of samples will not be shipped until receipt of the first shipment is confirmed. The inventory record will accompany the frozen plasma samples as per standard operating procedures.

For sample shipment requiring a third party courier, the samples will be packed in ample dry ice within a styrofoam container to ensure the samples will remain frozen for at least 72 hours and will be shipped via express delivery to the bioanalytical facility. Written notification of sample shipment will be communicated to the bioanalytical facility and the sponsor. The samples will be tracked to assure arrival in a safe and timely manner.

The shipment will be accompanied by logs showing the name of the study drug, protocol number, and the subject numbers and samples included in the shipment. Documentation noting what the condition of the samples upon arrival at the bioanalytical laboratory is and whether the amount of dry ice remaining is adequate or inadequate should be returned to the clinic.

The samples will be shipped frozen to:
PPD - Houston
10550 Rockley Road, Suite 150
Houston, TX 77099, USA

### 11.1.5 Analytical Procedures

#### 11.1.5.1 Bioanalytical Sample Analyses

Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be measured using a validated liquid chromatography–mass spectrometry assay method. The validated detection range for oxycodone is 0.2 to 125 ng/mL in human plasma.

Samples from subjects who withdraw consent/assent or are dropped from the study will not be analyzed unless otherwise requested by the sponsor.

Samples from subjects who have been dropped from the study because of emesis according to PPD's standard operating procedures will not be analyzed.

#### 11.1.5.2 Bioanalytical Methodology

The bioanalytical method, assay validation, and bioanalytical report for this study will be provided by the bioanalytical investigator. Full validation of a sensitive assay for the appropriate analytes in biological fluid, including precision, accuracy, reproducibility, and selectivity will be included in the final report. The bioanalytical report will include the stability of the frozen samples, limit of quantitation, recovery, and a summary of the standard curves.

## 11.2 Safety

Safety will be assessed during the study by the monitoring and recording of AEs, clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate, and respiratory rate), temperature, pulse oximetry, and physical examination findings.

### 11.2.1 Adverse Events

#### 11.2.1.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a subject or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease temporally associated with the product, whether or not it is related to the product.

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a preexisting condition is considered an AE.

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the investigator brochure. For a marketed drug, the known information is in the current package insert.

An unexpected AE is one for which the specificity or severity is not consistent with the current investigator brochure or package insert. For example, hepatic necrosis would be unexpected (greater severity) if the investigator brochure or package insert only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the investigator brochure or package insert only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected AEs. Examples include acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and hepatitis with a first occurrence of fulminate hepatitis.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be used in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE does not qualify the condition or event as an SAE. A newly diagnosed pregnancy in a subject who has received a study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy; however, the medical monitor should be made aware of a newly diagnosed pregnancy as soon as possible after site notification. A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE.

#### 11.2.1.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 11.2.1.1) are recorded in the CRF and reported to the medical monitor (Section 11.2.1.3). Adverse events will be collected from the time of the first dose of Oxycodone Oral Solution through the End of Study or Early Discontinuation visit.

At each visit, subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications). In addition to subject observations, AEs will be documented from any data collected on the AE page of the CRF (e.g., clinical laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

#### 11.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the CRF. Information to be collected includes drug treatment, type of event, time of onset, dose, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The latest version of the Medical Dictionary of Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator or designee must report any AE that meets the criteria for an SAE (Section 11.2.1.1) to the medical monitor within 24 hours of first becoming aware of the event by telephone. At the time of first notification, the investigator or designee should provide at a minimum the following information if available:

- Protocol number
- Subject's study identification and initials
- Subject's date of birth
- Date of dose of study drug
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken

Within 24 hours of the initial telephone notification, the investigator must fax a written SAE report form to the medical monitor. Any missing or additional relevant information about the SAE should be provided in a written follow-up SAE report form. The investigator should also ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of the institutional review board (IRB).

The following contact information is to be used for SAE reporting:

Thomas J. Hochadel, Pharm.D.
Cognitive Research Corporation
200 Central Ave, Suite 1230
Saint Petersburg, FL 33701
Telephone: 727-897-9000
Cell: 727-515-1334
Fax: 727-897-9000

#### 11.2.1.3.1 Assessment of Severity

The severity or intensity of an AE refers to the extent to which it affects the subject's daily activities. Severity will be rated as mild, moderate, or severe using the following criteria:

| | |
|---|---|
| Mild: | Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. |
| Moderate: | Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. |
| Severe: | Interrupts usual activities of daily living, significantly affects |

clinical status, or may require intensive therapeutic intervention

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

#### 11.2.1.3.2 Assessment of Relationship

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

| | |
|---|---|
| Not related: | An AE with sufficient evidence to accept that there is no causal relationship to administration of study drug (e.g., no temporal relationship because the study drug was administered after the onset of the event, an investigation shows that study drug was not administered, another cause was proven.) |
| Unlikely related: | An AE, including a clinical laboratory test abnormality, with a temporal relationship to administration of study drug that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations. |
| Possibly related: | An AE with a reasonable time sequence to administration of study drug but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear. |
| Related: | An AE occurring in a plausible time relationship to administration of study drug and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable. |

#### 11.2.1.3.3 Definition of Adverse Event Start Date, Stop Date, and Duration

| | |
|---|---|
| Start date: | The date at which the AE is first noted |
| Stop date: | The date at which the AE is known to be resolved. If it has not known to have stopped, then indicate "ongoing." |
| Duration: | A time in days, hours, or minutes |

#### 11.2.1.3.4 Action(s) Taken

Action(s) taken may consist of the following (as appropriate):

| | |
|---|---|
| None: | No actions taken. |
| Discontinued study drug: | Study drug was permanently discontinued because of the AE. |
| Treatment: | Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure. |
| Others: | Other actions, such as an operative procedure, were required because of the AE. |

#### 11.2.1.3.5 Definition of Adverse Event Outcome at the Time of Last Observation

The AE outcome at the time of last observation will be classified as "resolved," "resolved with sequelae," "ongoing," "death," "other," or "unknown."

"Death" should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "death" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

### 11.2.1.4 Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after dosing with study drug) to a satisfactory resolution or until the investigator deems the event to be chronic or not clinically significant or the subject to be stable. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate CRF.

### 11.2.2 Laboratory Safety Assessments

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 17).

| | |
|---|---|
| Hematology: | Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count) |
| Serum chemistry: | Includes blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose (fasting), albumin, and total protein |
| Serology: | Includes human immunodeficiency virus test, hepatitis B surface antigen test, and hepatitis C virus |
| Urinalysis: | Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive |
| Serum pregnancy test: | Conducted for women of childbearing potential only |
| Urine drug screen | Includes amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, ethyl alcohol, and benzodiazepines |

Each safety laboratory assessment blood sample will be 2.5 mL in volume. The total amount of blood to be drawn will be a maximum of 19.5 mL per subject, including 11 samples for PK assessments (0.5 mL each).

### 11.2.3 Vital Signs

Vital signs, including heart rate, respiratory rate, and blood pressure will be measured at the time points specified in the schedule of events (Section 17) after the subject has been in a sitting position for 5 minutes. Oral body temperature will also be measured.

### 11.2.4 Pulse Oximetry

Continuous pulse oximetry will begin as soon as possible following the procedure and will continue until 8 hours after the last study dose of Oxycodone Oral Solution. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last study dose of Oxycodone Oral Solution.

### 11.2.5 Electrocardiogram

An ECG will be performed at Screening only.

### 11.2.6 Physical Examination

A standard physical examination will be performed at Screening. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart,

cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the investigator's discretion if necessary to evaluate AEs or clinical laboratory abnormalities.

### 11.3 Faces, Legs, Activity, Crying, Consolability Scale (FLACC)

The Faces, Legs, Activity, Crying, Consolability Scale (FLACC) (See Attachment 17.4) will be used to measure pain in subjects under age 2 prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl.

The FLACC provides a simple framework for quantifying pain behaviors in children who are unable to verbalize the presence or severity of pain.[37]

Additionally, time of rescue medication will also be evaluated.

## 12. STATISTICAL METHODS

### 12.1 General Considerations

Descriptive statistics will be provided for all demographic, safety, and PK parameters. No formal statistical testing will be performed for this study.

A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written before database lock.

### 12.2 Analysis Populations

The following analysis populations are planned for this study:

- PK Population: the PK population will consist of all subjects who receive the study drug and have at least 1 measureable plasma concentration.
- Safety Population: the safety population will consist of all subjects who receive the study drug.

### 12.3 Statistical Analyses

#### 12.3.1 Subject Disposition and Demographic Characteristics

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized by using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

Baseline demographic and background variables will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized.

### 12.3.2 Pharmacokinetic Analyses

Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be listed and summarized. Each subject's oxycodone plasma concentrations will be graphed using both a normal scale y-axis and a logarithmic scale y-axis. Mean oxycodone plasma concentrations will also be graphed using scheduled elapsed sampling times for both the normal and logarithmic scale y-axis.

Pharmacokinetic parameters will be listed for each subject and summarized. Key PK parameters will be contrasted with adult values from the previously conducted PK studies.

Other PK analyses may be performed as appropriate.

### 12.3.3 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.

Actual values and changes from Baseline for clinical laboratory results, vital sign measurements, temperature, and pulse oximetry will be summarized at each time point using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or shift tables where appropriate. Physical examination findings will be presented in a listing.

### 12.3.4 Exploratory Analyses

The change from baseline in total FLACC Score will be summarized at each time point. The total amount of Fentanyl will also be evaluated.

### 12.3.5 Interim Analyses

An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 6 months to <2 years will receive will be based on this interim analysis.

An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on PK modeling from the interim analysis.

### 12.4 Sample Size Determination

The evaluable sample size for this study is powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for oxycodone with at least 80% power.

Estimates of the coefficient of variation for the clearance and volume of distribution of oxycodone were 25.72% and 71.12%, respectively, and were based on estimated standard deviations of (log-transformed) clearance and volume as provided in a June 28, 2012 PK modeling technical report. The above mentioned values for % coefficient of variation (*%CV*) are derived using the approximation:

$$\%CV = \sqrt{e^{SD^2} - 1},$$

where *SD* are the standard deviations given in the technical report, with values of 0.2531 and 0.6398 for clearance and volume, respectively. The methodology for samples size calculation is as given in Wang, et al.[27]

Because of an anticipated dropout rate of 33%, a recruited sample size of 30 subjects is considered sufficient to ensure 20 evaluable subjects to assess the PK profiles of Oxycodone Oral Solution.

While the PK analysis will require a recruited sample size of 30 subjects, the trial will enroll 110 subjects to gather adequate safety information.

## 13. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

### 13.1 Sponsor and Investigator Responsibilities

#### 13.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a subject from the study (Section 8.2), to terminate participation of a study site at any time (Section 13.7), or to discontinue the study (Section 13.6.2).

The sponsor agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

#### 13.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.3), the investigator indicates that he or she has carefully read the protocol, fully understands the requirements, and agrees to

conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and his or her specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

### 13.2 **Site Initiation**

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate informed assent and consent.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

## 13.3 Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening visit. If a subject is eligible to enter the study after having previously failed screening, he or she will be assigned a new subject identification number.

## 13.4 Study Documents

All documentation and material provided by the sponsor for this study are to be retained in a secure location and treated as confidential material.

### 13.4.1 Good Clinical Practice Documents

The GCP documents are listed below.

- Signed original protocol; (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and sub-investigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form *Signature Log/Delegation of Study-related Duties*
- FDA Form 1572
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by the sponsor or designee before the study site can initiate the study and before the sponsor will authorize shipment of study drug to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the study drug, CRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and study drug accountability records should also be retained as part of the investigator's GCP documents. It is the investigator's responsibility to ensure that copies of all required GCP documents are organized, current, and available for inspection.

### 13.4.2 Case Report Forms

By signing the Investigator's Agreement (Section 17.3), the investigator agrees to maintain accurate CRFs and source documentation as part of the case histories for all subjects whose legally responsible parent(s) or legal guardian(s) sign an informed consent form and subjects who sign assent (as appropriate).

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific CRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, CRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system, if applicable, according to the completion guidelines provided by the sponsor or its designee.

The CRFs may be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the CRF is accurate and true.

### 13.4.3 Source Documents

All information recorded in the EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select CRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files. Before the study starts, a list identifying any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

## 13.5 Data Quality Control

The sponsor and its designees will perform quality control checks on this clinical study.

### 13.5.1 Monitoring Procedures

The sponsor or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized sponsor personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review:

- Regulatory documents, directly comparing entries in the EDC system with the source documents
- Consenting procedures
- AE procedures
- Storage and accountability of study drug and study materials

The CRA will ask for clarification or correction of any noted inconsistencies. Procedures for correcting CRFs are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.3), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

### 13.5.2 Data Management

The sponsor or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the sponsor's or CRO's standard operating procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

### 13.5.3 Quality Assurance/Audit

This study will be subject to audit by the sponsor or designee. The audits will be undertaken to check compliance with GCP guidelines and will include a minimum of:

- In-house study file audit
- Audit of computer database quality control
- Audit of clinical report quality control

The sponsor or designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify the sponsor immediately.

## 13.6 Study Termination

The study may be terminated at the sponsor's discretion at any time and for any reason.

### 13.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, the sponsor or designee will notify the IRB and regulatory authorities about the regular termination of the study as required.

### 13.6.2 Premature Study Termination

The study may be terminated prematurely for any reason and at any time by the sponsor, IRB, regulatory authorities, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, the sponsor or designee will notify the IRB and regulatory authorities as required. The sponsor or designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all investigators must inform their subjects and take care of appropriate follow-up and further treatment of subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination visit.

## 13.7 Study Site Closure

At the end of the study, all study sites will be closed. The sponsor may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol, applicable regulations and guidelines, or both
- Inadequate subject enrollment

### 13.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until at least 2 years after the notification of submission of the final study report to regulatory authorities by the sponsor.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After completing the study, the sponsor will be provided with the original CRFs or at least a legible copy and retain the documents at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files, and other source data until at least 5 years after notification of submission of the final study report to the regulatory authorities by the sponsor. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

### 13.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

## 13.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval by the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency.

## 13.9 Use of Information and Publication

All information about the study drug, the sponsor's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by the sponsor in connection with the continued development of the study drug and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of the sponsor. Publication or other public presentation of study drug data resulting from this study requires prior review and written approval of the sponsor. Abstracts, manuscripts, and presentation

materials should be provided to the sponsor for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until the sponsor has reviewed, commented on, and authorized such a presentation or manuscript for publication.

## 14. FINAL CLINICAL STUDY REPORT

The sponsor will retain ownership of the data from this study.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR will be submitted to the regulatory authorities.

## 15. ETHICAL AND LEGAL CONSIDERATIONS

### 15.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents) and the 1996 Version of the Declaration of Helsinki.

### 15.2 Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed assent and consent documents, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, before any activity or procedure is undertaken that is not part of routine care.

### 15.3 Approval by Institutional Review Board

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the sponsor monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor IRB Approval Form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by the sponsor before implementation.

This written approval will consist of a completed IRB Approval form or written documentation from the IRB containing the same information.

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# 17. ATTACHMENTS

## 17.1 Schedule of Events

### Table 2: Schedule of Events

| STUDY PROCEDURES | Screening (Day −14 to −1) | OUTPATIENT HOSPITALIZATION | | End of Study/Early Discontinuation[c] |
|---|---|---|---|---|
| | | Predose Check-in (Day −1) [a,b] | Treatment (Day 1, Time Zero)[b] | |
| Informed consent/assent | X | | | |
| Eligibility (inclusion/exclusion) | X | X | | |
| Prior medication assessment | X | X | | |
| Medical history | X | X | | |
| Vital signs | X | X | X | X |
| Temperature | X | | X | |
| Pulse Oximetry | | | X | |
| FLACC | | | X | |
| Physical examination[d] | X | | | |
| Clinical laboratory tests[e] | X | | | X |
| Serum pregnancy test (females) | X | X | | |
| Urine drug screen[f] | X | | | |
| Safety 12-lead electrocardiogram | X | | | |
| Study drug administration | | | X | |
| Pharmacokinetic sampling | | | X | |
| Adverse event assessment | | | Xg | X |
| Concomitant medication assessment | X | X | X | X |

[a] The predose check-in (Day −1) can be performed the same day as surgery (Day 1). At the predose check-in, eligibility and prior medications will be reviewed and updated as needed. Medical history will be recorded if it was not completed at Screening.

[b] Day −1 and Day 1 are adjacent and not separated by a Day 0.

[c] Subjects will undergo an End-of-Study/Early Discontinuation assessment at least 24 hours after dosing with Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study.

[d] The physical examination will include measurements of height, weight, and body mass index.

[e] Complete blood count with differential and clinical chemistry will be performed at Screening and End of Study/Early Discontinuation. Human immunodeficiency virus antibody screen, hepatitis B and hepatitis C screen, and urinalysis will be performed at Screening only.

[f] The urine drug screen will test for drugs of abuse (amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, and benzodiazepines) and alcohol (not required for subjects less than 2 years of age).

g During the study, subjects will be asked about adverse events. If an adverse event occurs, clinic staff may advise the subject to remain at the hospital until a decision is made that it is safe for the subject to be discharged.

## 17.2 **Treatment Day Procedures**

### Table 3: Treatment Day Procedures

| **Time, related to 1st dose of Oxycodone Oral Solution** | **Pre-dose** | **0 min** | **5 min** | **10 min** | **15 min** | **30 min** | **45 min** | **60 min** | **1 hr 15 min** | **1 hr 30 min** | **1 hr 45 min** | **2 hr** | **2 hr 15 min** | **2 hr 30 min** | **2 hr 45 min** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs (BP, HR, Resp.) | X | | | | X | X | X | X | X | X | X | X | X | X | X |
| Temperature | X | | | | | | | | | | | X | | | |
| Pulse oximetry[a] | X | | X | X | | X | | X | | | | X | | | |
| PK sampling (Under age 2) | X[b] | | | | X | X | | X | | | | X | | | |
| PK sampling (2 to <17) | X[b] | | X | | X | X | | X | | | | X | | | |
| Study drug administration[c] | | X | | | | | | | | | | | | | |
| FLACC[d] | X | | | | | | | | | | | | | | |
| AE evaluation[e] | | | | | | | | | | | | | | | |
| Con meds query[e] | | | | | | | | | | | | | | | |

| **Time, related to 1st dose of Oxycodone Oral Solution** | **3 hr** | **3 hr 15 min** | **3 hr 30 min** | **3 hr 45 min** | **4 hr** | **6 hr** | **8 hr** | **10 hr** | **12 hr** | **14 hr** | **16 hr** | **18 hr** | **20 hr** | **22 hr** | **24 hr** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs (BP, HR, Resp.)[a] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Temperature | | | | | X | X | X | X | X | X | X | X | X | X | X |
| Pulse oximetry[a] | | | | | X | X | X | | | | | | | | |
| PK sampling (Under age 2) | | | | | | X | | | X | | | | | | X |
| PK sampling (2 to <17) | | | | | X | X | X | | X | | | | | | X |
| Study drug administration[c] | | | | | | X | | | | | | | | | |
| FLACC[d] | | | | | X | | | | | | | | | | |
| AE evaluation[e] | | | | | | | | | | | | | | | |
| Con meds query[e] | | | | | | | | | | | | | | | |

a Pulse oximetry will begin as soon as possible following the procedure and will continue until 8 hours after the last study dose. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last dose of Oxycodone Oral Solution.
b Blood samples for pharmacokinetic assessment will be collected at the predose time point (within 15 minutes of dosing);
c The study drug will be administered after the surgery when subjects have been postoperatively cleared to transition to oral pain medication in place of the standard analgesic medication. If pain control is inadequate with study drug, the investigator may administer rescue medication for breakthrough pain after dosing.
d The FLACC will also be administered prior to the subject receiving each rescue dose of Fentanyl.
e AEs and Con Meds will be monitored throughout the course of the study.

## 17.3 **Investigator's Agreement**

| | |
|---|---|
| PROTOCOL NUMBER: | 2012O004 |
| PROTOCOL TITLE: | A PHASE IV STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS |
| FINAL PROTOCOL: | [25 Apr 2013] |

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with VistaPharm, Inc. and Lehigh Technologies, Inc., or designee during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an investigational product during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

## 17.4 **Faces, Legs, Activity, Cry, Consolability Scale (FLACC)**

| **Categories** | **Scoring** | | |
|---|---|---|---|
| | **0** | **1** | **2** |
| **Face** | No particular expression or smile | Occasional grimace or frown, withdrawn, disinterested | Frequent to constant quivering chin, clenched jaw |
| **Legs** | Normal position or relaxed | Uneasy, restless, tense | Kicking, or legs drawn up |
| **Activity** | Lying quietly, normal position, moves easily | Squirming, shifting back and forth, tense | Arched, rigid or jerking |
| **Cry** | No cry, (awake or asleep) | Moans or whimpers; occasional complaint | Crying steadily, screams or sob, frequent complaints |
| **Consolability** | Content, relaxed | Reassured by occasional touching, hugging or being talked to, distractible | Difficult to console or comfort |

## 18. APPENDICES

A. Address List
B. OXYCODONE HYDROCHLORIDE USP ORAL SOLUTION, Approved Label and Full Prescribing Information

## A. Address List

### 18.1.1 Sponsors

| | |
|---|---|
| Name: | VistaPharm, Inc. |
| Address: | 7256 Ulmerton Road<br>Largo, FL 33771 |
| Phone: | (727) 530-1633 |
| Fax: | (727) 531-5427 |
| Project Manager: | Melissa L. Goodhead, MSc, RAC<br>President<br>Pharmaceutical Project Solutions, Inc. |

| | |
|---|---|
| Name: | Lehigh Valley Technologies, Inc. |
| Address: | 514 North 12th Street<br>Allentown, PA 18102 |
| Phone: | (610) 782-9780 |

| | |
|---|---|
| Project Manager: | Melissa L. Goodhead, MSc, RAC<br>President<br>Pharmaceutical Project Solutions, Inc. |

### 18.1.2 Clinical Research Organization

| | |
|---|---|
| Name: | Cognitive Research Corporation |
| Address: | 200 Central Avenue, Suite 1230<br>Saint Petersburg, FL 33703 |
| Phone: | (727) 897-9000 |
| Fax: | (727) 897-9009 |
| Project Manager: | Eva M. Kemper, MSHS<br>Director, Clinical Projects |

# B. OXYCODONE HYDROCHLORIDE USP ORAL SOLUTION, Approved Label and Full Prescribing Information

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Oxycodone Hydrochloride Oral Solution safely and effectively. See full prescribing information for Oxycodone Hydrochloride Oral Solution.**
**Oxycodone Hydrochloride Oral Solution CII**
**Initial U.S. Approval: 1950**

**WARNING: RISK OF MEDICATION ERRORS**

**Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution 5 mg per 5 mL to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.**

**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.**

**INDICATIONS AND USAGE**

Oxycodone Hydrochloride Oral Solution is an opioid agonist indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. (1)

**DOSAGE AND ADMINISTRATION**

- Dosage should be individualized based on the severity of pain, and patient response. (2.1)
- Patients who have not been receiving opioid analgesics should be started in dosing range of 5 to 15 mg every 4 to 6 hours as needed. (2.2)
- When converting from a fixed ratio opioid/non-opioid regimen, the dose should be titrated in response to the level of analgesia and adverse effects and depending on continuation or non-continuation of the non-opioid component. (2.3)
- In patients with hepatic impairment or end-stage renal failure, dose initiation should follow a conservative approach. (2.7)

**DOSAGE FORMS AND STRENGTHS**

- Oral Solution containing 5 mg per 5 mL oxycodone hydrochloride, available in 500 mL bottle and 5 mL unit dose cup. (3)

**CONTRAINDICATIONS**

- Respiratory depression in the absence of resuscitative equipment. (4)
- Suspected or confirmed paralytic ileus. (4)
- Acute or severe bronchial asthma or hypercarbia. (4)
- Known hypersensitivity to oxycodone. (4)

**WARNINGS AND PRECAUTIONS**

- Use caution when prescribing, dispensing, and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between different concentrations and between mg and mL, which could result in accidental overdose and death. (5.1)
- Increased risk or respiratory depression in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnea, or upper airway obstruction. (5.2)
- Oxycodone hydrochloride is a Schedule II controlled substance with an abuse liability similar to other opioids. (5.3)
- Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. (5.3)
- Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.4)
- Increased risk of respiratory depression and of elevation of cerebrospinal fluid pressure in patients with head injury, intracranial lesions or pre-existing increase in intracranial pressure. (5.5)
- Risk of severe hypotension in patients with compromised ability to maintain blood pressure. (5.6)
- May obscure the diagnosis or clinical course in patients with acute abdominal conditions. (5.7)
- Use with caution in patients with biliary tract disease and acute pancreatitis. (5.8)
- The mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery may be impaired. (5.10)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.11)

**ADVERSE REACTIONS**

- The most common adverse reactions are nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. (6)

**To report SUSPECTED ADVERSE REACTIONS CONTACT FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

**DRUG INTERACTIONS**

- Skeletal muscle relaxants: Enhance action of and increased degree of respiratory depression (7.2)
- Drugs that inhibit CYP3A4 activity may decrease clearance of oxycodone and lead to an increase in oxycodone plasma concentrations. (7.4)

**USE IN SPECIFIC POPULATIONS**

- Safety and efficacy in pediatric patients below the age of 18 have not been established. (8.4)
- Geriatric patients, Renal Impairment, and Hepatic impairment: Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects. (8.5, 8.6, 8.7)

**See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide**

**Revised: 03/2012**

**FULL PRESCRIBING INFORMATION: CONTENTS ***



*** Sections or subsections omitted from the full prescribing information are not listed**

## FULL PRESCRIBING INFORMATION

### WARNING: RISK OF MEDICATION ERRORS

**Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution 5 mg per 5 mL to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.**
**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.**

### 1 INDICATIONS AND USAGE

Oxycodone Hydrochloride Oral Solution is an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate.

### 2 DOSAGE AND ADMINISTRATION

Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume. Always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately.
Selection of patients for treatment with oxycodone hydrochloride should be governed by the same principles that apply to the use of similar opioid analgesics. Individualize treatment in every case, using non-opioid analgesics, opioids on as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

#### 2.1 Individualization of Dosage

As with any opioid drug product, adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of oxycodone hydrochloride, give attention to the following:
• the total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;

- the reliability of the relative potency estimate used to calculate the equivalent oxycodone hydrochloride dose needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medications;
- the type and severity of the patient's pain;
- risk factors for abuse, addiction or diversion, including a prior history of abuse, addiction or diversion.

The following dosing recommendations, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.
Continual re-evaluation of the patient receiving oxycodone hydrochloride is important, with special attention to the maintenance of pain management and the relative incidence of side effects associated with therapy. During chronic therapy, especially for non-cancer-related pain, periodically re-assess the continued need for the use of opioid analgesics.
During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient, and the caregiver/family.

**2.2 Initiation of Therapy**
Start patients who have not been receiving opioid analgesics on Oxycodone Hydrochloride Oral Solution in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Titrate the dose based upon the individual patient's response to their initial dose of Oxycodone Hydrochloride Oral Solution. Adjust the dose to an acceptable level of analgesia taking into account the improvement in pain intensity and the tolerability of the oxycodone by the patient.

**2.3 Conversion to Oral Oxycodone Oral Solution**
There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dose of Oxycodone Hydrochloride. It is better to underestimate a patient's 24-hour oral Oxycodone Hydrochloride dose and make available rescue medication than to overestimate the 24-hour oral Oxycodone Hydrochloride dose and manage an adverse experience of overdose.
**2.3.1 Conversion from Fixed-Ratio Opioid/Acetaminophen, Opioid/Aspirin, or Opioid/Nonsteroidal Combination Drugs**

When converting patients from fixed ratio opioid/non-opioid drug regimens it may be necessary to titrate the dose of Oxycodone Hydrochloride Oral Solution in response to the level of analgesia and adverse effects.

**2.3.2 Conversion from Non-Oxycodone Opioids**

In converting patients from other opioids to oxycodone hydrochloride, close observation and adjustment of dosage based upon the patient's response to oxycodone hydrochloride is imperative. Physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate.

**2.4 Conversion from Oral Oxycodone Hydrochloride to Controlled-Release Oral Oxycodone**
The relative bioavailability of Oxycodone Hydrochloride Oral Solution compared to controlled-release oxycodone is unknown, so conversion to controlled-release tablets must be accompanied by close observation for signs of excessive sedation.

**2.5 Maintenance of Therapy**
Continual re-evaluation of the patient receiving Oxycodone Hydrochloride Oral Solution is important, with special attention to the maintenance of pain management and the relative incidence of side effects associated with therapy. If the level of pain increases, effort should be made to identify the source of increased pain, while adjusting the dose as described above to decrease the level of pain.
During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), the continued need for the use of opioid analgesics should be re-assessed as appropriate.

**2.6 Cessation of Therapy**
When a patient no longer requires therapy with Oxycodone Hydrochloride Oral Solution for the treatment of their pain, it is important that therapy be gradually discontinued over time to prevent the development of an opioid abstinence syndrome (narcotic withdrawal). In general, therapy can be decreased by 25% to 50% per day with careful monitoring for signs and symptoms of withdrawal [see *Drug Abuse and Dependence (9.3) section for description of the signs and symptoms of withdrawal*]. If the patient develops these signs or symptoms, the dose should be raised to the previous level and titrated down more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. It is not known at what dose of Oxycodone Hydrochloride Oral Solution that treatment may be discontinued without risk of the opioid abstinence syndrome.

**2.7 Dosage in patients with Hepatic or Renal Impairment**
Follow a conservative approach to dose initiation in patients with hepatic or renal impairment. Monitor patients closely and adjust dose based on clinical response.

**3 DOSAGE FORMS AND STRENGTHS**
Oxycodone Hydrochloride Oral Solution, 5 mg per 5 mL is available in a 500 mL bottle and 5 mL unit dose cup.

**4 CONTRAINDICATIONS**
Oxycodone Hydrochloride Oral Solution is contraindicated in
• patients with respiratory depression in the absence of resuscitative equipment.

• any patient who has or is suspected of having paralytic ileus.

• patients with acute or severe bronchial asthma or hypercarbia.

• patients with known hypersensitivity to oxycodone, oxycodone salts, or any component of this product

**5 WARNINGS AND PRECAUTIONS**

**5.1 Risk of Medication Errors**
Use caution when prescribing, dispensing, and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Use caution to ensure the dose is communicated clearly and dispensed accurately. Always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately.

**5.2 Respiratory Depression**
Respiratory depression is the primary risk of Oxycodone Hydrochloride Oral Solution. Respiratory depression occurs most frequently in elderly or debilitated patients, and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation, or following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.
Use Oxycodone Hydrochloride Oral Solution with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of Oxycodone Hydrochloride Oral Solution may increase airway resistance and decrease respiratory drive to the point of apnea. Consider alternative non-opioid analgesics, and use Oxycodone Hydrochloride Oral Solution only under careful medical supervision at the lowest effective dose in such patients.

**5.3 Misuse and Abuse of Opioids**
Oxycodone Hydrochloride Oral Solution is a Schedule II controlled substance with an abuse liability similar to other opioids. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.
Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids.
Oxycodone Hydrochloride Oral Solution can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Oxycodone Hydrochloride Oral Solution in situations where the physician or pharmacist is concerned about an increased risk of misuse or abuse.
Oxycodone Hydrochloride Oral Solution may be abused by injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence (9.2) and Overdosage (10)]*.
Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

**5.4 Interactions with Alcohol and Drugs of Abuse**
Oxycodone Hydrochloride Oral Solution may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, profound sedation, coma or death may result *[see Drug Interactions (7.1)]*.

**5.5 Use in Head Injury and Increased Intracranial Pressure**
In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of Oxycodone Hydrochloride Oral Solution and its potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following $CO_2$ retention) may be markedly exaggerated. Furthermore, Oxycodone Hydrochloride Oral Solution can produce effects on

pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients w head injuries.

**5.6 Hypotensive Effect**
Oxycodone Hydrochloride Oral Solution may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or general anesthetics or other agents which compromise vasomotor tone. Oxycodone Hydrochloride Oral Solution may produce orthostatic hypotension in ambulatory patients. Administer Oxycodone Hydrochloride Oral Solution with caution in hypovolemic patients, sucl as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Administer Oxycodone Hydrochloride Oral Solution with caution to patients in circulatory shock, since vasodilatation produced by the drug ma further reduce cardiac output and blood pressure.

**5.7 Gastrointestinal Effects**
Do not administer Oxycodone Hydrochloride Oral Solution to patients with gastrointestinal obstruction, especially paralytic ileus because oxycodone hydrochloride diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction.
The administration of Oxycodone Hydrochloride Oral Solution may obscure the diagnosis or clinical course in patients with acute abdominal condition.

**5.8 Use in Pancreatic/Biliary Tract Disease**
Use Oxycodone Hydrochloride Oral Solution with caution in patients with biliary tract disease, including acute pancreatitis, as oxycodone hydrochloride may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

**5.9 Special Risk Groups**
Use Oxycodone Hydrochloride Oral Solution with caution and in reduced dosages in patients with severe renal or hepatic impairmer Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients *[see Use in Specific Populations (8.5)]* .
Exercise caution in the administration of Oxycodone Hydrochloride Oral Solution to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.
Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

**5.10 Driving and Operating Machinery**
Caution patients that oxycodone hydrochloride could impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
Caution patients about the potential combined effects of Oxycodone Hydrochloride Oral Solution with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol *[see Drug Interactions (7.)]*.

**5.11 Cytochrome P450 3A4 Inhibitors and Inducers**
Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations. The expected clinical results with CYP3A4 inhibitors would be an increase in oxycodone plasma concentrations and possibly increased or prolonged opioid effec The expected clinical results with CYP3A4 inducers would be a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.
If co-administration is necessary, caution is advised when initiating Oxycodone Hydrochloride Oral Solution treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.4) and Clinical Pharmacology (12.3)]*.

**5.12 Seizures**
Oxycodone Hydrochloride Oral Solution may aggravate convulsions in patients with convulsive disorders, and all opioids may indu or aggravate seizures in some clinical settings.

**6 ADVERSE REACTIONS**
The following serious adverse reactions are described, or described in greater detail, in other sections:
- Respiratory depression [see *Warnings and Precautions (5.2)*]
- Seizures [see *Warnings and Precautions (5.12)*]
- Hypotension [see *Warnings and Precautions (5.6)*]

• Spasm of the sphincter of Oddi and increases in the serum amylase level [see *Warnings and Precautions (5.8)*]

Serious adverse reactions that may be associated with oxycodone therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock [see *Overdose (10.1) and Warnings and Precautions (5.1, 5.3)*].
The less severe adverse events seen on initiation of therapy with oxycodone are also typical opioid side effects. These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include nausea, constipation, vomiting, headache, and pruritus.
In many cases the frequency of adverse events during initiation of opioid therapy may be minimized by careful individualization of starting dosage, slow titration and the avoidance of large rapid swings in plasma concentration of the opioid. Many of these adverse events will abate as therapy is continued and some degree of tolerance is developed, but others may be expected to remain throughout therapy.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In all patients for whom dosing information was available (n=191) from the open-label and double-blind studies involving immediate-release oxycodone, the following adverse events were recorded in oxycodone treated patients with an incidence ≥ 3%. In descending order of frequency they were: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.
The following adverse experiences occurred in less than 3% of patients involved in clinical trials with oxycodone:
*Body as a Whole:* abdominal pain, accidental injury, allergic reaction, back pain, chills and fever, fever, flu syndrome, infection, neck pain, pain, photosensitivity reaction, and sepsis.
*Cardiovascular:* deep thrombophlebitis, heart failure, hemorrhage, hypotension, migraine, palpitation, and tachycardia.
*Digestive:* anorexia, diarrhea, dyspepsia, dysphagia, gingivitis, glossitis, and nausea and vomiting.
*Hemic and Lymphatic:* anemia and leukopenia.
*Metabolic and Nutritional:* edema, gout, hyperglycemia, iron deficiency anemia and peripheral edema.
*Musculoskeletal:* arthralgia, arthritis, bone pain, myalgia and pathological fracture.
*Nervous:* agitation, anxiety, confusion, dry mouth, hypertonia, hypesthesia, nervousness, neuralgia, personality disorder, tremor, and vasodilation.
*Respiratory:* bronchitis, cough increased, dyspnea, epistaxis, laryngismus, lung disorder, pharyngitis, rhinitis, and sinusitis.
*Skin and Appendages:* herpes simplex, rash, sweating, and urticaria.
*Special Senses:* amblyopia.
*Urogenital:* urinary tract infection

## 7 DRUG INTERACTIONS

### 7.1 CNS Depressants
Patients receiving narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Oxycodone Hydrochloride Oral Solution may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dosage of Oxycodone Hydrochloride Oral Solution. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

### 7.2 Neuromuscular Blocking Agents
Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

### 7.3 Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as Oxycodone Hydrochloride Oral Solution. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of Oxycodone Hydrochloride Oral Solution and/or may precipitate withdrawal symptoms in these patients.

### 7.4 Agents Affecting Cytochrome P450 Enzymes
CYP3A4 Inhibitors

A published study showed that the co-administration with voriconazole, a CYP3A4 inhibitor, significantly increased the plasma concentrations of oxycodone. Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, significantly decreased plasma oxycodone concentrations. Induction of CYP3A4 activity by its inducers, such as rifampin, carbamazepine, and phenytoin, may lead to a lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via the Cytochrome P450 Isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. However, clinicians should be aware of this possible interaction.

**7.5 Monoamine Oxidase Inhibitors (MAOIs)**
MAOIs have been reported to intensify the effects of at least one opioid drug, causing anxiety, confusion and significant depression of respiration or coma. The use of Oxycodone Hydrochloride Oral Solution is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

**7.6 Anticholinergics**
Anticholinergics or other medications with anticholinergic activity, when used concurrently with opioid analgesics including oxycodone hydrochloride, may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**
Pregnancy Category B: There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed.

Teratogenic Effects

Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that oxycodone administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a $mg/m^2$ basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a $mg/m^2$ basis), respectively was not teratogenic or embryo-fetal toxic.

Nonteratogenic Effects

Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

**8.2 Labor and Delivery**
Oxycodone Hydrochloride Oral Solution is not recommended for use in women during or immediately prior to labor. Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. Neonates, whose mothers received opioid analgesics during labor, should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

**8.3 Nursing Mothers**
Low levels of oxycodone have been detected in maternal milk. The amount of oxycodone hydrochloride delivered to the infant depends on the plasma concentration of the mother, the amount of milk ingested by the infant, and the extent of first-pass metabolism. Because of the potential for serious adverse reactions in nursing infants from oxycodone hydrochloride including respiratory depression, sedation and possibly withdrawal symptoms, upon cessation of oxycodone hydrochloride administration to the mother, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**8.4 Pediatric Use**
The safety and efficacy of Oxycodone Hydrochloride Oral Solution in pediatric patients below the age of 18 have not been established.

**8.5 Geriatric Use**
Elderly patients (aged 65 years or older) may have increased sensitivity to oxycodone hydrochloride. In general, use caution when selecting a dose for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

**8.6 Hepatic Impairment**
Since oxycodone is extensively metabolized, its clearance may decrease in hepatic failure patients. Follow a conservative approach to dose initiation in patients with hepatic impairment, monitor patients closely and adjust the dose based on clinical response.

**8.7 Renal Impairment**
Information from oxycodone tablets indicate that patients with renal impairment (defined as a creatinine clearance <60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function. Use a conservative approach to dose initiation in patients with renal impairment, monitor patients closely and adjust the dose based on clinical response.

**9 DRUG ABUSE AND DEPENDENCE**

**9.1 Controlled Substance**
**Oxycodone hydrochloride is a mu-agonist opioid of the morphine type and is a Schedule II controlled substance. Oxycodone Hydrochloride Oral Solution, like other opioids used in analgesia, can be abused and is subject to criminal diversion.**

**9.2 Abuse**
Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.
"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.
The risks of misuse and abuse should be considered when prescribing or dispensing Oxycodone Hydrochloride Oral Solution. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.
Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.
**Oxycodone Hydrochloride Oral Solution is intended for oral use only. Abuse of Oxycodone Hydrochloride Oral Solution poses a risk of overdose and death. The risk is increased with concurrent abuse of alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.**
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.
**Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms** *[see Use in Specific Populations (8.2)].*

**9.3 Dependence**
Tolerance to opioids is demonstrated by the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). If tolerance develops, or if pain severity increases, a gradual increase in dose may be required. The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are frequent during chronic opioid therapy.
Patients using Oxycodone Hydrochloride Oral Solution chronically (for several weeks) should be instructed that they should contact their health care providers if they notice the need to increase dosing to treat symptoms of pain or they experience symptoms of withdrawal upon abrupt cessation of dosing.
The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.
In general, taper opioids rather than abruptly discontinue *[see Dosage and Administration (2.6)].*

## 10 OVERDOSAGE

### 10.1 Signs and Symptoms

Acute overdose with Oxycodone Hydrochloride Oral Solution can be manifested by respiratory depression (a decrease in respiratory rate and/or end tidal volume. Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, pulmonary edema, cardiac arrest, and death. Oxycodone Hydrochloride Oral Solution may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12)]* .

### 10.2 Treatment

Give primary attention to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures including oxygen and vasopressors should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of oxycodone hydrochloride, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to opioid antagonists is suboptimal or only brief in nature, administer additional antagonist as directed by the manufacturer of the product.

Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Administer such agents cautiously to persons who are known, or suspected to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

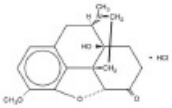
In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. Reserve use of an opioid antagonist for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, initiate administration of the antagonist with care and titrate with smaller than usual doses.

## 11 DESCRIPTION

Oxycodone Hydrochloride Oral Solution, USP, 5mg/5mL: Each 5 mL's is for oral administration and contains 5 mg of oxycodone hydrochloride USP.

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula:



$C_{18}H_{21}NO_4$•HCl MW 351.82

The 5 mg per 5 mL Oxycodone Hydrochloride Oral Solution contains equivalent of 4.5 mg of oxycodone free base per 5 mL's and contains the following inactive ingredients: Poloxamer 188 NF, Sodium Benzoate NF, Citric Acid Anhydrous USP, Glycerin Natural USP, Sorbitol Solution 70% USP, FD&C Red #40 , Raspberry Flavor and Water.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Oxycodone, as the hydrochloride salt, is a full opioid agonist whose principal therapeutic action is analgesia.

### 12.2 Pharmacodynamics

Effects on Central Nervous System

Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. A significant feature of opioid-induced analgesia is that it occurs without loss of consciousness. The relief of pain by morphine-like opioids is relatively selective, in that other sensory modalities, (e.g., touch, vibrations, vision, hearing, etc.) are not obtunded.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on Gastrointestinal Tract and Other Smooth Muscle

Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla. The frequency and severity of emesis gradually diminishes with time.

Oxycodone may cause a decrease in the secretion of hydrochloric acid in the stomach that reduces motility while increasing the tone of the antrum, stomach, and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone, in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown.

**12.3 Pharmacokinetics**

The activity of Oxycodone Hydrochloride Oral Solution is primarily due to the parent drug oxycodone.

Absorption

The oral bioavailability of oxycodone is 60 - 87%. This high oral bioavailability (compared to other oral opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone.

Food Effect

Presence of food may slightly delay the rate ($C_{max}$ and $T_{max}$) and enhance the extent of absorption (AUC) of oxycodone from Oxycodone Hydrochloride Oral Solution. Overall, food is not expected to have a clinically significant impact on the absorption of Oxycodone Hydrochloride Oral Solution.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.3)]*.

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, noroxymorphone, which are subsequently glucuronidated. CYP3A4 mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a less contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that

of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of Oxycodone Hydrochloride Oral Solution was approximately 3.5 hours.

Special Populations

*Geriatric*

Information obtained from oxycodone tablets indicate that the plasma concentrations of oxycodone did not appear to be increased in patients over of the age of 65.

*Gender*

Information obtained from oxycodone tablets support the lack of gender effect on the pharmacokinetics of oxycodone.

*Hepatic Impairment*

Since oxycodone is extensively metabolized, its clearance may be decreased in hepatic failure patients *[see Use in Special Populations (8.6)]*.

*Renal Impairment*

Information obtained from oxycodone tablets indicate that patients with renal impairment (defined as creatinine clearance < 60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function *[see Use in Special Populations (8.7)]*.

*Drug-Drug Interactions*

*CYP3A4 Inhibitors*

CYP3A4 is the major enzyme involved in noroxycodone formation. A published study showed that the co-administration of voriconazole, a CYP3A4 inhibitor, increased oxycodone AUC and $C_{max}$ by 3.6 and 1.7 fold, respectively.

*CYP3A4 Inducers*

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and $C_{max}$ values by 86% and 63%, respectively.

*CYP2D6 Inhibitors*

Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone hydrochloride was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay *(Salmonella typhimurium* and *Escherichia coli)* or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

Impairment of Fertility

The potential effects of oxycodone on male and female fertility have not been evaluated.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**
Oxycodone Hydrochloride Oral Solution, USP, 5 mg per 5 mL is available as follows:
NDC 66689-403-16: 500 mL bottle packaged with calibrated measuring cup
NDC 66689-401-01: 5 mL unit dose cup
NDC 66689-401-50: Case contains 50 unit dose cups of 5 mL (NDC 66689-401-01), packaged in 5 trays of 10 unit dose cups each

**16.2 Storage and Handling**
All opioids, including Oxycodone Hydrochloride Oral Solution, are liable to diversion and misuse both by the general public and healthcare workers and should be handled accordingly.
Dispense in a tight, light-resistant container as defined in the USP/NF.
Keep in secured area and protect from diversion.
Store at controlled room temperature 20°-25°C (68°- 77°F).

**17 PATIENT COUNSELING INFORMATION**
***See Medication Guide***
Provide the following information to patients receiving Oxycodone Hydrochloride Oral Solution or their caregivers:

- Advise patients that Oxycodone Hydrochloride Oral Solution is a narcotic pain medication, and should be taken only as directed.
- Advise patients that sharing oxycodone can result in fatal overdose and death.
- Advise patients that Oxycodone Hydrochloride Oral Solution is a potential drug of abuse. They must protect it from theft. It should never be given to anyone other than the individual for whom it was prescribed.
- Advise patients to keep Oxycodone Hydrochloride Oral Solution in a secure place out of the reach of children. When Oxycodone Hydrochloride Oral Solution is no longer needed, the unused solution should be destroyed by flushing down the toilet.
- Advise patients how to measure and take the correct dose of Oxycodone Hydrochloride Oral Solution, and to always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution, to ensure the dose is measured and administered accurately.
- Advise patients whenever the prescribed concentration is changed to avoid dosing errors which could result in accidental overdose and death.
- Advise patients not to adjust the dose of Oxycodone Hydrochloride Oral Solution without consulting with a physician or other healthcare professional.
- Advise patients that Oxycodone Hydrochloride Oral Solution may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Advise patients started on Oxycodone Hydrochloride Oral Solution or patients whose dose has been adjusted to refrain from any potentially dangerous activity until it is established that they are not adversely affected.
- Advise patients that Oxycodone Hydrochloride Oral Solution will add to the effect of alcohol and other CNS depressants (such as antihistamines, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and monoamine oxidase [MAO] inhibitors).
- Advise patients not to combine Oxycodone Hydrochloride Oral Solution with central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, and not to combine with alcohol because dangerous additive effects may occur, resulting in serious injury or death.
- Advise women of childbearing potential who become or are planning to become pregnant to consult a physician prior to initiating or continuing therapy with Oxycodone Hydrochloride Oral Solution.

- Advise patients that safe use in pregnancy has not been established and that prolonged use of opioid analgesics including Oxycodone Hydrochloride Oral Solution during pregnancy may cause fetal-neonatal physical dependence, and neonatal withdrawal may occur.
- If patients have been receiving treatment with Oxycodone Hydrochloride Oral Solution for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Advise patients taking Oxycodone Hydrochloride Oral Solution of the potential for severe constipation; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of opioid therapy.
- Advise patients of the most common adverse events that may occur while taking Oxycodone Hydrochloride Oral Solution: constipation, nausea, somnolence, lightheadedness, dizziness, sedation, vomiting, and sweating.
- Advise patients to call 911 or the local Poison Control center, and get emergency help immediately if they take more Oxycodone Hydrochloride Oral Solution than prescribed, or overdose.
- Advise patients, that if they miss a dose, to take the missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to their regular dosing schedule. Do not take two doses at once unless instructed by their healthcare provider.

**DEA Order Form Required**
Manufactured by:
*VistaPharm®*
Largo, FL 33771
VP 2013R1
01/12
To request medical information contact VistaPharm, Inc. at 1-727-530-1633.

**MEDICATION GUIDE**
**Oxycodone Hydrochloride**
**(ox-ee-CO-dohn) (CII)**
**Oral Solution**
Rx Only

**IMPORTANT: Keep Oxycodone Hydrochloride Oral Solution in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes Oxycodone Hydrochloride Oral Solution, get emergency help right away.**

Read the Medication Guide that comes with Oxycodone Hydrochloride Oral Solution before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Oral Solution?**
**Oxycodone Hydrochloride Oral Solution can cause serious side effects, including death.**
- **Take Oxycodone Hydrochloride Oral Solution exactly as prescribed by your healthcare provider.** If you take the wrong dose or strength of Oxycodone Hydrochloride Oral Solution, you could overdose and die.
- **It is especially important when you take Oxycodone Hydrochloride Oral Solution that you know exactly what dose and strength to take, and the right way to measure your medicine.** Your healthcare provider or pharmacist should show you the right way to measure your medicine. Always use the dosing cup provided with Oxycodone Hydrochloride Oral Solution to help make sure you measure the right amount.
- **Do not drink alcohol.** Using alcohol with Oxycodone Hydrochloride Oral Solution may increase your risk of dangerous side effects, including death.

**What is Oxycodone Hydrochloride Oral Solution?**
Oxycodone Hydrochloride Oral Solution is in a group of drugs called narcotic pain medicine. Oxycodone Hydrochloride Oral Solution is only for adults who have moderate to severe pain.
- A prescription medicine that is used to manage moderate to severe pain that is expected to last a short period of time (acute), and pain that continues around-the-clock and is expected to last for a long period of time (chronic).

- Oxycodone Hydrochloride Oral Solution is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.
- Prevent theft, misuse or abuse. Keep Oxycodone Hydrochloride Oral Solution in a safe place to keep it from being stolen. Oxycodone Hydrochloride Oral Solution can be a target for people who misuse or abuse prescription medicines or street drugs.
- Never give Oxycodone Hydrochloride Oral Solution to anyone else, even if they have the same symptoms you have. It may harm them or even cause death.
- Selling or giving away this medicine is against the law.
- It is not known if Oxycodone Hydrochloride Oral Solution is safe and effective in children under age 18 years of age.

**Who Should Not Take Oxycodone Oral Solution?**
**Do not take Oxycodone if you:**
- are having breathing problems and there is no emergency medical equipment nearby
- have a bowel blockage called paralytic ileus
- are having an asthma attack or have severe asthma, trouble breathing, or lung problems
- are allergic to oxycodone or any of the ingredients in Oxycodone Hydrochloride Oral Solution. See the end of this Medication Guide for a complete list of ingredients in Oxycodone Hydrochloride Oral Solution

**What should I tell my healthcare provider before taking Oxycodone Hydrochloride Oral Solution?**
**Before taking Oxycodone Hydrochloride Oral Solution, tell your healthcare provider if you:**
- have trouble breathing or lung problems
- have had a head injury
- have liver or kidney problems
- have adrenal gland problems, such as Addison's disease
- have severe scoliosis that affects your breathing
- have thyroid problems
- have problems urinating or enlargement of your prostate
- have or had convulsions or seizures
- have a past or present drinking problem or alcoholism
- have hallucinations (seeing or hearing things that are not really there) or other severe mental problems
- have constipation or other bowel problems
- have problems with your pancreas or gallbladder
- have past or present substance abuse or drug addiction
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if Oxycodone Hydrochloride Oral Solution will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  If you take Oxycodone Hydrochloride Oral Solution regularly before your baby is born, your newborn baby may have signs of withdrawal because their body has become used to the medicine. Signs of withdrawal in a newborn baby can include:

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| • irritability | • vomiting |
| • being very active | • diarrhea or more stools than normal |
| • problems sleeping | • weight loss |
| • high pitched cry | • shaking (tremors) |

If you are taking Oxycodone Hydrochloride Oral Solution right before your baby is born, your baby could have breathing problems.

- are breast-feeding or plan to breastfeed. Some Oxycodone Hydrochloride Oral Solution passes into your breast milk. A nursing baby could become very sleepy or have difficulty breathing or feeding well. If you stop breastfeeding, your baby may have withdrawal symptoms. See the list of withdrawal symptoms above. You and your healthcare provider should decide if you will take Oxycodone Hydrochloride Oral Solution or breastfeed.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes the doses of medicines that you take with Oxycodone Hydrochloride Oral Solution may need to be changed if used together. Be especially careful about taking other medicines that make you sleepy such as:

- sleeping pills
- other pain medicines
- anti-nausea medicines
- tranquilizers
- muscle relaxants
- anti-anxiety medicines
- antihistamines
- anti-depressants
- monoamine oxidase inhibitors (MAOIs): Do not take Oxycodone Hydrochloride Oral Solution if you already take an MAOI or within 14 days after you stop taking an MAOI medicine

Ask your healthcare provider if you are not sure if your medicine is one listed above.
Do not take other medicines while using Oxycodone Hydrochloride Oral Solution until you have talked with your healthcare provider or pharmacist. They will tell you if it is safe to take other medicines with Oxycodone Hydrochloride Oral Solution.
**Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.**

**How Should I Take Oxycodone?**

- See **"What is the most important information I should know about Oxycodone Hydrochloride Oral Solution?"**
- **Take Oxycodone Hydrochloride Oral Solution exactly as prescribed**. Do not change your dose unless your healthcare provider tells you to. Your healthcare provider may change your dose after seeing how the medicine affects you. Call your healthcare provider if your pain is not well controlled with your prescribed dose of Oxycodone Hydrochloride Oral Solution.
- **Make sure you understand exactly how to measure your dose**. Always use the dosing cup provided with our Oxycodone Hydrochloride Oral Solution to help make sure you measure the right amount. See the Patient Instructions for Use at the end of this Medication Guide for information about how to measure your dose the right way. Ask your healthcare provider or pharmacist if you are not sure what dose of Oxycodone Hydrochloride Oral Solution you should take or if you are not sure how to use the dosing cup.
- **Do not stop taking Oxycodone Hydrochloride Oral Solution suddenly**. If you have been taking Oxycodone Hydrochloride Oral Solution for more than a few weeks, stopping it suddenly can make you sick with withdrawal symptoms (for example, nausea, vomiting, diarrhea, anxiety, and shivering). If your healthcare provider decides you no longer need Oxycodone Hydrochloride Oral Solution, ask how to slowly reduce this medicine. Do not stop taking Oxycodone Hydrochloride Oral Solution without talking to your healthcare provider.
- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at one time unless your healthcare provider tells you to.
- If you take too much Oxycodone Hydrochloride Oral Solution call your healthcare provider or your local Poison Control Center right away or go to the nearest hospital emergency room right away.
- Talk with your healthcare provider regularly about your pain to see if you still need to take Oxycodone Hydrochloride Oral Solution.

**What Should I Avoid While Taking Oxycodone?**

- **You should not drink alcohol while using Oxycodone Hydrochloride Oral Solution. Drinking alcohol with Oxycodone Hydrochloride Oral Solution may increase your risk of having dangerous side effects or death.**

- **Do not drive, operate heavy machinery, or do other dangerous activities,** especially when you start taking Oxycodone Hydrochloride Oral Solution and when your dose is changed, until you know how Oxycodone Hydrochloride Oral Solution affects you. Oxycodone can make you sleepy. Ask your healthcare provider to tell you when it is okay to do these activities.

**What are the Possible Side Effects of Oxycodone?**

**Oxycodone Hydrochloride Oral Solution can cause serious side effects, including:**

- See **"What is the most important information I should know about Oxycodone Hydrochloride Oral Solution?"**

- **Oxycodone can cause serious breathing problems that can become life-threatening, especially if Oxycodone Hydrochloride Oral Solution is used the wrong way.** Call your healthcare provider or get help right away if:
- your breathing slows down
- you have shallow breathing (little chest movement with breathing)
- you feel faint, dizzy, confused, or
- you have any other unusual symptoms

  These can be symptoms that you have taken too much Oxycodone Hydrochloride Oral Solution (overdose) or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- **Oxycodone Hydrochloride Oral Solution can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down. Low blood pressure is also more likely to happen if you take other medicines that can also lower your blood pressure. Severe low blood pressure can happen if you lose blood or take certain other medicines.

- **Oxycodone can cause physical dependence.** Do not stop taking Oxycodone or any other opioid without talking to your healthcare provider about how to slowly stop your medicine. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction. Tell your healthcare provider if you have any of these symptoms of withdrawal while slowly stopping Oxycodone:

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| • feel restless | • trouble sleeping |
| • tearing eyes | • runny nose |
| • sweating | • yawning |
| • chills or hair on your arms "stand up" | • nausea, loss of appetite, vomiting |
| • muscle aches, backache | • diarrhea, stomach area (abdominal) cramps |
| • dilated pupils of your eyes | • increase in your blood pressure |
| • feel irritable or anxious | • breathing faster, or your heart beats faster |

- **There is a chance of abuse or addiction with Oxycodone Hydrochloride Oral Solution.** The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

- **Seizures: Oxycodone Hydrochloride Oral Solution may cause seizures or make seizures that you already have worse.**

**Call your healthcare provider if you have any of the symptoms listed above.**

**Common side effects of Oxycodone Hydrochloride Oral Solution include:**

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| • nausea | • dizziness |
| • constipation | • weakness |
| • vomiting | • drowsiness |
| • headache | • sweating |
| • itching | • lightheadedness |
| • trouble sleeping | |

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including Oxycodone Hydrochloride Oral Solution. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking Oxycodone Hydrochloride Oral Solution.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of Oxycodone Hydrochloride Oral Solution. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Oxycodone Hydrochloride Oral Solution?**

- Store Oxycodone Hydrochloride Oral Solution at controlled room temperature between 68°F - 77°F (20°C - 25°C).
- Protect Oxycodone Hydrochloride Oral Solution from moisture and light.
- When Oxycodone Hydrochloride Oral Solution is no longer needed, the unused solution should be destroyed by flushing down the toilet.

**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. Accidental overdose by a child is a medical emergency and can lead to death.**

**General information about Oxycodone Hydrochloride Oral Solution**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Oxycodone Hydrochloride Oral Solution for a condition for which it was not prescribed.
**Do not give your Oxycodone Hydrochloride Oral Solution to other people, even if they have the same symptoms you have. Selling or giving away Oxycodone Hydrochloride Oral Solution may harm others, may cause death, and is against the law.**
This Medication Guide summarizes the most important information about Oxycodone Hydrochloride Oral Solution. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Oxycodone Hydrochloride Oral Solution that is written for healthcare professionals.
For more information about Oxycodone Hydrochloride Oral Solution, contact VistaPharm, Inc. at (727) 530-1633.

**What are the ingredients in Oxycodone Hydrochloride Oral Solution?**

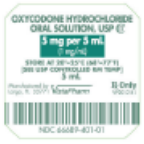
**Active ingredient: oxycodone hydrochloride**
**Inactive ingredients:** anhydrous citric acid, FD&C red #40, glycerin, poloxamer 188, purified water, raspberry flavor, sodium benzoate and sorbitol solution.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

**Manufactured by:**

*VistaPharm®*
Largo, FL 33771
VP2100
01/12
**Rx Only**

**PRINCIPAL DISPLAY PANEL - 5 mL Cup Label**

**OXYCODONE HYDROCHLORIDE**
**ORAL SOLUTION, USP CII**
**5 mg per 5 mL**
(1 mg/mL)
**STORE AT 20°-25°C (68°-77°F)**
**[SEE USP CONTROLLED RM TEMP]**
**5 mL**
Manufactured by VistaPharm® Largo, FL 33771
**Rx Only**
VP2012 R1
NDC 66689-401-01




**PRINCIPAL DISPLAY PANEL - 500 mL Bottle Carton**

**NDC 66689-403-16**
**Oxycodone Hydrochloride**
**Oral Solution, USP CII**
**5 mg per 5 mL**
(1 mg/mL)
Each 5 mL Contains:
**Oxycodone Hydrochloride — 5 mg**
**USUAL DOSAGE:** See Package Insert for Complete Prescribing Information.
**PHARMACIST: Dispense the enclosed Medication Guide to each patient.**
**500 mL**
VistaPharm, Inc., Largo, FL 33771
**Rx**
**only**
**VP 2089**
*VistaPharm*®
66689-403-16


Revised: 03/2012

Distributed by: VistaPharm Inc.

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# A PHASE IV STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS

PROTOCOL DATE: Version 7.1, Final 25 April 2013
Amendment #1, 11 July 2013

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7256 Ulmerton Road
Largo, FL 33771
Phone: (727) 530-1633

Lehigh Valley Technologies, Inc.
514 North 12th Street
Allentown, PA 18102
Phone: (610) 782-9780

CONTRACT RESEARCH ORGANIZATION: Cognitive Research Corporation
200 Central Avenue, Suite 1230
St. Petersburg, FL 33701
Phone: (727) 897-9000
Fax: (727) 897-9009

# 1. PROCEDURES IN CASE OF EMERGENCY

## Table 1: Sponsor Contact Information

| Role in Study | Name | Address and Telephone Number |
|---|---|---|
| Clinical Study Leader | Thomas J. Hochadel, Pharm.D.<br>Chief Operating Officer | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 727-515-1334 |
| Clinical Operations Leader | Eva M. Kemper, MSHS<br>Director, Clinical Projects | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 813-690-2667 |
| Physician | Lawrence Blob, M.D. | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 410-262-1908 |
| 24-hour Emergency Contact | Thomas J. Hochadel, Pharm.D.<br>Chief Operating Officer<br><br><u>Secondary Contact:</u><br>Deborah Lees, R.N.<br>Assistant Project Manager | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 727-515-1334<br><br>Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 813-943-8249 |

## 2. SYNOPSIS

| | |
|---|---|
| PRODUCT NAME | OXYCODONE ORAL SOLUTION |
| PROTOCOL NUMBER | 2012O004 |
| DEVELOPMENT PHASE | PHASE IV |
| PROTOCOL TITLE | A PHASE IV STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS |
| INDICATION | Moderate to severe pain |
| PRINCIPAL INVESTIGATOR | This is a multicenter study. The lead Principal Investigator will be:<br>Senthilkumar Sadhasivam, M.D.<br>Cincinnati Children's Hospital Medical Center<br>3333Burnet Avenue, MLC2001<br>Cincinnati, OH 45229 |
| PLANNED STUDY SITES | Up to 10 sites in the US. |
| OBJECTIVE | The objective of this study is to characterize the pharmacokinetics and to evaluate the safety of single and multiple doses of Oxycodone Oral Solution in pediatric and adolescent subjects for postoperative pain. |
| STUDY DESIGN | This is a Phase IV study to characterize the pharmacokinetics and to evaluate the safety of Oxycodone Oral Solution administered to pediatric and adolescent subjects for postoperative pain. It is an open-label, multicenter study conducted at up to 10 sites. Subjects will be enrolled preoperatively up to 14 days before surgery with the expectation that they will require intravenous (IV) access after the surgery for at least 24 hours and postoperative analgesia with an opiate-level medication. After dosing with Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to 17, and a dose to be determined based on pharmacokinetic (PK) modeling from the interim analyses for subjects under age 2), subjects will be carefully monitored for safety. A total of 110 pediatric and adolescent male or female subjects will be enrolled, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years. Subjects within each age group will be evenly distributed by age and gender.<br>An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 6 months to <2 years will receive will be based on PK modeling from the interim analysis.<br>An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that |

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| | the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on PK modeling from the interim analysis.<br><br>The study will consist of a Screening period within 14 days of surgery; a predose check-in (Day −1); a treatment period after surgery (Day 1, Time Zero); and an End-of-Study assessment. The total duration of the study, excluding Screening, will be approximately 1 full day.<br><br>Eligible subjects who provide assent (7 to <17 years old) and whose parent(s) or legal guardian(s) provide consent as required will have study assessments performed at Screening. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone. At this time (during Day −1), they will have a predose check-in to have eligibility confirmed.<br><br>After subjects ages 2 to <17 have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.<br><br>After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via Nurse-Controlled Analgesia (NCA). The Fentanyl will be provided by the study site pharmacy.<br><br>Subjects will undergo an End-of-Study assessment at least 24 hours after receiving the first dose of Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study.<br><br>Safety will be assessed by monitoring AEs, clinical laboratory test results, vital sign measurements, temperature, pulse oximetry, and physical examination findings.<br><br>The Faces, Legs, Activity, Crying, Consolability Scale (FLACC) will be used to measure pain prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution in subjects under age 2. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl.<br><br>Serial blood samples for PK analysis will be collected for the determination of plasma concentrations of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) prior to the first dose (within 15 minutes of dosing); 5 (between 3-8 min), 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; |

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| | and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing. |
| PLANNED NUMBER OF SUBJECTS | A total of 110 subjects, including a minimum of 20 subjects under age 2, 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years, are planned for this study to ensure adequate evaluation of the safety and PK profiles of Oxycodone Oral Solution. |
| STUDY ENTRY CRITERIA | Inclusion criteria<br>A subject will be eligible for inclusion in the study if he or she meets the following criteria:<br>1. Is male or female <17 years of age at the time of dosing.<br>2. Subject 2 to <17 years of age, be in at least the 25% for weight according to the Center for Disease Control pediatric growth charts and weighs at least 28 lb at the time of dosing with study drug.<br>3. Is generally healthy as documented by medical history (except for the condition for which the procedure is being performed); physical examination (including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; electrocardiogram; clinical laboratory assessments; and general observations. Has a negative serum pregnancy test at Screening and predose check-in for females of childbearing potential.<br>4. Is an outpatient for a surgical procedure and is expected to remain hospitalized for at least 24 hours after dosing with study drug.<br>5. Is anticipated to have postsurgical pain requiring a parenteral analgesic regimen using a short-acting opioid analgesic and is anticipated to be switched to an oral opioid for at least 1 dose (according to institution standard of care).<br>6. Has an indwelling access catheter for blood sampling.<br>7. Agrees to comply with all protocol requirements. If not old enough, the legally responsible parent(s) or legal guardian(s) must agree to comply with all protocol requirements.<br>8. Has been informed of the nature of the study and informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, in accordance with institutional review board requirements.<br>Exclusion criteria<br>A subject will be excluded from the study if he or she meets the following criteria:<br>1. Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (except for the condition for which the procedure is being performed) as determined by the clinical investigator. |

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| | 2. Has any clinical laboratory test result outside the normal range.<br>3. Had a clinically significant illness, except for the condition for which the procedure is being performed, in the 28 days before dosing with study drug as determined by the clinical investigator.<br>4. Is a lactating or breastfeeding female.<br>5. Uses any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug. Use of all other prescription medications, except required pre-op medications and birth control, is prohibited within 3 days of dosing with study drug. Use of any over-the-counter medications (including herbal or dietary supplements and therapeutic doses of vitamins), except for required pre-op medications, is prohibited within 24 hours of dosing with study drug, with the exception of topical spermicide. Use of St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.<br>6. Consumes alcohol-, caffeine-, or xanthine-containing products within 8 hours before dosing and during periods when blood samples are collected.<br>7. Consumes grapefruit, grapefruit products, Seville oranges, or pomelo-containing products within 5 days of dosing. Fruit juices, with the exception of apple and grape, will be prohibited during the study.<br>8. Is a smoker or has used nicotine or nicotine-containing products within 30 days of dosing.<br>9. Has a history of alcohol or drug addiction or abuse within the last year.<br>10. Subject 2 to <17 years of age, has a positive urine test result for drugs of abuse (amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, and benzodiazepines) or alcohol at Screening (not required for subjects less than 2 years of age).<br>11. Donated blood within 28 days or plasma within 14 days of dosing or plans to donate them within 4 weeks after completing the study.<br>12. Has a history of relevant drug allergies, food allergies, or both (i.e., allergy to oxycodone, allergy to related drugs, or any significant food allergy that could interfere with the study).<br>13. Is intolerant to direct venipuncture.<br>14. Received an investigational drug within 28 days of dosing.<br>15. Has taken oxycodone or oxymorphone within the 48 hours before anticipated dosing with study drug.<br>16. Is not suitable for entry into the study in the opinion of the investigator. |
| INVESTIGATIONAL PRODUCT | Oxycodone Oral Solution provided by VistaPharm, Inc., supplied in 500-mL bottles. Oxycodone Oral Solution contains 4.5 mg of oxycodone free base per 5 mL (5 mg oxycodone HCl/5 ml) and the following inactive ingredients: poloxamer 188 NF, sodium benzoate NF, citric acid anhydrous |

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| | US Pharmacopeia (USP), glycerin natural USP, sorbitol solution 70% USP, FD&C Red #40 , raspberry flavor, and water. |
| TREATMENT REGIMEN | Each subject in the 2 to 6, 7 to 12 and 13 to <17 age groups will receive a dose of Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, and 0.07 mg/kg for ages 13 to 17) in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain medication. The first 10 subjects in each of these age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. Each subject under age 2 will receive a single dose of Oxycodone Oral Solution. The dose will be determined based on PK modeling from the interim analyses. Oxycodone Oral Solution will be administered with an oral medication syringe. |
| CRITERIA FOR EVALUATION | Pharmacokinetic endpoints:<br>• Area under the plasma concentration versus time curve from Time Zero to the last measurable concentration ($AUC_{0-t}$)<br>• Area under the plasma concentration versus time curve from Time Zero to infinity ($AUC_{0-inf}$)<br>• Ratio of $AUC_{0-t}$ to $AUC_{0-inf}$ ($AUC_{0-t}/AUC_{0-inf}$)<br>• Maximum measured plasma concentration ($C_{max}$)<br>• Time of the maximum measured plasma concentration ($T_{max}$)<br>• Apparent first-order terminal elimination rate constant ($K_{el}$)<br>• Apparent first-order terminal elimination half-life ($t_{1/2}$)<br>• Apparent clearance (CL/F)<br>• Volume of distribution (V/F)<br>Other PK parameters may be calculated if deemed necessary.<br>Safety endpoints:<br>Safety will be assessed by the monitoring and recording of AEs; clinical laboratory results (including hematology, serum chemistry, and urinalysis); vital sign measurements (systolic and diastolic blood pressures, heart rate, and respiratory rate); temperature; pulse oximetry; and physical examination findings.<br>Exploratory Study Endpoints:<br>Analgesic sparing will be the surrogate efficacy endpoint in children under age 2.The Total FLACC Score will be an exploratory endpoint in children under age 2. |
| STATISTICAL METHODS | <u>Analysis Populations</u><br>PK Population: the PK population will consist of all subjects who receive study drug and have at least 1 measureable plasma concentration.<br>Safety Population: the safety population will consist of all subjects who receive study drug.<br><u>Subject Characteristics and Disposition</u><br>For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). |

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| | Baseline demographic and background variables will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized.<br><br>Pharmacokinetic Analyses<br><br>Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be listed and summarized. Each subject's oxycodone plasma concentrations will be graphed by using both a normal scale y-axis and a logarithmic scale y-axis. Mean oxycodone plasma concentrations will also be graphed using scheduled elapsed sampling times for both the normal and logarithmic scale y-axis.<br><br>Pharmacokinetic parameters will be listed for each subject and summarized. Key PK parameters will be contrasted with adult values from the literature.<br><br>Other PK analyses may be performed as appropriate.<br><br>Safety Analyses<br><br>Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.<br><br>Actual values and changes from Baseline for clinical laboratory results, pulse oximetry, and vital sign measurements will be summarized at each time point using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or shift tables where appropriate. Physical examination findings will be presented in a listing. |
| SAMPLE SIZE DETERMINATION | The evaluable sample size for this study is powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for oxycodone with at least 80% power.<br><br>Because of an anticipated dropout rate of 33%, a recruited sample size of 30 subjects is considered sufficient to ensure 20 evaluable subjects to assess the PK profiles of Oxycodone Oral Solution.<br><br>While the PK analysis will require a recruited sample size of 30 subjects, the trial will enroll 110 subjects to gather adequate safety information in the pediatric/adolescent patient population. |
| STUDY AND TREATMENT DURATION | The sequence and maximum duration of the study periods will be as follows:<br><br>Screening is up to 14 days.<br><br>The total study duration for each subject is 1 full day, excluding Screening.<br><br>The maximum treatment duration for each subject is 1 full day. |

## 3. TABLE OF CONTENTS

## 3.1 List of Tables

## 4. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AUC | Area under the curve |
| $AUC_{0\text{-}inf}$ | Area under the concentration-time curve from Time Zero to infinity |
| $AUC_{0\text{-}t}$ | Area under the concentration-time curve from Time Zero to the last measurable concentration |
| $C_{max}$ | Observed maximum plasma concentration |
| CRA | Clinical research associate |
| CRF | Case report form |
| CRO | Contract Research Organization |
| CSR | Clinical study report |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |
| FLACC | Face, Legs, Activity, Cry, Consolability Scale |
| GCP | Good Clinical Practice |
| HCl | Hydrochloride |
| ICH | International Conference on Harmonisation |
| IRB | Institutional review board |
| ITT | Intention-to-Treat Population |
| IV | Intravenous |
| $K_{el}$ | Elimination rate constant |
| kg | Kilogram |
| L | Liter |
| lbs | Pounds |
| mg | Milligram |
| min | Minutes |
| mL | Milliliter |
| NCA | Nurse-Controlled Analgesia |
| PK | Pharmacokinetic |
| RPM | Revolutions per minute |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SOC | Standard of care |

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|---|---|
| $t_{1/2}$ | Apparent elimination half-life |
| TBV | Total blood volume |
| $T_{max}$ | Time of maximum concentration |
| USP | United States Pharmacopeia |

# 5. INTRODUCTION

## 5.1 Background and Rationale

### 5.1.1 Indication and Usage

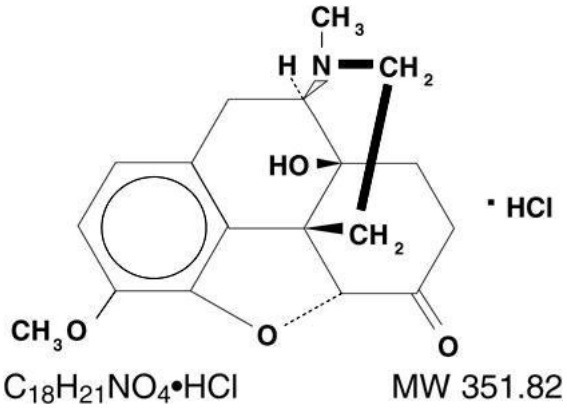
Oxycodone (4, 5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride) is a semisynthetic opioid that has been in clinical use since 1917 and approved for use in the US since 1950. Developed by VistaPharm, Inc., oxycodone hydrochloride (HCl) US Pharmacopeia (USP) oral solution, 5 mg per 5 mL, is an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate. This product was approved by the Food and Drug Administration (FDA) on January 12, 2012 (application New Drug Application 201194). In addition, Lehigh Valley Technologies, Inc. has developed Oxycodone Hydrochloride Oral Solution available as a 100 mg/5 mL (20 mg/mL) concentration which is indicated for use in opioid-tolerant patients only. This product was approved by the Food and Drug Administration (FDA) on October 20, 2010 (application New Drug Application 200535). The results of the study described with the current protocol will be utilized to meet regulatory requirements for both VistaPharm, Inc. and Lehigh Valley Technologies, Inc.

Oxycodone HCl is currently available in the US in a number of other forms and combinations. Oxycodone is a Schedule II controlled substance. The VistaPharm, Inc., oxycodone hydrochloride (HCl) (USP) oral solution, 5 mg per 5 mL, will be utilized for the purposes of this protocol.

### 5.1.2 Description

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride and has the following structural formula:




### 5.1.3 Pharmacodynamics

Oxycodone is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of oxycodone are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Additional detailed information on the pharmacodynamic properties of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

### 5.1.4 Pharmacokinetics

#### 5.1.4.1 Absorption

About 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison with a parenteral dose. This high oral bioavailability (compared to other oral opioids) is due to lower presystemic metabolism, first-pass metabolism, or both of oxycodone.

A single-dose food effect study was conducted in normal adult volunteers using the 5 mg/5 mL solution. The concurrent intake of a high fat meal was shown to enhance the extent (a 27% increase in the area under the plasma concentration versus time curve [AUC]) but not the rate of oxycodone absorption from the oral solution. In addition, food caused a delay in the time of maximum concentration ($T_{max}$) (1.25 to 2.54 hours).

#### 5.1.4.2 Distribution

Following intravenous (IV) administration, the volume of distribution for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk.

#### 5.1.4.3 Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone but not noroxycodone is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs.

#### 5.1.4.4 Elimination

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: up to 19% was reported for free oxycodone; up to 50% was reported for conjugated oxycodone; 0% was reported for free oxymorphone; no greater than 14% was reported for conjugated oxymorphone; and both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Additional detailed information on the physical, chemical, and pharmaceutical properties of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

### 5.1.5 Clinical Experience

Oxycodone hydrochloride USP oral solution has been studied in adult populations, with a focus on pharmacokinetics, safety, and tolerability. A total of 4 clinical pharmacokinetic (PK) and bioavailability studies have been conducted to support the development and labeling of oxycodone hydrochloride USP oral solution.

In addition, there are a number of published studies in the medical literature that report on the pharmacokinetics of oxycodone in clinical and nonclinical settings, in a variety of doses and routes of administration.[1-19]

### 5.1.6 Study Rationale

Despite published studies on dosing and pharmacokinetics in pediatric populations,[20-25] oxycodone has never received an official indication for use in children. Pursuant to the Pediatric Research Equity Act (21 USC 355c), the FDA has requested that VistaPharm, Inc. and Lehigh Valley Technologies, Inc. conduct a postapproval and postmarketing (Phase IV) PK and safety study in subjects < 17 years of age.

## 5.2 Summary of Potential Risks and Benefits

### 5.2.1 Potential Risks

The most frequently observed adverse events (AEs) reported with oxycodone include light headedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in subjects who can walk than in subjects who cannot walk, and some of

these adverse reactions may be alleviated if the subject lies down. Other AEs include euphoria, dysphoria, constipation, skin rash, and pruritus.

Additional detailed information on potential AEs and on specific warnings and precautions with the use of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

Given that some of the subjects will be infants and young children, the effect of multiple blood draws can be considered a potential risk or adverse situation. A published review of the safe limits of blood sample volumes in child health research suggests that existing guidelines specify limits ranging from 1% to 5% of total blood volume (TBV) over 24 hours. However, the limited available evidence that includes findings from nonrandomized studies shows a minimal risk with one-off sampling of up to 5% of TBV.[26]

For subjects 2 <17 years of age, this protocol specifies a maximum of 11 serial blood samples of 0.5 mL each for a total of 5.5 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. In addition, up to 10 mL will be allotted as discard volume for the 11 PK samples and the final laboratory testing drawn through the indwelling catheter. Existing blood draw guidelines for pediatric research suggest minimal risk is between 3% and 5% of total blood volume (TBV) over 24 hours or on a single draw and TBV is generally estimated at 75-80 mL/kg. For the smallest child permitted per protocol, 2 to <17 years of age (weight: 28 lbs or 12.7 kg), the TBV would be estimated at 952.5 ml. The maximum safe volume drawn would therefore be between 28 and 47 mL, based on minimal risk at 3-5% TBV over 24 hours. The required 10.5 mL plus up to 10 mL of discard volume, or a cumulative volume of 20.5 mL, is well under the 3-5% of TBV guideline for the smallest eligible participant using the smallest estimation of TBV. [26]

For the child less than 2 years of age, there is a maximum of 8 serial blood samples of 0.5 mL each for a total of 4.0 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. The required 9 mL is under the 3-5% of TBV guideline.

### 5.2.2 Benefits

The size of the test dose (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to 17, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2) is designed to provide adequate analgesia for moderate to severe pain in substituting for the routinely prescribed postoperative pain regimen according to the custom of the attending physician and the institutional standard of care (SOC).

No other benefit is anticipated or expected for subjects participating in this study.

## 6. OBJECTIVE

The objective of this study is to characterize the pharmacokinetics and to evaluate the safety of single and multiple doses of Oxycodone Oral Solution in pediatric and adolescent subjects.

## 7. STUDY DESIGN

### 7.1 Overall Study Design and Plan

This is a Phase IV study to characterize the pharmacokinetics and to evaluate the safety of Oxycodone Oral Solution administered to pediatric and adolescent subjects following a surgical procedure. It is an open-label, multicenter study conducted at up to 10 sites. Subjects will be enrolled preoperatively up to 14 days before surgery with the expectation that they will require IV access after the surgery for at least 24 hours and postoperative analgesia with an opiate-level medication. After dosing with Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to 17, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2), subjects will be carefully monitored for safety. A total of 110 pediatric and adolescent male or female subjects will be enrolled, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years. Subjects within each age group will be evenly distributed by age and gender.

An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects under age 2 will receive will be based on PK modeling from the interim analysis.

An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on PK modeling from the interim analysis.

The study will consist of a Screening period within 14 days of surgery; a predose check-in (Day −1); a treatment period after surgery (Day 1, Time Zero); and an End-of-Study assessment. The total duration of the study, excluding Screening, will be approximately 1 full day.

Eligible subjects who provide assent (7 to <17 years old) and whose parent(s) or legal guardian(s) provide consent as required will have study assessments performed at Screening. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone. At this time (during Day −1), they will have a predose check-in to have eligibility confirmed.

After subjects ages 2 to <17 years have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA. The Fentanyl will be provided by the study site pharmacy.

Water, Gatorade, Powerade, Pedialite, or Popsicles will be allowed for the first hour (1 hour) following dosing, but subjects must avoid fruit juice (excluding apple and grape), including fruit-containing popsicles, throughout the course of the study.

Subjects will undergo an End-of-Study assessment at least 24 hours after dosing with Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study. Subjects who discontinue the study for any reason will not be replaced.

Safety will be assessed, between time 0 and 24 hours post first study medication administration, by monitoring AEs, clinical laboratory test results, vital sign measurements, temperature, pulse oximetry, and physical examination findings.

The FLACC will be used to measure pain prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution in subjects under 2 years of age. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl.

For subjects 2 to <17 years of age, serial blood samples for PK analysis will be collected for the determination of plasma concentrations of oxycodone at the predose time point (within 15 minutes of dosing); 5 (between 3-8 min), 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing.

## 7.2 Discussion of Study Design

This is an open-label, nonrandomized, multicenter study designed to assess the pharmacokinetics and safety of the product oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, in pediatric and adolescent subjects <17 years of age following a surgical procedure and expected to require postoperative opioid analgesia and to require an indwelling IV catheter for a minimum of 24 hours after being cleared for oral intake. Target enrollment will be 110 subjects, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years, to evaluate safety in the population. Subjects within each age group will be evenly distributed by age and gender. In addition, this sample size will allow for an adequate evaluable population according to published population PK studies in children[21] and unofficial FDA guidance on sample size calculations based on estimates of clearance and volume of distribution.[27] Recruitment projections are based on a review of recent reports of adolescent scoliosis surgery showing that major specialty surgical centers average 10 to 20 patients per year in this age group.[28-32]

## 7.3 Study Sites

The study will take place at up to 10 sites in the US.

## 7.4 Point of Contact

A point of contact will be identified to provide subjects with information on the study, subject rights, and whom to contact in case of study-related injury. This information will be provided in the subject information and informed assent and consent forms.

# 8. SUBJECT POPULATION

## 8.1 Selection of Study Population

### 8.1.1 Inclusion Criteria

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1 Is male or female <17 years of age at the time of dosing.

2 Subject 2 to <17 years of age, be in at least the 25% for weight according to the Center for Disease Control pediatric growth charts and weighs at least 28 lb at the time of dosing with study drug.

3 Is generally healthy as documented by medical history (except for the condition for which the procedure is being performed); physical examination (including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; electrocardiogram (ECG); clinical laboratory assessments; and general observations. Has a negative serum pregnancy test at Screening and predose check-in for females of childbearing potential.

4 Is an outpatient for a surgical procedure and is expected to remain hospitalized for at least 24 hours after dosing with study drug.

5 Is anticipated to have postsurgical pain requiring a parenteral analgesic regimen by using a short-acting opioid analgesic and is anticipated to be switched to an oral opioid for at least 1 dose (according to institution standard of care).

6 Has an indwelling access catheter for blood sampling.

7 Agrees to comply with all protocol requirements. If not old enough, the legally responsible parent(s) or legal guardian(s) must agree to comply with all protocol requirements.

8 Has been informed of the nature of the study, and informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, in accordance with institutional review board requirements.

### 8.1.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets the following criteria:

1 Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (except for the condition for which the procedure is being performed) as determined by the clinical investigator.

2 Has any clinical laboratory test result outside the normal range.

3 Has a clinically significant illness, except for the condition for which the procedure is being performed, in the 28 days before dosing with study drug as determined by the clinical investigator.

4 Is a lactating or breastfeeding female.

5 Uses any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug. Use of all other prescription medications, except required pre-op medications and birth control, is prohibited within 3 days of dosing with study drug. Use of any over-the-counter medications (including herbal or dietary supplements and therapeutic doses of vitamins), except for required pre-op medications, is prohibited within 24 hours of dosing with study drug, with the exception of topical spermicide. Use of St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.

6 Consumes alcohol-, caffeine-, or xanthine-containing products within 8 hours before dosing and during periods when blood samples are collected.

7 Consumes grapefruit, grapefruit products, Seville oranges, or pomelo-containing products within 5 days of dosing. Fruit juices, with the exception of apple and grape, will be prohibited during the study.

8 Is a smoker or has used nicotine or nicotine-containing products within 30 days of dosing.

9 Has a history of alcohol or drug addiction or abuse within the last year.

10 Subject 2 to <17 years of age, has a positive urine test result for drugs of abuse (amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, and benzodiazepines) or alcohol at Screening (not required for subjects less than 2 years of age).

11 Donated blood within 28 days or plasma within 14 days of dosing or plans to donate them within 4 weeks after completing the study.

12 Has a history of relevant drug allergies, food allergies, or both (i.e., allergy to oxycodone, allergy to related drugs, or any significant food allergy that could interfere with the study).

13 Is intolerant to direct venipuncture.

14 Received an investigational drug within 28 days of dosing.

15 Has taken oxycodone or oxymorphone within the 48 hours before anticipated dosing with study drug.

16 Is not suitable for entry into the study in the opinion of the investigator.

## 8.2 Removal of Subjects from Therapy or Assessment

All subjects are free to withdraw from participation in this study at any time for any reason and without prejudice.

The investigator may terminate a subject from the study at any time for lack of therapeutic effect that is intolerable to the subject or otherwise considered unacceptable, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or unsuitability for the study in the investigator's opinion to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate case report form (CRF). Whenever possible and reasonable, evaluations that were scheduled for study completion should be performed at the time of premature discontinuation.

Subjects who discontinue from the study will not be replaced.

# 9. STUDY TREATMENTS

## 9.1 Method of Assigning Subjects to Treatment Groups

### 9.1.1 Under Age 2

Subjects under age 2 who meet all eligibility criteria will receive a single dose of Oxycodone Oral Solution. This will be an open-label study and does not require randomization.

### 9.1.2 Ages 2 to <17

Subjects ages 2 to <17 who meet all eligibility criteria will be scheduled to receive single or multiple doses of Oxycodone Oral Solution. This will be an open-label study and does not require randomization.

## 9.2 Identification of Investigational Products

The study drug is Oxycodone Oral Solution (5 mg/5 mL) manufactured by VistaPharm (Largo, FL). Oxycodone Oral Solution is a red solution intended for oral administration.

Oxycodone Oral Solution will be supplied in 500-mL bottles. Oxycodone Oral Solution contains 4.5 mg of oxycodone free base per 5 mL (5 mg oxycodone HCl/5 ml) and the following inactive ingredients: poloxamer 188 NF, sodium benzoate NF, citric acid anhydrous USP, glycerin natural USP, sorbitol solution 70% USP, FD&C Red #40, raspberry flavor, and water.

VistaPharm will provide an adequate supply of study drug to the sites.

Ketorolac for injection (15 mg/mL or 30 mg/mL), Morphine Sulfate for injection (2 mg/mL), and Fentanyl via NCA for use as a rescue medication will be provided by the study site pharmacy. Should other rescue medication be required they will be provided by the study site pharmacy.

## 9.3 Treatment Administered

The study drug will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s).

### 9.3.1 Under Age 2

Each subject will receive a single dose of Oxycodone Oral Solution in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain medication. The dose will be determined based on PK modeling from the interim analyses. Oxycodone Oral Solution will be administered with an oral medication syringe.

### 9.3.2 Ages 2 to <17

Each subject will receive a dose of Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, and 0.07 mg/kg for ages 13 to 17) in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain

medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. Oxycodone Oral Solution will be administered with an oral medication syringe.

## 9.4 Storage

Oxycodone Oral Solution will be stored in a locked facility with restricted access. This may be a locked cabinet or room for which the number of keys is limited and in compliance with standards of the Drug Enforcement Administration for Schedule II narcotics. Chain of custody of the study drug will be followed in accordance with the individual site's standard procedures, which will be documented by the site and provided to the sponsor. The study drug will be stored at controlled room temperature between 20°C and 25°C (68°F-77°F). The sponsor will provide to the site personnel instructions for the storage and return of used and unused study drug.

## 9.5 Labeling

Each container of study drug will be labeled with study-specific information that meets all applicable regulatory requirements.

## 9.6 Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of study drug, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received study drug. The investigator will not supply study drug to any person except those named as subinvestigators on the FDA 1572, designated staff, and subjects in this study. The investigator will not dispense study drug from any sites other than those listed on the FDA 1572. Study drug may not be relabeled or reassigned for use by other subjects.

Upon completion of the study, unused supplies of study drug will be reconciled by the investigator and returned to the sponsor as directed.

## 9.7 Blinding and Unblinding Treatment Assignment

Not applicable.

## 9.8 Selection of Dose in the Study

The published literature on treatment of pediatric pain with oxycodone reports doses ranging from 0.125 to 0.2 mg/kg, up to a maximum of 15 mg, for treatment of acute musculoskeletal pain, including suspected fractures in emergency room settings, for treatment of undifferentiated abdominal pain, and for pediatric burn wound care in outpatient clinics.[33-36] A PK modeling has been conducted using the data derived from the 4 studies conducted in the adult population. Based on these population data, the test dose chosen for subjects ages 2 to 6 is 0.1 mg/kg, ages 7 to 12 is 0.08 mg/kg, ages 13 to 17 is 0.07 mg/kg, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2, given when the subjects have been cleared for oral

intake and in place of the analgesic regimen (nonoxycodone and nonoxymorphone) prescribed postoperatively for subjects by their attending physicians according to institutional SOCs. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed.

The dose for subjects under age 2 will be determined based on PK modeling from the interim analyses.

## 9.9 Selection of Timing of Dose for Each Subject

The design of the study and the timing of dosing were selected to provide the appropriate basis for assessing the PK parameters of oxycodone following administration of the first dose.

## 9.10 Treatment Compliance

All study drugs will be administered in the hospital by study personnel and recorded in the CRF. Study personnel will confirm that the subject ingests the entire dose of study drug.

The date and time of study drug administration will be recorded on the appropriate page of the CRF. If a subject does not receive the study drug, the reason for the missed dose will be recorded.

## 9.11 Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate CRF. The medication name, dose, including frequency, date, and indication for use must be recorded. Time of rescue medication will also be recorded. The medical monitor should be notified in advance of (or as soon as possible after) any instances in which prohibited therapies or rescue medications are administered. Medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the study medication may be given at the discretion of the investigator.

### 9.11.1 Permitted Therapies

Concomitant medications (with the exceptions described in Section 9.11.2) are allowed, but should be limited to only those medications considered necessary.

Nausea and vomiting are common opioid-induced AEs for which subjects do develop a tolerance. Subjects who undergo surgery requiring opioid analgesia for an extended period of time may develop these AEs. Therefore, it is expected that some subjects will need to be given an antiemetic. Any antiemetic used during treatment with study drug should be recorded as a concomitant medication.

### 9.11.2 Prohibited Therapies

Use of any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug through the end of the study is prohibited. Use of all other prescription medications, with the exception of allowable pre-op medications and birth control, is prohibited within 3 days of dosing with study drug. Use of any monoamine oxidase inhibitor is prohibited until 14 days after the final dose of study drug.

Use of any over-the-counter medications (including herbal or dietary supplements and therapeutic doses of vitamins), except for allowable pre-op medications, is prohibited within 24 hours of dosing with study drug, with the exception of topical spermicide. Use of St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.

Restrictions:

Females of childbearing potential must be practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or double-barrier method). For the purpose of this study, all females who are menstruating will be considered to be of childbearing potential unless they are biologically sterile or surgically sterile for more than 1 year.

Consumption of alcohol-, caffeine-, or xanthine-containing products within 8 hours before dosing and during periods when blood samples are collected is prohibited. Consumption of grapefruit, grapefruit products, Seville oranges, or pomelo-containing products is prohibited within 5 days of dosing with study drug. All types of fruit juices, with the exception of apple and grape, and fruit-containing popsicles will be prohibited during the study.

Subjects who smoke or use nicotine or nicotine-containing products within 30 days of Screening will be excluded from study participation.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continuation in the study at the discretion of the sponsor, investigator, medical monitor, or other authority.

## 9.12 Rescue Medication

In subjects ages 2 to <17 years, if pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

In subjects under age 2, if pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA. The Fentanyl will be provided by the study site pharmacy.

## 10. STUDY PROCEDURES

Subjects' legally responsible parent(s) or legal guardian(s) will provide written informed consent and subjects will provide written informed assent (as appropriate) before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Table 2 (Section 17) presents the schedule of events to be performed during the study.

### 10.1 Screening (Day −14 to Day −1)

Subjects must be screened within 14 days before enrollment in the study. The following procedures will be performed at Screening:

- Obtain written informed consent and assent (as appropriate).
- Review inclusion and exclusion criteria.
- Collect demographic information.
- Record medical history, including prior and current therapies (e.g. prescription and nonprescription medications).
- Perform a physical examination including weight, height, body mass index, and vital signs (blood pressure, heart rate, respiratory rate, and oral temperature).
- Perform serum pregnancy test for all females of childbearing potential.
- Perform urine drug screen (Section 11.2.2), excluding subjects < 2 years of age.
- Perform ECG. This may occur at the screening visit or at any time prior to study medication dosing.
- Collect blood and urine samples for clinical laboratory tests (complete blood count with differential, clinical chemistry, serology, and urinalysis) (Section 11.2.2).

### 10.2 Predose Check-in (Day −1)

The predose check-in (Day −1) can be performed the same day as surgery (Day 1) at which time eligibility and prior medications will be reviewed and updated as needed. Medical history will be recorded, if it was not completed at Screening, and vital signs will be obtained. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone.

### 10.3 Open-Label Treatment (Day 1, After Surgery)

The following procedures will be performed on Day 1:

- Measure blood pressure, heart rate, and respiratory rate before dosing (within 90 minutes) with Oxycodone Oral Solution and every 15 minutes for 4 hours after

dosing, then every 2 hours until 24 hours after the first dose of Oxycodone Oral Solution.

- Measure temperature every 2 hours for 24 hours after the first dose of Oxycodone Oral Solution.
- Continuous pulse oximetry beginning as soon as possible following procedure through 8 hours after the last study dose of Oxycodone Oral Solution. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last study dose of Oxycodone Oral Solution.
- Assess pain in subjects under 2 years of age by using the FLACC prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the first dose of Oxycodone Oral Solution. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl**.**
- Record concomitant medication use.
- Assess and record AEs prior to dosing and throughout the remainder of Day 1.
- For subjects 2 to <17 years of age, collect serial blood samples for PK analysis at the predose time point (within 15 minutes of dosing); 5 (between 3-8 min), 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing.
- After subjects ages 2 to <17 have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care.
- After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with

Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA.

Water, Gatorade, Powerade, and Popsicles will be allowed for the first hour (1 hour) following dosing, but subjects must avoid fruit juice (excluding apple and grape), including fruit-containing popsicles, throughout the course of the study.

### 10.4 **End-of-Study/Early Discontinuation**

Subjects will undergo an End-of-Study/Early Discontinuation assessment at least 24 hours after dosing with Oxycodone Oral Solution.

The following procedures will be performed at the End-of-Study/ Early Discontinuation visit:

- Measure vital signs (blood pressure, heart rate, and respiratory rate).
- Clinical laboratory testing (complete blood count with differential and clinical chemistry).
- Record concomitant medications.
- Record AEs.

After these procedures are performed, the study staff will determine whether it is safe for the subject to be discharged from the study.

# 11. STUDY ASSESSMENTS

## 11.1 Pharmacokinetics

Blood samples for PK assessments in the subjects 2 to <17 years of age will be collected at the predose time point (within 15 minutes of the first dose of Oxycodone Oral Solution); 5 (between 3-8 min), 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 15 (between 10-20 min), 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing. Time Zero is the time of the first dose of Oxycodone Oral Solution.

The following PK parameters will be calculated:

- Area under the plasma concentration versus time curve from Time Zero to the last measurable concentration ($AUC_{0-t}$)
- Area under the plasma concentration versus time curve from Time Zero to infinity ($AUC_{0-inf}$)
- Ratio of $AUC_{0-t}$ to $AUC_{0-inf}$ ($AUC_{0-t}/AUC_{0-inf}$)
- Maximum measured plasma concentration ($C_{max}$)
- Time of the maximum measured plasma concentration ($T_{max}$)
- Apparent first-order terminal elimination rate constant ($K_{el}$)
- Apparent first-order terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Volume of Distribution (V/F)

Other PK parameters may be calculated if deemed necessary.

### 11.1.1 Sample Collection

Blood collection will be performed using an existing indwelling access catheter (arterial or venous noted on CRF) at the start of the study (the use of Emla at the insertion site is permitted). All catheter lines should be appropriately flushed per institutional SOC before each blood draw. The 0.5-mL blood samples will be obtained and placed into 2.0-mL K3 ethylenediamine tetra-acetic acid tubes at each blood collection time point. The labels for all biological sample collection and storage containers will contain, at a minimum, the subject's number, protocol number, collection date, and scheduled collection time (study hour).

| Study Visit/Phase | Amount Collected (mL) | Number of Samples Collected | Total Amount Collected per Subject (mL) |
|---|---|---|---|
| Screening Serum Chemistry and Hematology[a] | 2.5 mL | 1 | 2.5 mL |
| Pharmacokinetics (2 to <17 years old) or | 0.5 mL | 11 | 5.5 mL |
| Pharmacokinetics (<2 years old) | 0.5 mL | 8 | 4.0 mL |
| End of Study Serum Chemistry and Hematology | 2.5 mL | 1 | 2.5 mL |
| Grand Total | -- | -- | 14.0 – 20.5 mL[b] |

[a] Where possible, results from clinical laboratory tests performed as part of the standard of care (SOC) will be used for study purposes. A separate blood draw for the clinical laboratory test portion of this protocol will occur only if the clinical laboratory tests as part of the SOC will not be available to coincide with the approximate time scheduled by the protocol. Preoperative or intraoperative (collected before the incision) test results must be available for review by the investigator before enrolling any subject into the study. Procedures for blood draws should follow institutional SOC.

[b] The total includes up to 10-mL discard volume for all 11 pharmacokinetic and laboratory testing samples, for the 2 to <17 year olds. Total blood volume drawn for research purposes must not exceed 3% of subject's total blood volume, which is assumed to be 75 mL/kg.

### 11.1.2 Blood Volumes

Existing blood draw guidelines for pediatric research suggest minimal risk is between 3% and 5% of total blood volume (TBV) over 24 hours or on a single draw, and TBV is generally estimated at 75-80 mL/kg. For the smallest child permitted per protocol from ages 2 to <17 years (weight: 28 lbs or 12.7 kg), the TBV would be estimated at 952.5 ml. The maximum safe volume drawn would therefore be between 28 and 47 mL, based on minimal risk at 3-5% TBV over 24 hours. The required 10.5 mL plus up to 10 mL of discard volume, or a cumulative volume of 20.5 mL, is well under the 3-5% of TBV guideline for the smallest eligible participant using the smallest estimation of TBV.[26] For the child less than 2 years of age, there is a maximum of 8 serial blood samples of 0.5 mL each for a total of 4.0 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. The required 9 mL is under the 3-5% of TBV guideline.

### 11.1.3 Sample Processing

Immediately after collection, the tube will be gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction will be separated by placing the collection tube into a refrigerated centrifuge (4°C to 8°C) for 10 minutes at approximately 1500*g* or 3000 RPM. The plasma fraction will be withdrawn by pipette and placed into polypropylene freezing tubes in 2 approximately equal aliquots. All sample collection and freezing tubes will be clearly labeled in a manner that identifies the subject and the collection time. Labels will be fixed to the freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be placed into a freezer at approximately –20°C (± 10°C) or below until transfer or shipment to the bioanalytical laboratory. The time between sample collection and freezer storage should not exceed 90 minutes. The additional blood draws for the purposes of pharmacokinetic assessment in this study do not pose more than a minor risk to the subjects.

### 11.1.4 Transport of Samples

The clinic staff will inventory the samples that are to be shipped to the bioanalytical laboratory. Each shipment will contain a complete set of samples. The second set of samples will not be shipped until receipt of the first shipment is confirmed. The inventory record will accompany the frozen plasma samples as per standard operating procedures.

For sample shipment requiring a third party courier, the samples will be packed in ample dry ice within a styrofoam container to ensure the samples will remain frozen for at least 72 hours and will be shipped via express delivery to the bioanalytical facility. Written notification of sample shipment will be communicated to the bioanalytical facility and the sponsor. The samples will be tracked to assure arrival in a safe and timely manner.

The shipment will be accompanied by logs showing the name of the study drug, protocol number, and the subject numbers and samples included in the shipment. Documentation noting what the condition of the samples upon arrival at the bioanalytical laboratory is and whether the amount of dry ice remaining is adequate or inadequate should be returned to the clinic.

The samples will be shipped frozen to:
PPD - Houston
10550 Rockley Road, Suite 150
Houston, TX 77099, USA

### 11.1.5 Analytical Procedures

#### 11.1.5.1 Bioanalytical Sample Analyses

Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be measured using a validated liquid chromatography–mass spectrometry assay method. The validated detection range for oxycodone is 0.2 to 125 ng/mL in human plasma.

Samples from subjects who withdraw consent/assent or are dropped from the study will not be analyzed unless otherwise requested by the sponsor.

Samples from subjects who have been dropped from the study because of emesis according to PPD's standard operating procedures will not be analyzed.

#### 11.1.5.2 Bioanalytical Methodology

The bioanalytical method, assay validation, and bioanalytical report for this study will be provided by the bioanalytical investigator. Full validation of a sensitive assay for the appropriate analytes in biological fluid, including precision, accuracy, reproducibility, and selectivity will be included in the final report. The bioanalytical report will include the stability of the frozen samples, limit of quantitation, recovery, and a summary of the standard curves.

## 11.2 **Safety**

Safety will be assessed during the study by the monitoring and recording of AEs, clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate, and respiratory rate), temperature, pulse oximetry, and physical examination findings.

### 11.2.1 Adverse Events

#### 11.2.1.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a subject or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease temporally associated with the product, whether or not it is related to the product.

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a preexisting condition is considered an AE.

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the investigator brochure. For a marketed drug, the known information is in the current package insert.

An unexpected AE is one for which the specificity or severity is not consistent with the current investigator brochure or package insert. For example, hepatic necrosis would be unexpected (greater severity) if the investigator brochure or package insert only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the investigator brochure or package insert only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected AEs. Examples include acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and hepatitis with a first occurrence of fulminate hepatitis.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be used in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE does not qualify the condition or event as an SAE. A newly diagnosed pregnancy in a subject who has received a study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy; however, the medical monitor should be made aware of a newly diagnosed pregnancy as soon as possible after site notification. A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE.

#### 11.2.1.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 11.2.1.1) are recorded in the CRF and reported to the medical monitor (Section 11.2.1.3). Adverse events will be collected from the time of the first dose of Oxycodone Oral Solution through the End of Study or Early Discontinuation visit.

At each visit, subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications). In addition to subject observations, AEs will be documented from any data collected on the AE page of the CRF (e.g., clinical laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

#### 11.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the CRF. Information to be collected includes drug treatment, type of event, time of onset, dose, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The latest version of the Medical Dictionary of Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator or designee must report any AE that meets the criteria for an SAE (Section 11.2.1.1) to the medical monitor within 24 hours of first becoming aware of the event by telephone. At the time of first notification, the investigator or designee should provide at a minimum the following information if available:

- Protocol number
- Subject's study identification and initials
- Subject's date of birth
- Date of dose of study drug
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken

Within 24 hours of the initial telephone notification, the investigator must fax a written SAE report form to the medical monitor. Any missing or additional relevant information about the SAE should be provided in a written follow-up SAE report form. The investigator should also ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of the institutional review board (IRB).

The following contact information is to be used for SAE reporting:

Thomas J. Hochadel, Pharm.D.
Cognitive Research Corporation
200 Central Ave, Suite 1230
Saint Petersburg, FL 33701
Telephone: 727-897-9000
Cell: 727-515-1334
Fax: 727-897-9000

#### 11.2.1.3.1 Assessment of Severity

The severity or intensity of an AE refers to the extent to which it affects the subject's daily activities. Severity will be rated as mild, moderate, or severe using the following criteria:

| | |
|---|---|
| Mild: | Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. |
| Moderate: | Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. |
| Severe: | Interrupts usual activities of daily living, significantly affects |

clinical status, or may require intensive therapeutic intervention

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

#### 11.2.1.3.2 Assessment of Relationship

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

| | |
|---|---|
| Not related: | An AE with sufficient evidence to accept that there is no causal relationship to administration of study drug (e.g., no temporal relationship because the study drug was administered after the onset of the event, an investigation shows that study drug was not administered, another cause was proven.) |
| Unlikely related: | An AE, including a clinical laboratory test abnormality, with a temporal relationship to administration of study drug that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations. |
| Possibly related: | An AE with a reasonable time sequence to administration of study drug but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear. |
| Related: | An AE occurring in a plausible time relationship to administration of study drug and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable. |

#### 11.2.1.3.3 Definition of Adverse Event Start Date, Stop Date, and Duration

| | |
|---|---|
| Start date: | The date at which the AE is first noted |
| Stop date: | The date at which the AE is known to be resolved. If it has not known to have stopped, then indicate "ongoing." |
| Duration: | A time in days, hours, or minutes |

#### 11.2.1.3.4 Action(s) Taken

Action(s) taken may consist of the following (as appropriate):

| | |
|---|---|
| None: | No actions taken. |
| Discontinued study drug: | Study drug was permanently discontinued because of the AE. |
| Treatment: | Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure. |
| Others: | Other actions, such as an operative procedure, were required because of the AE. |

#### 11.2.1.3.5 Definition of Adverse Event Outcome at the Time of Last Observation

The AE outcome at the time of last observation will be classified as "resolved," "resolved with sequelae," "ongoing," "death," "other," or "unknown."

"Death" should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "death" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

### 11.2.1.4 Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after dosing with study drug) to a satisfactory resolution or until the investigator deems the event to be chronic or not clinically significant or the subject to be stable. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate CRF.

### 11.2.2 Laboratory Safety Assessments

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 17).

| | |
|---|---|
| Hematology: | Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count) |
| Serum chemistry: | Includes blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose (fasting), albumin, and total protein |
| Urinalysis: | Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive |
| Serum pregnancy test: | Conducted for women of childbearing potential only |
| Urine drug screen | Includes amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, ethyl alcohol, and benzodiazepines |

Each safety laboratory assessment blood sample will be 2.5 mL in volume. The total amount of blood to be drawn will be a maximum of 19.5 mL per subject, including 11 samples for PK assessments (0.5 mL each).

### 11.2.3 Vital Signs

Vital signs, including heart rate, respiratory rate, and blood pressure will be measured at the time points specified in the schedule of events (Section 17) after the subject has been in a sitting position for 5 minutes. Oral body temperature will also be measured.

### 11.2.4 Pulse Oximetry

Continuous pulse oximetry will begin as soon as possible following the procedure and will continue until 8 hours after the last study dose of Oxycodone Oral Solution. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last study dose of Oxycodone Oral Solution.

### 11.2.5 Electrocardiogram

An ECG will be performed pre-dose. This may occur at Screening or any time pre-dose, including intra-op.

### 11.2.6 Physical Examination

A standard physical examination will be performed at Screening. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart,

cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at the investigator's discretion if necessary to evaluate AEs or clinical laboratory abnormalities.

### 11.3 Faces, Legs, Activity, Crying, Consolability Scale (FLACC)

The Faces, Legs, Activity, Crying, Consolability Scale (FLACC) (See Attachment 17.4) will be used to measure pain in subjects under age 2 prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl.

The FLACC provides a simple framework for quantifying pain behaviors in children who are unable to verbalize the presence or severity of pain.[37]

Additionally, time of rescue medication will also be evaluated.

## 12. STATISTICAL METHODS

### 12.1 General Considerations

Descriptive statistics will be provided for all demographic, safety, and PK parameters. No formal statistical testing will be performed for this study.

A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written before database lock.

### 12.2 Analysis Populations

The following analysis populations are planned for this study:

- PK Population: the PK population will consist of all subjects who receive the study drug and have at least 1 measureable plasma concentration.
- Safety Population: the safety population will consist of all subjects who receive the study drug.

### 12.3 Statistical Analyses

#### 12.3.1 Subject Disposition and Demographic Characteristics

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized by using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

Baseline demographic and background variables will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized.

### 12.3.2 Pharmacokinetic Analyses

Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be listed and summarized. Each subject's oxycodone plasma concentrations will be graphed using both a normal scale y-axis and a logarithmic scale y-axis. Mean oxycodone plasma concentrations will also be graphed using scheduled elapsed sampling times for both the normal and logarithmic scale y-axis.

Pharmacokinetic parameters will be listed for each subject and summarized. Key PK parameters will be contrasted with adult values from the previously conducted PK studies.

Other PK analyses may be performed as appropriate.

### 12.3.3 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.

Actual values and changes from Baseline for clinical laboratory results, vital sign measurements, temperature, and pulse oximetry will be summarized at each time point using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or shift tables where appropriate. Physical examination findings will be presented in a listing.

### 12.3.4 Exploratory Analyses

The change from baseline in total FLACC Score will be summarized at each time point. The total amount of Fentanyl will also be evaluated.

### 12.3.5 Interim Analyses

An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 6 months to <2 years will receive will be based on this interim analysis.

An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on PK modeling from the interim analysis.

### 12.4 Sample Size Determination

The evaluable sample size for this study is powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for oxycodone with at least 80% power.

Estimates of the coefficient of variation for the clearance and volume of distribution of oxycodone were 25.72% and 71.12%, respectively, and were based on estimated standard deviations of (log-transformed) clearance and volume as provided in a June 28, 2012 PK modeling technical report. The above mentioned values for % coefficient of variation (*%CV*) are derived using the approximation:

$$\%CV = \sqrt{e^{SD^2} - 1},$$

where *SD* are the standard deviations given in the technical report, with values of 0.2531 and 0.6398 for clearance and volume, respectively. The methodology for samples size calculation is as given in Wang, et al.[27]

Because of an anticipated dropout rate of 33%, a recruited sample size of 30 subjects is considered sufficient to ensure 20 evaluable subjects to assess the PK profiles of Oxycodone Oral Solution.

While the PK analysis will require a recruited sample size of 30 subjects, the trial will enroll 110 subjects to gather adequate safety information.

## 13. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

### 13.1 Sponsor and Investigator Responsibilities

#### 13.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a subject from the study (Section 8.2), to terminate participation of a study site at any time (Section 13.7), or to discontinue the study (Section 13.6.2).

The sponsor agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

#### 13.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.3), the investigator indicates that he or she has carefully read the protocol, fully understands the requirements, and agrees to

conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and his or her specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

### 13.2 **Site Initiation**

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate informed assent and consent.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

## 13.3 Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening visit. If a subject is eligible to enter the study after having previously failed screening, he or she will be assigned a new subject identification number.

## 13.4 Study Documents

All documentation and material provided by the sponsor for this study are to be retained in a secure location and treated as confidential material.

### 13.4.1 Good Clinical Practice Documents

The GCP documents are listed below.

- Signed original protocol; (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and sub-investigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form *Signature Log/Delegation of Study-related Duties*
- FDA Form 1572
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by the sponsor or designee before the study site can initiate the study and before the sponsor will authorize shipment of study drug to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the study drug, CRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and study drug accountability records should also be retained as part of the investigator's GCP documents. It is the investigator's responsibility to ensure that copies of all required GCP documents are organized, current, and available for inspection.

### 13.4.2 Case Report Forms

By signing the Investigator's Agreement (Section 17.3), the investigator agrees to maintain accurate CRFs and source documentation as part of the case histories for all subjects whose legally responsible parent(s) or legal guardian(s) sign an informed consent form and subjects who sign assent (as appropriate).

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific CRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, CRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system, if applicable, according to the completion guidelines provided by the sponsor or its designee.

The CRFs may be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the CRF is accurate and true.

### 13.4.3 Source Documents

All information recorded in the EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select CRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files. Before the study starts, a list identifying any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

## 13.5 Data Quality Control

The sponsor and its designees will perform quality control checks on this clinical study.

### 13.5.1 Monitoring Procedures

The sponsor or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized sponsor personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review:

- Regulatory documents, directly comparing entries in the EDC system with the source documents
- Consenting procedures
- AE procedures
- Storage and accountability of study drug and study materials

The CRA will ask for clarification or correction of any noted inconsistencies. Procedures for correcting CRFs are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.3), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

### 13.5.2 Data Management

The sponsor or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the sponsor's or CRO's standard operating procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

### 13.5.3 Quality Assurance/Audit

This study will be subject to audit by the sponsor or designee. The audits will be undertaken to check compliance with GCP guidelines and will include a minimum of:

- In-house study file audit
- Audit of computer database quality control
- Audit of clinical report quality control

The sponsor or designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify the sponsor immediately.

## 13.6 Study Termination

The study may be terminated at the sponsor's discretion at any time and for any reason.

### 13.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, the sponsor or designee will notify the IRB and regulatory authorities about the regular termination of the study as required.

### 13.6.2 Premature Study Termination

The study may be terminated prematurely for any reason and at any time by the sponsor, IRB, regulatory authorities, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, the sponsor or designee will notify the IRB and regulatory authorities as required. The sponsor or designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all investigators must inform their subjects and take care of appropriate follow-up and further treatment of subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination visit.

## 13.7 Study Site Closure

At the end of the study, all study sites will be closed. The sponsor may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol, applicable regulations and guidelines, or both
- Inadequate subject enrollment

### 13.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until at least 2 years after the notification of submission of the final study report to regulatory authorities by the sponsor.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After completing the study, the sponsor will be provided with the original CRFs or at least a legible copy and retain the documents at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files, and other source data until at least 5 years after notification of submission of the final study report to the regulatory authorities by the sponsor. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

### 13.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

## 13.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval by the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency.

## 13.9 Use of Information and Publication

All information about the study drug, the sponsor's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by the sponsor in connection with the continued development of the study drug and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of the sponsor. Publication or other public presentation of study drug data resulting from this study requires prior review and written approval of the sponsor. Abstracts, manuscripts, and presentation

materials should be provided to the sponsor for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until the sponsor has reviewed, commented on, and authorized such a presentation or manuscript for publication.

## 14. FINAL CLINICAL STUDY REPORT

The sponsor will retain ownership of the data from this study.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR will be submitted to the regulatory authorities.

## 15. ETHICAL AND LEGAL CONSIDERATIONS

### 15.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents) and the 1996 Version of the Declaration of Helsinki.

### 15.2 Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed assent and consent documents, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, before any activity or procedure is undertaken that is not part of routine care.

### 15.3 Approval by Institutional Review Board

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the sponsor monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor IRB Approval Form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by the sponsor before implementation.

This written approval will consist of a completed IRB Approval form or written documentation from the IRB containing the same information.

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# 17. ATTACHMENTS

## 17.1 Schedule of Events

### Table 2: Schedule of Events

| STUDY PROCEDURES | Screening (Day −14 to −1) | OUTPATIENT HOSPITALIZATION | | End of Study/Early Discontinuation[c] |
|---|---|---|---|---|
| | | Predose Check-in (Day −1) [a,b] | Treatment (Day 1, Time Zero)[b] | |
| Informed consent/assent | X | | | |
| Eligibility (inclusion/exclusion) | X | X | | |
| Prior medication assessment | X | X | | |
| Medical history | X | X | | |
| Vital signs | X | X | X | X |
| Temperature | X | | X | |
| Pulse Oximetry | | | X | |
| FLACC | | | X | |
| Physical examination[d] | X | | | |
| Clinical laboratory tests[e] | X | | | X |
| Serum pregnancy test (females) | X | X | | |
| Urine drug screen[f] | X | | | |
| Safety electrocardiogram | X or | X | | |
| Study drug administration | | | X | |
| Pharmacokinetic sampling | | | X | |
| Adverse event assessment | | | Xg | X |
| Concomitant medication assessment | X | X | X | X |

[a] The predose check-in (Day −1) can be performed the same day as surgery (Day 1). At the predose check-in, eligibility and prior medications will be reviewed and updated as needed. Medical history will be recorded if it was not completed at Screening.

[b] Day −1 and Day 1 are adjacent and not separated by a Day 0.

[c] Subjects will undergo an End-of-Study/Early Discontinuation assessment at least 24 hours after dosing with Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study.

[d] The physical examination will include measurements of height, weight, and body mass index.

[e] Complete blood count with differential and clinical chemistry will be performed at Screening and End of Study/Early Discontinuation. Urinalysis will be performed at Screening only.

[f] The urine drug screen will test for drugs of abuse (amphetamines, barbiturates, cannabinoids, cocaine metabolites, opiates, phencyclidine, and benzodiazepines) and alcohol (not required for subjects less than 2 years of age).

g During the study, subjects will be asked about adverse events. If an adverse event occurs, clinic staff may advise the subject to remain at the hospital until a decision is made that it is safe for the subject to be discharged.

## 17.2 **Treatment Day Procedures**

### Table 3: Treatment Day Procedures

| **Time, related to 1st dose of Oxycodone Oral Solution** | **Pre-dose** | **0 min** | **5 min** | **10 min** | **15 min** | **30 min** | **45 min** | **60 min** | **1 hr 15 min** | **1 hr 30 min** | **1 hr 45 min** | **2 hr** | **2 hr 15 min** | **2 hr 30 min** | **2 hr 45 min** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs (BP, HR, Resp.) | X | | | | X | X | X | X | X | X | X | X | X | X | X |
| Temperature | X | | | | | | | | | | | X | | | |
| Pulse oximetry[a] | X | | X | X | | X | | X | | | | X | | | |
| PK sampling (Under age 2) | X[b] | | | | X | X | | X | | | | X | | | |
| PK sampling (2 to <17) | X[b] | | X | | X | X | | X | | | | X | | | |
| Study drug administration[c] | | X | | | | | | | | | | | | | |
| FLACC[d] | X | | | | | | | | | | | | | | |
| AE evaluation[e] | | | | | | | | | | | | | | | |
| Con meds query[e] | | | | | | | | | | | | | | | |

| **Time, related to 1st dose of Oxycodone Oral Solution** | **3 hr** | **3 hr 15 min** | **3 hr 30 min** | **3 hr 45 min** | **4 hr** | **6 hr** | **8 hr** | **10 hr** | **12 hr** | **14 hr** | **16 hr** | **18 hr** | **20 hr** | **22 hr** | **24 hr** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs (BP, HR, Resp.)[a] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Temperature | | | | | X | X | X | X | X | X | X | X | X | X | X |
| Pulse oximetry[a] | | | | | X | X | X | | | | | | | | |
| PK sampling (Under age 2) | | | | | | X | | | X | | | | | | X |
| PK sampling (2 to <17) | | | | | X | X | X | | X | | | | | | X |
| Study drug administration[c] | | | | | | X | | | | | | | | | |
| FLACC[d] | | | | | X | | | | | | | | | | |
| AE evaluation[e] | | | | | | | | | | | | | | | |
| Con meds query[e] | | | | | | | | | | | | | | | |

a Pulse oximetry will begin as soon as possible following the procedure and will continue until 8 hours after the last study dose. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last dose of Oxycodone Oral Solution.
b Blood samples for pharmacokinetic assessment will be collected at the predose time point (within 15 minutes of dosing);
c The study drug will be administered after the surgery when subjects have been postoperatively cleared to transition to oral pain medication in place of the standard analgesic medication. If pain control is inadequate with study drug, the investigator may administer rescue medication for breakthrough pain after dosing.
d The FLACC will also be administered prior to the subject receiving each rescue dose of Fentanyl.
e AEs and Con Meds will be monitored throughout the course of the study.

## 17.3 **Investigator's Agreement**

| | |
|---|---|
| PROTOCOL NUMBER: | 2012O004 |
| PROTOCOL TITLE: | A PHASE IV STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS |
| FINAL PROTOCOL: | AMENDMENT #1; 11 July 2013 |

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with VistaPharm, Inc. and Lehigh Technologies, Inc., or designee during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an investigational product during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

## 17.4 **Faces, Legs, Activity, Cry, Consolability Scale (FLACC)**

| **Categories** | **Scoring** | | |
|---|---|---|---|
| | **0** | **1** | **2** |
| **Face** | No particular expression or smile | Occasional grimace or frown, withdrawn, disinterested | Frequent to constant quivering chin, clenched jaw |
| **Legs** | Normal position or relaxed | Uneasy, restless, tense | Kicking, or legs drawn up |
| **Activity** | Lying quietly, normal position, moves easily | Squirming, shifting back and forth, tense | Arched, rigid or jerking |
| **Cry** | No cry, (awake or asleep) | Moans or whimpers; occasional complaint | Crying steadily, screams or sob, frequent complaints |
| **Consolability** | Content, relaxed | Reassured by occasional touching, hugging or being talked to, distractible | Difficult to console or comfort |

## 18. APPENDICES

A. Address List
B. OXYCODONE HYDROCHLORIDE USP ORAL SOLUTION, Approved Label and Full Prescribing Information

## A. Address List

### 18.1.1 Sponsors

| | |
|---|---|
| Name: | VistaPharm, Inc. |
| Address: | 7256 Ulmerton Road<br>Largo, FL 33771 |
| Phone: | (727) 530-1633 |
| Fax: | (727) 531-5427 |
| Project Manager: | Melissa L. Goodhead, MSc, RAC<br>President<br>Pharmaceutical Project Solutions, Inc. |

| | |
|---|---|
| Name: | Lehigh Valley Technologies, Inc. |
| Address: | 514 North 12th Street<br>Allentown, PA 18102 |
| Phone: | (610) 782-9780 |
| Project Manager: | Melissa L. Goodhead, MSc, RAC<br>President<br>Pharmaceutical Project Solutions, Inc. |

### 18.1.2 Clinical Research Organization

| | |
|---|---|
| Name: | Cognitive Research Corporation |
| Address: | 200 Central Avenue, Suite 1230<br>Saint Petersburg, FL 33703 |
| Phone: | (727) 897-9000 |
| Fax: | (727) 897-9009 |
| Project Manager: | Eva M. Kemper, MSHS<br>Director, Clinical Projects |

# B. OXYCODONE HYDROCHLORIDE USP ORAL SOLUTION, Approved Label and Full Prescribing Information

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Oxycodone Hydrochloride Oral Solution safely and effectively. See full prescribing information for Oxycodone Hydrochloride Oral Solution.**
**Oxycodone Hydrochloride Oral Solution CII**
**Initial U.S. Approval: 1950**

**WARNING: RISK OF MEDICATION ERRORS**

**Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution 5 mg per 5 mL to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.**

**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.**

**INDICATIONS AND USAGE**

Oxycodone Hydrochloride Oral Solution is an opioid agonist indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. (1)

**DOSAGE AND ADMINISTRATION**

- Dosage should be individualized based on the severity of pain, and patient response. (2.1)
- Patients who have not been receiving opioid analgesics should be started in dosing range of 5 to 15 mg every 4 to 6 hours as needed. (2.2)
- When converting from a fixed ratio opioid/non-opioid regimen, the dose should be titrated in response to the level of analgesia and adverse effects and depending on continuation or non-continuation of the non-opioid component. (2.3)
- In patients with hepatic impairment or end-stage renal failure, dose initiation should follow a conservative approach. (2.7)

**DOSAGE FORMS AND STRENGTHS**

- Oral Solution containing 5 mg per 5 mL oxycodone hydrochloride, available in 500 mL bottle and 5 mL unit dose cup. (3)

**CONTRAINDICATIONS**

- Respiratory depression in the absence of resuscitative equipment. (4)
- Suspected or confirmed paralytic ileus. (4)
- Acute or severe bronchial asthma or hypercarbia. (4)
- Known hypersensitivity to oxycodone. (4)

**WARNINGS AND PRECAUTIONS**

- Use caution when prescribing, dispensing, and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between different concentrations and between mg and mL, which could result in accidental overdose and death. (5.1)
- Increased risk or respiratory depression in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnea, or upper airway obstruction. (5.2)
- Oxycodone hydrochloride is a Schedule II controlled substance with an abuse liability similar to other opioids. (5.3)
- Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. (5.3)
- Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.4)
- Increased risk of respiratory depression and of elevation of cerebrospinal fluid pressure in patients with head injury, intracranial lesions or pre-existing increase in intracranial pressure. (5.5)
- Risk of severe hypotension in patients with compromised ability to maintain blood pressure. (5.6)
- May obscure the diagnosis or clinical course in patients with acute abdominal conditions. (5.7)
- Use with caution in patients with biliary tract disease and acute pancreatitis. (5.8)
- The mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery may be impaired. (5.10)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.11)

**ADVERSE REACTIONS**

- The most common adverse reactions are nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. (6)

**To report SUSPECTED ADVERSE REACTIONS CONTACT FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

**DRUG INTERACTIONS**

- Skeletal muscle relaxants: Enhance action of and increased degree of respiratory depression (7.2)
- Drugs that inhibit CYP3A4 activity may decrease clearance of oxycodone and lead to an increase in oxycodone plasma concentrations. (7.4)

**USE IN SPECIFIC POPULATIONS**

- Safety and efficacy in pediatric patients below the age of 18 have not been established. (8.4)
- Geriatric patients, Renal Impairment, and Hepatic impairment: Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects. (8.5, 8.6, 8.7)

**See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide**

**Revised: 03/2012**

**FULL PRESCRIBING INFORMATION: CONTENTS ***



*** Sections or subsections omitted from the full prescribing information are not listed**

## FULL PRESCRIBING INFORMATION

### WARNING: RISK OF MEDICATION ERRORS

**Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution 5 mg per 5 mL to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.**
**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.**

### 1 INDICATIONS AND USAGE

Oxycodone Hydrochloride Oral Solution is an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate.

### 2 DOSAGE AND ADMINISTRATION

Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume. Always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately.
Selection of patients for treatment with oxycodone hydrochloride should be governed by the same principles that apply to the use of similar opioid analgesics. Individualize treatment in every case, using non-opioid analgesics, opioids on as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

#### 2.1 Individualization of Dosage

As with any opioid drug product, adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of oxycodone hydrochloride, give attention to the following:
• the total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;

- the reliability of the relative potency estimate used to calculate the equivalent oxycodone hydrochloride dose needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medications;
- the type and severity of the patient's pain;
- risk factors for abuse, addiction or diversion, including a prior history of abuse, addiction or diversion.

The following dosing recommendations, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.
Continual re-evaluation of the patient receiving oxycodone hydrochloride is important, with special attention to the maintenance of pain management and the relative incidence of side effects associated with therapy. During chronic therapy, especially for non-cancer-related pain, periodically re-assess the continued need for the use of opioid analgesics.
During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient, and the caregiver/family.

**2.2 Initiation of Therapy**
Start patients who have not been receiving opioid analgesics on Oxycodone Hydrochloride Oral Solution in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Titrate the dose based upon the individual patient's response to their initial dose of Oxycodone Hydrochloride Oral Solution. Adjust the dose to an acceptable level of analgesia taking into account the improvement in pain intensity and the tolerability of the oxycodone by the patient.

**2.3 Conversion to Oral Oxycodone Oral Solution**
There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dose of Oxycodone Hydrochloride. It is better to underestimate a patient's 24-hour oral Oxycodone Hydrochloride dose and make available rescue medication than to overestimate the 24-hour oral Oxycodone Hydrochloride dose and manage an adverse experience of overdose.
**2.3.1 Conversion from Fixed-Ratio Opioid/Acetaminophen, Opioid/Aspirin, or Opioid/Nonsteroidal Combination Drugs**

When converting patients from fixed ratio opioid/non-opioid drug regimens it may be necessary to titrate the dose of Oxycodone Hydrochloride Oral Solution in response to the level of analgesia and adverse effects.

**2.3.2 Conversion from Non-Oxycodone Opioids**

In converting patients from other opioids to oxycodone hydrochloride, close observation and adjustment of dosage based upon the patient's response to oxycodone hydrochloride is imperative. Physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate.

**2.4 Conversion from Oral Oxycodone Hydrochloride to Controlled-Release Oral Oxycodone**
The relative bioavailability of Oxycodone Hydrochloride Oral Solution compared to controlled-release oxycodone is unknown, so conversion to controlled-release tablets must be accompanied by close observation for signs of excessive sedation.

**2.5 Maintenance of Therapy**
Continual re-evaluation of the patient receiving Oxycodone Hydrochloride Oral Solution is important, with special attention to the maintenance of pain management and the relative incidence of side effects associated with therapy. If the level of pain increases, effort should be made to identify the source of increased pain, while adjusting the dose as described above to decrease the level of pain.
During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), the continued need for the use of opioid analgesics should be re-assessed as appropriate.

**2.6 Cessation of Therapy**
When a patient no longer requires therapy with Oxycodone Hydrochloride Oral Solution for the treatment of their pain, it is important that therapy be gradually discontinued over time to prevent the development of an opioid abstinence syndrome (narcotic withdrawal). In general, therapy can be decreased by 25% to 50% per day with careful monitoring for signs and symptoms of withdrawal [see *Drug Abuse and Dependence (9.3) section for description of the signs and symptoms of withdrawal*]. If the patient develops these signs or symptoms, the dose should be raised to the previous level and titrated down more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. It is not known at what dose of Oxycodone Hydrochloride Oral Solution that treatment may be discontinued without risk of the opioid abstinence syndrome.

**2.7 Dosage in patients with Hepatic or Renal Impairment**
Follow a conservative approach to dose initiation in patients with hepatic or renal impairment. Monitor patients closely and adjust dose based on clinical response.

**3 DOSAGE FORMS AND STRENGTHS**
Oxycodone Hydrochloride Oral Solution, 5 mg per 5 mL is available in a 500 mL bottle and 5 mL unit dose cup.

**4 CONTRAINDICATIONS**
Oxycodone Hydrochloride Oral Solution is contraindicated in
• patients with respiratory depression in the absence of resuscitative equipment.

• any patient who has or is suspected of having paralytic ileus.

• patients with acute or severe bronchial asthma or hypercarbia.

• patients with known hypersensitivity to oxycodone, oxycodone salts, or any component of this product

**5 WARNINGS AND PRECAUTIONS**

**5.1 Risk of Medication Errors**
Use caution when prescribing, dispensing, and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Use caution to ensure the dose is communicated clearly and dispensed accurately. Always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately.

**5.2 Respiratory Depression**
Respiratory depression is the primary risk of Oxycodone Hydrochloride Oral Solution. Respiratory depression occurs most frequently in elderly or debilitated patients, and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation, or following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.
Use Oxycodone Hydrochloride Oral Solution with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of Oxycodone Hydrochloride Oral Solution may increase airway resistance and decrease respiratory drive to the point of apnea. Consider alternative non-opioid analgesics, and use Oxycodone Hydrochloride Oral Solution only under careful medical supervision at the lowest effective dose in such patients.

**5.3 Misuse and Abuse of Opioids**
Oxycodone Hydrochloride Oral Solution is a Schedule II controlled substance with an abuse liability similar to other opioids. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.
Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids.
Oxycodone Hydrochloride Oral Solution can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Oxycodone Hydrochloride Oral Solution in situations where the physician or pharmacist is concerned about an increased risk of misuse or abuse.
Oxycodone Hydrochloride Oral Solution may be abused by injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence (9.2) and Overdosage (10)]*.
Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

**5.4 Interactions with Alcohol and Drugs of Abuse**
Oxycodone Hydrochloride Oral Solution may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, profound sedation, coma or death may result *[see Drug Interactions (7.1)]*.

**5.5 Use in Head Injury and Increased Intracranial Pressure**
In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of Oxycodone Hydrochloride Oral Solution and its potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following $CO_2$ retention) may be markedly exaggerated. Furthermore, Oxycodone Hydrochloride Oral Solution can produce effects on

pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients w head injuries.

**5.6 Hypotensive Effect**
Oxycodone Hydrochloride Oral Solution may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or general anesthetics or other agents which compromise vasomotor tone. Oxycodone Hydrochloride Oral Solution may produce orthostatic hypotension in ambulatory patients. Administer Oxycodone Hydrochloride Oral Solution with caution in hypovolemic patients, sucl as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Administer Oxycodone Hydrochloride Oral Solution with caution to patients in circulatory shock, since vasodilatation produced by the drug ma further reduce cardiac output and blood pressure.

**5.7 Gastrointestinal Effects**
Do not administer Oxycodone Hydrochloride Oral Solution to patients with gastrointestinal obstruction, especially paralytic ileus because oxycodone hydrochloride diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction.
The administration of Oxycodone Hydrochloride Oral Solution may obscure the diagnosis or clinical course in patients with acute abdominal condition.

**5.8 Use in Pancreatic/Biliary Tract Disease**
Use Oxycodone Hydrochloride Oral Solution with caution in patients with biliary tract disease, including acute pancreatitis, as oxycodone hydrochloride may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

**5.9 Special Risk Groups**
Use Oxycodone Hydrochloride Oral Solution with caution and in reduced dosages in patients with severe renal or hepatic impairmer Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients *[see Use in Specific Populations (8.5)]* .
Exercise caution in the administration of Oxycodone Hydrochloride Oral Solution to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.
Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

**5.10 Driving and Operating Machinery**
Caution patients that oxycodone hydrochloride could impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
Caution patients about the potential combined effects of Oxycodone Hydrochloride Oral Solution with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol *[see Drug Interactions (7.)]*.

**5.11 Cytochrome P450 3A4 Inhibitors and Inducers**
Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations. The expected clinical results with CYP3A4 inhibitors would be an increase in oxycodone plasma concentrations and possibly increased or prolonged opioid effec The expected clinical results with CYP3A4 inducers would be a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.
If co-administration is necessary, caution is advised when initiating Oxycodone Hydrochloride Oral Solution treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.4) and Clinical Pharmacology (12.3)]*.

**5.12 Seizures**
Oxycodone Hydrochloride Oral Solution may aggravate convulsions in patients with convulsive disorders, and all opioids may indu or aggravate seizures in some clinical settings.

**6 ADVERSE REACTIONS**
The following serious adverse reactions are described, or described in greater detail, in other sections:
- Respiratory depression [see *Warnings and Precautions (5.2)*]
- Seizures [see *Warnings and Precautions (5.12)*]
- Hypotension [see *Warnings and Precautions (5.6)*]

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• Spasm of the sphincter of Oddi and increases in the serum amylase level [see *Warnings and Precautions (5.8)*]

Serious adverse reactions that may be associated with oxycodone therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock [see *Overdose (10.1) and Warnings and Precautions (5.1, 5.3)*].
The less severe adverse events seen on initiation of therapy with oxycodone are also typical opioid side effects. These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include nausea, constipation, vomiting, headache, and pruritus.
In many cases the frequency of adverse events during initiation of opioid therapy may be minimized by careful individualization of starting dosage, slow titration and the avoidance of large rapid swings in plasma concentration of the opioid. Many of these adverse events will abate as therapy is continued and some degree of tolerance is developed, but others may be expected to remain throughout therapy.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In all patients for whom dosing information was available (n=191) from the open-label and double-blind studies involving immediate-release oxycodone, the following adverse events were recorded in oxycodone treated patients with an incidence ≥ 3%. In descending order of frequency they were: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.
The following adverse experiences occurred in less than 3% of patients involved in clinical trials with oxycodone:
*Body as a Whole:* abdominal pain, accidental injury, allergic reaction, back pain, chills and fever, fever, flu syndrome, infection, neck pain, pain, photosensitivity reaction, and sepsis.
*Cardiovascular:* deep thrombophlebitis, heart failure, hemorrhage, hypotension, migraine, palpitation, and tachycardia.
*Digestive:* anorexia, diarrhea, dyspepsia, dysphagia, gingivitis, glossitis, and nausea and vomiting.
*Hemic and Lymphatic:* anemia and leukopenia.
*Metabolic and Nutritional:* edema, gout, hyperglycemia, iron deficiency anemia and peripheral edema.
*Musculoskeletal:* arthralgia, arthritis, bone pain, myalgia and pathological fracture.
*Nervous:* agitation, anxiety, confusion, dry mouth, hypertonia, hypesthesia, nervousness, neuralgia, personality disorder, tremor, and vasodilation.
*Respiratory:* bronchitis, cough increased, dyspnea, epistaxis, laryngismus, lung disorder, pharyngitis, rhinitis, and sinusitis.
*Skin and Appendages:* herpes simplex, rash, sweating, and urticaria.
*Special Senses:* amblyopia.
*Urogenital:* urinary tract infection

## 7 DRUG INTERACTIONS

### 7.1 CNS Depressants
Patients receiving narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Oxycodone Hydrochloride Oral Solution may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dosage of Oxycodone Hydrochloride Oral Solution. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

### 7.2 Neuromuscular Blocking Agents
Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

### 7.3 Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as Oxycodone Hydrochloride Oral Solution. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of Oxycodone Hydrochloride Oral Solution and/or may precipitate withdrawal symptoms in these patients.

### 7.4 Agents Affecting Cytochrome P450 Enzymes
CYP3A4 Inhibitors

A published study showed that the co-administration with voriconazole, a CYP3A4 inhibitor, significantly increased the plasma concentrations of oxycodone. Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, significantly decreased plasma oxycodone concentrations. Induction of CYP3A4 activity by its inducers, such as rifampin, carbamazepine, and phenytoin, may lead to a lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via the Cytochrome P450 Isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. However, clinicians should be aware of this possible interaction.

**7.5 Monoamine Oxidase Inhibitors (MAOIs)**
MAOIs have been reported to intensify the effects of at least one opioid drug, causing anxiety, confusion and significant depression of respiration or coma. The use of Oxycodone Hydrochloride Oral Solution is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

**7.6 Anticholinergics**
Anticholinergics or other medications with anticholinergic activity, when used concurrently with opioid analgesics including oxycodone hydrochloride, may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**
Pregnancy Category B: There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed.

Teratogenic Effects

Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that oxycodone administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a $mg/m^2$ basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a $mg/m^2$ basis), respectively was not teratogenic or embryo-fetal toxic.

Nonteratogenic Effects

Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

**8.2 Labor and Delivery**
Oxycodone Hydrochloride Oral Solution is not recommended for use in women during or immediately prior to labor. Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. Neonates, whose mothers received opioid analgesics during labor, should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

**8.3 Nursing Mothers**
Low levels of oxycodone have been detected in maternal milk. The amount of oxycodone hydrochloride delivered to the infant depends on the plasma concentration of the mother, the amount of milk ingested by the infant, and the extent of first-pass metabolism. Because of the potential for serious adverse reactions in nursing infants from oxycodone hydrochloride including respiratory depression, sedation and possibly withdrawal symptoms, upon cessation of oxycodone hydrochloride administration to the mother, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**8.4 Pediatric Use**
The safety and efficacy of Oxycodone Hydrochloride Oral Solution in pediatric patients below the age of 18 have not been established.

**8.5 Geriatric Use**
Elderly patients (aged 65 years or older) may have increased sensitivity to oxycodone hydrochloride. In general, use caution when selecting a dose for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

**8.6 Hepatic Impairment**
Since oxycodone is extensively metabolized, its clearance may decrease in hepatic failure patients. Follow a conservative approach to dose initiation in patients with hepatic impairment, monitor patients closely and adjust the dose based on clinical response.

**8.7 Renal Impairment**
Information from oxycodone tablets indicate that patients with renal impairment (defined as a creatinine clearance <60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function. Use a conservative approach to dose initiation in patients with renal impairment, monitor patients closely and adjust the dose based on clinical response.

**9 DRUG ABUSE AND DEPENDENCE**

**9.1 Controlled Substance**
**Oxycodone hydrochloride is a mu-agonist opioid of the morphine type and is a Schedule II controlled substance. Oxycodone Hydrochloride Oral Solution, like other opioids used in analgesia, can be abused and is subject to criminal diversion.**

**9.2 Abuse**
Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.
"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.
The risks of misuse and abuse should be considered when prescribing or dispensing Oxycodone Hydrochloride Oral Solution. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.
Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.
**Oxycodone Hydrochloride Oral Solution is intended for oral use only. Abuse of Oxycodone Hydrochloride Oral Solution poses a risk of overdose and death. The risk is increased with concurrent abuse of alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.**
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.
**Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms** *[see Use in Specific Populations (8.2)].*

**9.3 Dependence**
Tolerance to opioids is demonstrated by the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). If tolerance develops, or if pain severity increases, a gradual increase in dose may be required. The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are frequent during chronic opioid therapy.
Patients using Oxycodone Hydrochloride Oral Solution chronically (for several weeks) should be instructed that they should contact their health care providers if they notice the need to increase dosing to treat symptoms of pain or they experience symptoms of withdrawal upon abrupt cessation of dosing.
The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.
In general, taper opioids rather than abruptly discontinue *[see Dosage and Administration (2.6)].*

## 10 OVERDOSAGE

### 10.1 Signs and Symptoms

Acute overdose with Oxycodone Hydrochloride Oral Solution can be manifested by respiratory depression (a decrease in respiratory rate and/or end tidal volume. Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, pulmonary edema, cardiac arrest, and death. Oxycodone Hydrochloride Oral Solution may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12)]* .

### 10.2 Treatment

Give primary attention to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures including oxygen and vasopressors should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of oxycodone hydrochloride, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to opioid antagonists is suboptimal or only brief in nature, administer additional antagonist as directed by the manufacturer of the product.

Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Administer such agents cautiously to persons who are known, or suspected to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

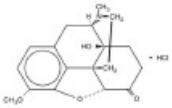
In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. Reserve use of an opioid antagonist for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, initiate administration of the antagonist with care and titrate with smaller than usual doses.

## 11 DESCRIPTION

Oxycodone Hydrochloride Oral Solution, USP, 5mg/5mL: Each 5 mL's is for oral administration and contains 5 mg of oxycodone hydrochloride USP.

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula:



$C_{18}H_{21}NO_4$•HCl MW 351.82

The 5 mg per 5 mL Oxycodone Hydrochloride Oral Solution contains equivalent of 4.5 mg of oxycodone free base per 5 mL's and contains the following inactive ingredients: Poloxamer 188 NF, Sodium Benzoate NF, Citric Acid Anhydrous USP, Glycerin Natural USP, Sorbitol Solution 70% USP, FD&C Red #40 , Raspberry Flavor and Water.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Oxycodone, as the hydrochloride salt, is a full opioid agonist whose principal therapeutic action is analgesia.

### 12.2 Pharmacodynamics

Effects on Central Nervous System

Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. A significant feature of opioid-induced analgesia is that it occurs without loss of consciousness. The relief of pain by morphine-like opioids is relatively selective, in that other sensory modalities, (e.g., touch, vibrations, vision, hearing, etc.) are not obtunded.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on Gastrointestinal Tract and Other Smooth Muscle

Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla. The frequency and severity of emesis gradually diminishes with time.

Oxycodone may cause a decrease in the secretion of hydrochloric acid in the stomach that reduces motility while increasing the tone of the antrum, stomach, and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone, in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown.

**12.3 Pharmacokinetics**

The activity of Oxycodone Hydrochloride Oral Solution is primarily due to the parent drug oxycodone.

Absorption

The oral bioavailability of oxycodone is 60 - 87%. This high oral bioavailability (compared to other oral opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone.

Food Effect

Presence of food may slightly delay the rate ($C_{max}$ and $T_{max}$) and enhance the extent of absorption (AUC) of oxycodone from Oxycodone Hydrochloride Oral Solution. Overall, food is not expected to have a clinically significant impact on the absorption of Oxycodone Hydrochloride Oral Solution.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.3)]*.

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, noroxymorphone, which are subsequently glucuronidated. CYP3A4 mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a less contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that

of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of Oxycodone Hydrochloride Oral Solution was approximately 3.5 hours.

Special Populations

*Geriatric*

Information obtained from oxycodone tablets indicate that the plasma concentrations of oxycodone did not appear to be increased in patients over of the age of 65.

*Gender*

Information obtained from oxycodone tablets support the lack of gender effect on the pharmacokinetics of oxycodone.

*Hepatic Impairment*

Since oxycodone is extensively metabolized, its clearance may be decreased in hepatic failure patients *[see Use in Special Populations (8.6)]*.

*Renal Impairment*

Information obtained from oxycodone tablets indicate that patients with renal impairment (defined as creatinine clearance < 60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function *[see Use in Special Populations (8.7)]*.

*Drug-Drug Interactions*

*CYP3A4 Inhibitors*

CYP3A4 is the major enzyme involved in noroxycodone formation. A published study showed that the co-administration of voriconazole, a CYP3A4 inhibitor, increased oxycodone AUC and $C_{max}$ by 3.6 and 1.7 fold, respectively.

*CYP3A4 Inducers*

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and $C_{max}$ values by 86% and 63%, respectively.

*CYP2D6 Inhibitors*

Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone hydrochloride was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay *(Salmonella typhimurium* and *Escherichia coli)* or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

Impairment of Fertility

The potential effects of oxycodone on male and female fertility have not been evaluated.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**
Oxycodone Hydrochloride Oral Solution, USP, 5 mg per 5 mL is available as follows:
NDC 66689-403-16: 500 mL bottle packaged with calibrated measuring cup
NDC 66689-401-01: 5 mL unit dose cup
NDC 66689-401-50: Case contains 50 unit dose cups of 5 mL (NDC 66689-401-01), packaged in 5 trays of 10 unit dose cups each

**16.2 Storage and Handling**
All opioids, including Oxycodone Hydrochloride Oral Solution, are liable to diversion and misuse both by the general public and healthcare workers and should be handled accordingly.
Dispense in a tight, light-resistant container as defined in the USP/NF.
Keep in secured area and protect from diversion.
Store at controlled room temperature 20°-25°C (68°- 77°F).

**17 PATIENT COUNSELING INFORMATION**
***See Medication Guide***
Provide the following information to patients receiving Oxycodone Hydrochloride Oral Solution or their caregivers:

- Advise patients that Oxycodone Hydrochloride Oral Solution is a narcotic pain medication, and should be taken only as directed.
- Advise patients that sharing oxycodone can result in fatal overdose and death.
- Advise patients that Oxycodone Hydrochloride Oral Solution is a potential drug of abuse. They must protect it from theft. It should never be given to anyone other than the individual for whom it was prescribed.
- Advise patients to keep Oxycodone Hydrochloride Oral Solution in a secure place out of the reach of children. When Oxycodone Hydrochloride Oral Solution is no longer needed, the unused solution should be destroyed by flushing down the toilet.
- Advise patients how to measure and take the correct dose of Oxycodone Hydrochloride Oral Solution, and to always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution, to ensure the dose is measured and administered accurately.
- Advise patients whenever the prescribed concentration is changed to avoid dosing errors which could result in accidental overdose and death.
- Advise patients not to adjust the dose of Oxycodone Hydrochloride Oral Solution without consulting with a physician or other healthcare professional.
- Advise patients that Oxycodone Hydrochloride Oral Solution may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Advise patients started on Oxycodone Hydrochloride Oral Solution or patients whose dose has been adjusted to refrain from any potentially dangerous activity until it is established that they are not adversely affected.
- Advise patients that Oxycodone Hydrochloride Oral Solution will add to the effect of alcohol and other CNS depressants (such as antihistamines, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and monoamine oxidase [MAO] inhibitors).
- Advise patients not to combine Oxycodone Hydrochloride Oral Solution with central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, and not to combine with alcohol because dangerous additive effects may occur, resulting in serious injury or death.
- Advise women of childbearing potential who become or are planning to become pregnant to consult a physician prior to initiating or continuing therapy with Oxycodone Hydrochloride Oral Solution.

- Advise patients that safe use in pregnancy has not been established and that prolonged use of opioid analgesics including Oxycodone Hydrochloride Oral Solution during pregnancy may cause fetal-neonatal physical dependence, and neonatal withdrawal may occur.
- If patients have been receiving treatment with Oxycodone Hydrochloride Oral Solution for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Advise patients taking Oxycodone Hydrochloride Oral Solution of the potential for severe constipation; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of opioid therapy.
- Advise patients of the most common adverse events that may occur while taking Oxycodone Hydrochloride Oral Solution: constipation, nausea, somnolence, lightheadedness, dizziness, sedation, vomiting, and sweating.
- Advise patients to call 911 or the local Poison Control center, and get emergency help immediately if they take more Oxycodone Hydrochloride Oral Solution than prescribed, or overdose.
- Advise patients, that if they miss a dose, to take the missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to their regular dosing schedule. Do not take two doses at once unless instructed by their healthcare provider.

**DEA Order Form Required**
Manufactured by:
*VistaPharm®*
Largo, FL 33771
VP 2013R1
01/12
To request medical information contact VistaPharm, Inc. at 1-727-530-1633.

**MEDICATION GUIDE**
**Oxycodone Hydrochloride**
**(ox-ee-CO-dohn) (CII)**
**Oral Solution**
Rx Only

**IMPORTANT: Keep Oxycodone Hydrochloride Oral Solution in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes Oxycodone Hydrochloride Oral Solution, get emergency help right away.**

Read the Medication Guide that comes with Oxycodone Hydrochloride Oral Solution before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Oral Solution?**
**Oxycodone Hydrochloride Oral Solution can cause serious side effects, including death.**
- **Take Oxycodone Hydrochloride Oral Solution exactly as prescribed by your healthcare provider.** If you take the wrong dose or strength of Oxycodone Hydrochloride Oral Solution, you could overdose and die.
- **It is especially important when you take Oxycodone Hydrochloride Oral Solution that you know exactly what dose and strength to take, and the right way to measure your medicine.** Your healthcare provider or pharmacist should show you the right way to measure your medicine. Always use the dosing cup provided with Oxycodone Hydrochloride Oral Solution to help make sure you measure the right amount.
- **Do not drink alcohol.** Using alcohol with Oxycodone Hydrochloride Oral Solution may increase your risk of dangerous side effects, including death.

**What is Oxycodone Hydrochloride Oral Solution?**
Oxycodone Hydrochloride Oral Solution is in a group of drugs called narcotic pain medicine. Oxycodone Hydrochloride Oral Solution is only for adults who have moderate to severe pain.
- A prescription medicine that is used to manage moderate to severe pain that is expected to last a short period of time (acute), and pain that continues around-the-clock and is expected to last for a long period of time (chronic).

- Oxycodone Hydrochloride Oral Solution is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.
- Prevent theft, misuse or abuse. Keep Oxycodone Hydrochloride Oral Solution in a safe place to keep it from being stolen. Oxycodone Hydrochloride Oral Solution can be a target for people who misuse or abuse prescription medicines or street drugs.
- Never give Oxycodone Hydrochloride Oral Solution to anyone else, even if they have the same symptoms you have. It may harm them or even cause death.
- Selling or giving away this medicine is against the law.
- It is not known if Oxycodone Hydrochloride Oral Solution is safe and effective in children under age 18 years of age.

**Who Should Not Take Oxycodone Oral Solution?**
**Do not take Oxycodone if you:**
- are having breathing problems and there is no emergency medical equipment nearby
- have a bowel blockage called paralytic ileus
- are having an asthma attack or have severe asthma, trouble breathing, or lung problems
- are allergic to oxycodone or any of the ingredients in Oxycodone Hydrochloride Oral Solution. See the end of this Medication Guide for a complete list of ingredients in Oxycodone Hydrochloride Oral Solution

**What should I tell my healthcare provider before taking Oxycodone Hydrochloride Oral Solution?**
**Before taking Oxycodone Hydrochloride Oral Solution, tell your healthcare provider if you:**
- have trouble breathing or lung problems
- have had a head injury
- have liver or kidney problems
- have adrenal gland problems, such as Addison's disease
- have severe scoliosis that affects your breathing
- have thyroid problems
- have problems urinating or enlargement of your prostate
- have or had convulsions or seizures
- have a past or present drinking problem or alcoholism
- have hallucinations (seeing or hearing things that are not really there) or other severe mental problems
- have constipation or other bowel problems
- have problems with your pancreas or gallbladder
- have past or present substance abuse or drug addiction
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if Oxycodone Hydrochloride Oral Solution will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  If you take Oxycodone Hydrochloride Oral Solution regularly before your baby is born, your newborn baby may have signs of withdrawal because their body has become used to the medicine. Signs of withdrawal in a newborn baby can include:

| | |
|---|---|
| • irritability | • vomiting |
| • being very active | • diarrhea or more stools than normal |
| • problems sleeping | • weight loss |
| • high pitched cry | • shaking (tremors) |

If you are taking Oxycodone Hydrochloride Oral Solution right before your baby is born, your baby could have breathing problems.

- are breast-feeding or plan to breastfeed. Some Oxycodone Hydrochloride Oral Solution passes into your breast milk. A nursing baby could become very sleepy or have difficulty breathing or feeding well. If you stop breastfeeding, your baby may have withdrawal symptoms. See the list of withdrawal symptoms above. You and your healthcare provider should decide if you will take Oxycodone Hydrochloride Oral Solution or breastfeed.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes the doses of medicines that you take with Oxycodone Hydrochloride Oral Solution may need to be changed if used together. Be especially careful about taking other medicines that make you sleepy such as:

- sleeping pills
- other pain medicines
- anti-nausea medicines
- tranquilizers
- muscle relaxants
- anti-anxiety medicines
- antihistamines
- anti-depressants
- monoamine oxidase inhibitors (MAOIs): Do not take Oxycodone Hydrochloride Oral Solution if you already take an MAOI or within 14 days after you stop taking an MAOI medicine

Ask your healthcare provider if you are not sure if your medicine is one listed above.
Do not take other medicines while using Oxycodone Hydrochloride Oral Solution until you have talked with your healthcare provider or pharmacist. They will tell you if it is safe to take other medicines with Oxycodone Hydrochloride Oral Solution.
**Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.**

**How Should I Take Oxycodone?**

- See **"What is the most important information I should know about Oxycodone Hydrochloride Oral Solution?"**
- **Take Oxycodone Hydrochloride Oral Solution exactly as prescribed**. Do not change your dose unless your healthcare provider tells you to. Your healthcare provider may change your dose after seeing how the medicine affects you. Call your healthcare provider if your pain is not well controlled with your prescribed dose of Oxycodone Hydrochloride Oral Solution.
- **Make sure you understand exactly how to measure your dose**. Always use the dosing cup provided with our Oxycodone Hydrochloride Oral Solution to help make sure you measure the right amount. See the Patient Instructions for Use at the end of this Medication Guide for information about how to measure your dose the right way. Ask your healthcare provider or pharmacist if you are not sure what dose of Oxycodone Hydrochloride Oral Solution you should take or if you are not sure how to use the dosing cup.
- **Do not stop taking Oxycodone Hydrochloride Oral Solution suddenly**. If you have been taking Oxycodone Hydrochloride Oral Solution for more than a few weeks, stopping it suddenly can make you sick with withdrawal symptoms (for example, nausea, vomiting, diarrhea, anxiety, and shivering). If your healthcare provider decides you no longer need Oxycodone Hydrochloride Oral Solution, ask how to slowly reduce this medicine. Do not stop taking Oxycodone Hydrochloride Oral Solution without talking to your healthcare provider.
- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at one time unless your healthcare provider tells you to.
- If you take too much Oxycodone Hydrochloride Oral Solution call your healthcare provider or your local Poison Control Center right away or go to the nearest hospital emergency room right away.
- Talk with your healthcare provider regularly about your pain to see if you still need to take Oxycodone Hydrochloride Oral Solution.

**What Should I Avoid While Taking Oxycodone?**

- **You should not drink alcohol while using Oxycodone Hydrochloride Oral Solution. Drinking alcohol with Oxycodone Hydrochloride Oral Solution may increase your risk of having dangerous side effects or death.**

- **Do not drive, operate heavy machinery, or do other dangerous activities,** especially when you start taking Oxycodone Hydrochloride Oral Solution and when your dose is changed, until you know how Oxycodone Hydrochloride Oral Solution affects you. Oxycodone can make you sleepy. Ask your healthcare provider to tell you when it is okay to do these activities.

**What are the Possible Side Effects of Oxycodone?**

**Oxycodone Hydrochloride Oral Solution can cause serious side effects, including:**

- See **"What is the most important information I should know about Oxycodone Hydrochloride Oral Solution?"**

- **Oxycodone can cause serious breathing problems that can become life-threatening, especially if Oxycodone Hydrochloride Oral Solution is used the wrong way.** Call your healthcare provider or get help right away if:
- your breathing slows down
- you have shallow breathing (little chest movement with breathing)
- you feel faint, dizzy, confused, or
- you have any other unusual symptoms

  These can be symptoms that you have taken too much Oxycodone Hydrochloride Oral Solution (overdose) or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- **Oxycodone Hydrochloride Oral Solution can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down. Low blood pressure is also more likely to happen if you take other medicines that can also lower your blood pressure. Severe low blood pressure can happen if you lose blood or take certain other medicines.

- **Oxycodone can cause physical dependence.** Do not stop taking Oxycodone or any other opioid without talking to your healthcare provider about how to slowly stop your medicine. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction. Tell your healthcare provider if you have any of these symptoms of withdrawal while slowly stopping Oxycodone:

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| • feel restless | • trouble sleeping |
| • tearing eyes | • runny nose |
| • sweating | • yawning |
| • chills or hair on your arms "stand up" | • nausea, loss of appetite, vomiting |
| • muscle aches, backache | • diarrhea, stomach area (abdominal) cramps |
| • dilated pupils of your eyes | • increase in your blood pressure |
| • feel irritable or anxious | • breathing faster, or your heart beats faster |

- **There is a chance of abuse or addiction with Oxycodone Hydrochloride Oral Solution.** The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

- **Seizures: Oxycodone Hydrochloride Oral Solution may cause seizures or make seizures that you already have worse.**

**Call your healthcare provider if you have any of the symptoms listed above.**

**Common side effects of Oxycodone Hydrochloride Oral Solution include:**

| | |
|---|---|
| • nausea | • dizziness |
| • constipation | • weakness |
| • vomiting | • drowsiness |
| • headache | • sweating |
| • itching | • lightheadedness |
| • trouble sleeping | |

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including Oxycodone Hydrochloride Oral Solution. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking Oxycodone Hydrochloride Oral Solution.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of Oxycodone Hydrochloride Oral Solution. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Oxycodone Hydrochloride Oral Solution?**

- Store Oxycodone Hydrochloride Oral Solution at controlled room temperature between 68°F - 77°F (20°C - 25°C).
- Protect Oxycodone Hydrochloride Oral Solution from moisture and light.
- When Oxycodone Hydrochloride Oral Solution is no longer needed, the unused solution should be destroyed by flushing down the toilet.

**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. Accidental overdose by a child is a medical emergency and can lead to death.**

**General information about Oxycodone Hydrochloride Oral Solution**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Oxycodone Hydrochloride Oral Solution for a condition for which it was not prescribed.
**Do not give your Oxycodone Hydrochloride Oral Solution to other people, even if they have the same symptoms you have. Selling or giving away Oxycodone Hydrochloride Oral Solution may harm others, may cause death, and is against the law.**
This Medication Guide summarizes the most important information about Oxycodone Hydrochloride Oral Solution. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Oxycodone Hydrochloride Oral Solution that is written for healthcare professionals.
For more information about Oxycodone Hydrochloride Oral Solution, contact VistaPharm, Inc. at (727) 530-1633.

**What are the ingredients in Oxycodone Hydrochloride Oral Solution?**

**Active ingredient: oxycodone hydrochloride**
**Inactive ingredients:** anhydrous citric acid, FD&C red #40, glycerin, poloxamer 188, purified water, raspberry flavor, sodium benzoate and sorbitol solution.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

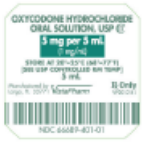
**Manufactured by:**

*VistaPharm®*
Largo, FL 33771
VP2100
01/12

**Rx Only**

**PRINCIPAL DISPLAY PANEL - 5 mL Cup Label**

**OXYCODONE HYDROCHLORIDE**
**ORAL SOLUTION, USP CII**
**5 mg per 5 mL**
(1 mg/mL)
**STORE AT 20°-25°C (68°-77°F)**
**[SEE USP CONTROLLED RM TEMP]**
**5 mL**
Manufactured by VistaPharm® Largo, FL 33771
**Rx Only**
VP2012 R1
NDC 66689-401-01




**PRINCIPAL DISPLAY PANEL - 500 mL Bottle Carton**

**NDC 66689-403-16**
**Oxycodone Hydrochloride**
**Oral Solution, USP CII**
**5 mg per 5 mL**
(1 mg/mL)
Each 5 mL Contains:
**Oxycodone Hydrochloride — 5 mg**
**USUAL DOSAGE:** See Package Insert for Complete Prescribing Information.
**PHARMACIST: Dispense the enclosed Medication Guide to each patient.**
**500 mL**
VistaPharm, Inc., Largo, FL 33771
**Rx**
**only**
**VP 2089**
*VistaPharm*®
66689-403-16


Revised: 03/2012

Distributed by: VistaPharm Inc.

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# A PHASE IV STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS

| | |
|---|---|
| PROTOCOL DATE: | Version 7.1, Final 25 April 2013<br>Amendment #1, 11 July 2013<br>Amendment #2, 18 September 2013 |
| SPONSORED BY: | VistaPharm, Inc.<br>7256 Ulmerton Road<br>Largo, FL 33771<br>Phone: (727) 530-1633<br><br>Lehigh Valley Technologies, Inc.<br>514 North 12th Street<br>Allentown, PA 18102<br>Phone: (610) 782-9780 |
| CONTRACT RESEARCH ORGANIZATION: | Cognitive Research Corporation<br>200 Central Avenue, Suite 1230<br>St. Petersburg, FL 33701<br>Phone: (727) 897-9000<br>Fax: (727) 897-9009 |

# 1. PROCEDURES IN CASE OF EMERGENCY

## Table 1: Sponsor Contact Information

| Role in Study | Name | Address and Telephone Number |
|---|---|---|
| Clinical Study Leader | Thomas J. Hochadel, Pharm.D.<br>Chief Operating Officer | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 727-515-1334 |
| Clinical Operations Leader | Eva M. Kemper, MSHS<br>Director, Clinical Projects | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 813-690-2667 |
| Physician | Lawrence Blob, M.D. | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 410-262-1908 |
| 24-hour Emergency Contact | Thomas J. Hochadel, Pharm.D.<br>Chief Operating Officer<br><br><u>Secondary Contact:</u><br>Deborah Lees, R.N.<br>Assistant Project Manager | Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 727-515-1334<br><br>Company Name: CRC<br>Address: 200 Central Ave,<br>Suite 1230<br>Saint Petersburg, FL 33701<br>Telephone: 727-897-9000<br>Cell: 813-943-8249 |

## 2. SYNOPSIS

| | |
|---|---|
| PRODUCT NAME | OXYCODONE ORAL SOLUTION |
| PROTOCOL NUMBER | 2012O004 |
| DEVELOPMENT PHASE | PHASE IV |
| PROTOCOL TITLE | A PHASE IV STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS |
| INDICATION | Moderate to severe pain |
| PRINCIPAL INVESTIGATOR | This is a multicenter study. The lead Principal Investigator will be:<br>Senthilkumar Sadhasivam, M.D.<br>Cincinnati Children's Hospital Medical Center<br>3333Burnet Avenue, MLC2001<br>Cincinnati, OH 45229 |
| PLANNED STUDY SITES | Up to 10 sites in the US. |
| OBJECTIVE | The objective of this study is to characterize the pharmacokinetics and to evaluate the safety of single and multiple doses of Oxycodone Oral Solution in pediatric and adolescent subjects for postoperative pain. |
| STUDY DESIGN | This is a Phase IV study to characterize the pharmacokinetics and to evaluate the safety of Oxycodone Oral Solution administered to pediatric and adolescent subjects for postoperative pain. It is an open-label, multicenter study conducted at up to 10 sites. Subjects may be enrolled preoperatively, up to 14 days before surgery, or postoperatively with the expectation that they will require intravenous (IV) access after the surgery and postoperative analgesia with an opiate-level medication. After dosing with Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to <17, and a dose to be determined based on pharmacokinetic (PK) modeling from the interim analyses for subjects under age 2), subjects will be carefully monitored for safety. A total of 110 pediatric and adolescent male or female subjects will be enrolled, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years. Subjects within each age group will be evenly distributed by age and gender.<br><br>An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 6 months to <2 years will receive will be based on an evaluation of the safety and PK observed from this interim analysis.<br><br>An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs |

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| | and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on an evaluation of the safety and PK observed from this interim analysis.<br><br>The study will consist of a Screening period (preoperatively, up to 14 days before surgery, or postoperatively); a predose check-in (Predose); a treatment period after surgery (Day 1, Time Zero); and an End-of-Study assessment. The total duration of the study, excluding Screening, will be approximately 1 full day.<br><br>Eligible subjects who provide assent (according to local standard of care or IRB directive) and whose parent(s) or legal guardian(s) provide consent as required will have study assessments performed at Screening. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone. At this time (Predose), they will have a predose check-in to have eligibility confirmed.<br><br>After subjects ages 2 to <17 have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.<br><br>After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via Nurse-Controlled Analgesia (NCA). Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy..<br><br>Subjects will undergo an End-of-Study assessment at least 24 hours after receiving the first dose of Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study.<br><br>Safety will be assessed by monitoring AEs, clinical laboratory test results, vital sign measurements, temperature, pulse oximetry, and physical examination findings.<br><br>The Faces, Legs, Activity, Crying, Consolability Scale (FLACC) will be used to measure pain prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution in subjects under age 2. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl or other rescue pain medication. |

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| | Serial blood samples for PK analysis will be collected for the determination of plasma concentrations of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone). For subjects 2 years old and above, samples will be collected prior to the first dose (within 15 minutes of dosing); 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing. |
| PLANNED NUMBER OF SUBJECTS | A total of 110 subjects, including a minimum of 20 subjects under age 2, 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years, are planned for this study to ensure adequate evaluation of the safety and PK profiles of Oxycodone Oral Solution. |
| STUDY ENTRY CRITERIA | Inclusion criteria<br>A subject will be eligible for inclusion in the study if he or she meets the following criteria:<br>1. Is male or female <17 years of age at the time of dosing.<br>2. Subject 2 to <17 years of age, be in at least the 25% for weight according to the Center for Disease Control pediatric growth charts and weighs at least 28 lb at the time of dosing with study drug.<br>3. Is generally healthy defined as American Society of Anesthesiologists (ASA) Physical Status classification grade I or II (except for the condition for which the procedure is being performed), documented by medical history; physical examination (including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; electrocardiogram; clinical laboratory assessments; and general observations.<br>4. Has a negative urine pregnancy test predose (for females of childbearing potential).<br>5. Is an outpatient prior to admission for a surgical procedure and is expected to remain hospitalized for at least 24 hours after dosing with study drug.<br>6. Is anticipated to have postsurgical pain requiring a parenteral analgesic regimen using a short-acting opioid analgesic and is anticipated to be switched to an oral opioid for at least 1 dose (according to institution standard of care).<br>7. Has an indwelling access catheter for blood sampling.<br>8. Agrees to comply with all protocol requirements. If not old enough, the legally responsible parent(s) or legal guardian(s) must agree to comply with all protocol requirements.<br>9. Has been informed of the nature of the study and informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, in accordance with institutional review board requirements. |

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| | Exclusion criteria<br>A subject will be excluded from the study if he or she meets the following criteria:<br>1. Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (except for the condition for which the procedure is being performed) greater than grade II on ASA Physical Status classification as determined by the clinical investigator.<br>2. Has any clinical laboratory test result documented as "alert", "critical" or "panic" per institution laboratory ranges or has aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2.0 x the upper limit of normal (ULN); total bilirubin > 1.5 x the ULN; serum creatinine > 1.5 x the ULN; or blood urea nitrogen > 1.5 x the ULN.<br>3. Had a clinically significant illness (ASA Physical Status classification >II), except for the condition for which the procedure is being performed, in the 28 days before dosing with study drug as determined by the clinical investigator.<br>4. Is a lactating or breastfeeding female.<br>5. Uses any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug. Use of any monoamine oxidase inhibitor or St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.<br>6. Consumes alcohol- or xanthine-containing products within 8 hours before dosing and during periods when blood samples are collected.<br>7. Consumes grapefruit, grapefruit products, Seville oranges, or pomelo-containing products within 5 days of dosing. Fruit juices, with the exception of apple and grape, will be prohibited during the study.<br>8. Is a smoker or has used nicotine or nicotine-containing products within 30 days of dosing.<br>9. Has a history of alcohol or drug addiction or abuse within the last year.<br>10. Temperature >100°F at time of initial administration of study medication.<br>11. Donated blood within 28 days or plasma within 14 days of dosing or plans to donate them within 4 weeks after completing the study.<br>12. Has a history of relevant drug allergies, food allergies, or both (i.e., allergy to oxycodone, allergy to related drugs, or any significant food allergy that could interfere with the study).<br>13. Is intolerant to direct venipuncture.<br>14. Received an investigational drug within 28 days of dosing. |

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| | 15. Has taken oxycodone or oxymorphone within the 48 hours before anticipated dosing with study drug.<br>16. Is not suitable for entry into the study in the opinion of the investigator. |
| INVESTIGATIONAL PRODUCT | Oxycodone Oral Solution provided by VistaPharm, Inc., supplied in 500-mL bottles. Oxycodone Oral Solution contains 4.5 mg of oxycodone free base per 5 mL (5 mg oxycodone HCl/5 ml) and the following inactive ingredients: poloxamer 188 NF, sodium benzoate NF, citric acid anhydrous US Pharmacopeia (USP), glycerin natural USP, sorbitol solution 70% USP, FD&C Red #40 , raspberry flavor, and water. |
| TREATMENT REGIMEN | Each subject in the 2 to 6, 7 to 12 and 13 to <17 age groups will receive a dose of Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, and 0.07 mg/kg for ages 13 to <17) in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain medication. The first 10 subjects in each of these age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. Each subject under age 2 will receive a single dose of Oxycodone Oral Solution. The dose will be determined based on PK modeling from the interim analyses. Oxycodone Oral Solution will be administered with an oral medication syringe. |
| CRITERIA FOR EVALUATION | Pharmacokinetic endpoints:<br>• Area under the plasma concentration versus time curve from Time Zero to the last measurable concentration ($AUC_{0-t}$)<br>• Area under the plasma concentration versus time curve from Time Zero to infinity ($AUC_{0-inf}$)<br>• Ratio of $AUC_{0-t}$ to $AUC_{0-inf}$ ($AUC_{0-t}/AUC_{0-inf}$)<br>• Maximum measured plasma concentration ($C_{max}$)<br>• Time of the maximum measured plasma concentration ($T_{max}$)<br>• Apparent first-order terminal elimination rate constant ($K_{el}$)<br>• Apparent first-order terminal elimination half-life ($t_{1/2}$)<br>• Apparent clearance (CL/F)<br>• Volume of distribution (V/F)<br>Other PK parameters may be calculated if deemed necessary.<br>Safety endpoints:<br>Safety will be assessed by the monitoring and recording of AEs; clinical laboratory results (including hematology, serum chemistry, and urinalysis); vital sign measurements (systolic and diastolic blood pressures, heart rate, and respiratory rate); temperature; pulse oximetry; and physical examination findings.<br>Exploratory Study Endpoints:<br>Analgesic sparing will be the surrogate efficacy endpoint in children under age 2.The Total FLACC Score will be an exploratory endpoint in children under age 2. |

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| STATISTICAL METHODS | Analysis Populations<br>PK Population: the PK population will consist of all subjects who receive study drug and have at least 1 measureable plasma concentration.<br>PK Parameter Population: all subjects who receive study drug and for which at least one PK parameter can be determined.<br>Safety Population: the safety population will consist of all subjects who receive study drug.<br>Subject Characteristics and Disposition<br>For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).<br>Baseline demographic and background variables will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized.<br>Pharmacokinetic Analyses<br>Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be listed and summarized. Each subject's oxycodone plasma concentrations will be graphed by using both a normal scale y-axis and a logarithmic scale y-axis. Mean oxycodone plasma concentrations for each age group will also be graphed using scheduled elapsed sampling times for both the normal and logarithmic scale y-axis.<br>Pharmacokinetic parameters will be listed for each subject and summarized by group. Key PK parameters will be contrasted with adult values from the literature.<br>Other PK analyses may be performed as appropriate.<br>Safety Analyses<br>Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.<br>Actual values and changes from Baseline for clinical laboratory results, pulse oximetry, and vital sign measurements will be summarized at each time point using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or shift tables where appropriate. Physical examination findings will be presented in a listing. |
| SAMPLE SIZE DETERMINATION | The evaluable sample size for this study is powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for oxycodone with at least 80% power.<br>Because of an anticipated dropout rate of 33%, a recruited sample size of 30 subjects is considered sufficient to ensure 20 evaluable subjects to assess the PK profiles of Oxycodone Oral Solution.<br>While the PK analysis will require a recruited sample size of 30 subjects, |

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| | the trial will enroll 110 subjects to gather adequate safety information in the pediatric/adolescent patient population. |
| STUDY AND TREATMENT DURATION | The sequence and maximum duration of the study periods will be as follows:<br>Screening is up to 14 days.<br>The total study duration for each subject is approximately 1 full day, excluding Screening.<br>The maximum treatment duration for each subject is 1 full day. |

## 3. TABLE OF CONTENTS

## 3.1 List of Tables

## 4. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ASA | American Society of Anesthesiologists |
| AUC | Area under the curve |
| $AUC_{0\text{-}inf}$ | Area under the concentration-time curve from Time Zero to infinity |
| $AUC_{0\text{-}t}$ | Area under the concentration-time curve from Time Zero to the last measurable concentration |
| $C_{max}$ | Observed maximum plasma concentration |
| CRA | Clinical research associate |
| CRF | Case report form |
| CRO | Contract Research Organization |
| CSR | Clinical study report |
| ECG | Electrocardiogram |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |
| FLACC | Face, Legs, Activity, Cry, Consolability Scale |
| GCP | Good Clinical Practice |
| HCl | Hydrochloride |
| ICH | International Conference on Harmonisation |
| IRB | Institutional review board |
| ITT | Intention-to-Treat Population |
| IV | Intravenous |
| $K_{el}$ | Elimination rate constant |
| kg | Kilogram |
| L | Liter |
| lbs | Pounds |
| mg | Milligram |
| min | Minutes |
| mL | Milliliter |
| NCA | Nurse-Controlled Analgesia |
| PK | Pharmacokinetic |
| RPM | Revolutions per minute |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |

| | |
|---|---|
| SOC | Standard of care |
| $t_{1/2}$ | Apparent elimination half-life |
| TBV | Total blood volume |
| $T_{max}$ | Time of maximum concentration |
| ULN | Upper Limit of Normal |
| USP | United States Pharmacopeia |

# 5. INTRODUCTION

## 5.1 Background and Rationale

### 5.1.1 Indication and Usage

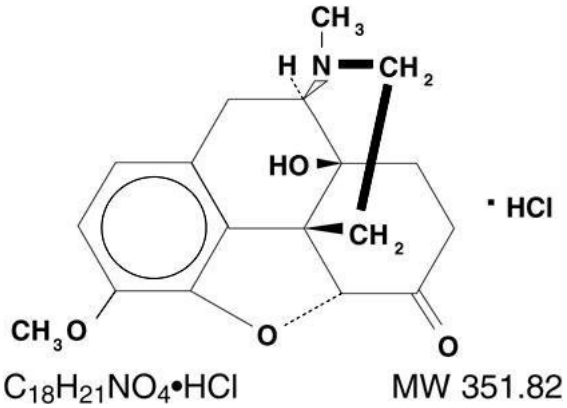
Oxycodone (4, 5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride) is a semisynthetic opioid that has been in clinical use since 1917 and approved for use in the US since 1950. Developed by VistaPharm, Inc., oxycodone hydrochloride (HCl) US Pharmacopeia (USP) oral solution, 5 mg per 5 mL, is an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate. This product was approved by the Food and Drug Administration (FDA) on January 12, 2012 (application New Drug Application 201194). In addition, Lehigh Valley Technologies, Inc. has developed Oxycodone Hydrochloride Oral Solution available as a 100 mg/5 mL (20 mg/mL) concentration which is indicated for use in opioid-tolerant patients only. This product was approved by the Food and Drug Administration (FDA) on October 20, 2010 (application New Drug Application 200535). The results of the study described with the current protocol will be utilized to meet regulatory requirements for both VistaPharm, Inc. and Lehigh Valley Technologies, Inc.

Oxycodone HCl is currently available in the US in a number of other forms and combinations. Oxycodone is a Schedule II controlled substance. The VistaPharm, Inc., oxycodone hydrochloride (HCl) (USP) oral solution, 5 mg per 5 mL, will be utilized for the purposes of this protocol.

### 5.1.2 Description

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17methylmorphinan-6-one hydrochloride and has the following structural formula:




### 5.1.3 Pharmacodynamics

Oxycodone is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of oxycodone are analgesia and sedation.

Oxycodone is similar to codeine and methadone in that it retains at least one-half of its analgesic activity when administered orally.

Additional detailed information on the pharmacodynamic properties of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

### 5.1.4 Pharmacokinetics

#### 5.1.4.1 Absorption

About 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison with a parenteral dose. This high oral bioavailability (compared to other oral opioids) is due to lower presystemic metabolism, first-pass metabolism, or both of oxycodone.

A single-dose food effect study was conducted in normal adult volunteers using the 5 mg/5 mL solution. The concurrent intake of a high fat meal was shown to enhance the extent (a 27% increase in the area under the plasma concentration versus time curve [AUC]) but not the rate of oxycodone absorption from the oral solution. In addition, food caused a delay in the time of maximum concentration ($T_{max}$) (1.25 to 2.54 hours).

#### 5.1.4.2 Distribution

Following intravenous (IV) administration, the volume of distribution for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk.

#### 5.1.4.3 Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone but not noroxycodone is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs.

#### 5.1.4.4 Elimination

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: up to 19% was reported for free oxycodone; up to 50% was reported for conjugated oxycodone; 0% was reported for free oxymorphone; no greater than 14% was reported for conjugated oxymorphone; and both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Additional detailed information on the physical, chemical, and pharmaceutical properties of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

### 5.1.5 Clinical Experience

Oxycodone hydrochloride USP oral solution has been studied in adult populations, with a focus on pharmacokinetics, safety, and tolerability. A total of 4 clinical pharmacokinetic (PK) and bioavailability studies have been conducted to support the development and labeling of oxycodone hydrochloride USP oral solution.

In addition, there are a number of published studies in the medical literature that report on the pharmacokinetics of oxycodone in clinical and nonclinical settings, in a variety of doses and routes of administration.[1-19]

### 5.1.6 Study Rationale

Despite published studies on dosing and pharmacokinetics in pediatric populations,[20-25] oxycodone has never received an official indication for use in children. Pursuant to the Pediatric Research Equity Act (21 USC 355c), the FDA has requested that VistaPharm, Inc. and Lehigh Valley Technologies, Inc. conduct a postapproval and postmarketing (Phase IV) PK and safety study in subjects < 17 years of age.

## 5.2 Summary of Potential Risks and Benefits

### 5.2.1 Potential Risks

The most frequently observed adverse events (AEs) reported with oxycodone include light headedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in subjects who can walk than in subjects who cannot walk, and some of

these adverse reactions may be alleviated if the subject lies down. Other AEs include euphoria, dysphoria, constipation, skin rash, and pruritus.

Additional detailed information on potential AEs and on specific warnings and precautions with the use of oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, can be found in the Approved Label and Full Prescribing Information (Appendix B).

Given that some of the subjects will be infants and young children, the effect of multiple blood draws can be considered a potential risk or adverse situation. A published review of the safe limits of blood sample volumes in child health research suggests that existing guidelines specify limits ranging from 1% to 5% of total blood volume (TBV) over 24 hours. However, the limited available evidence that includes findings from nonrandomized studies shows a minimal risk with one-off sampling of up to 5% of TBV.[26]

For subjects 2 to <17 years of age, this protocol specifies a maximum of 9 serial blood samples of 0.5 mL each for a total of 4.5 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. In addition, up to 10 mL will be allotted as discard volume for the 9 PK samples and the final laboratory testing drawn through the indwelling catheter. Existing blood draw guidelines for pediatric research suggest minimal risk is between 3% and 5% of total blood volume (TBV) over 24 hours or on a single draw and TBV is generally estimated at 75-80 mL/kg. For the smallest child permitted per protocol, in the 2 to <17 years of age group (weight: 28 lbs or 12.7 kg), the TBV would be estimated at 952.5 ml. The maximum safe volume drawn would therefore be between 28 and 47 mL, based on minimal risk at 3-5% TBV over 24 hours. The required 9.5 mL plus up to 10 mL of discard volume, or a cumulative volume of 19.5 mL, is well under the 3-5% of TBV guideline for the smallest eligible participant using the smallest estimation of TBV. [26]

For the child less than 2 years of age, there is a maximum of 7 serial blood samples of 0.5 mL each for a total of 3.5 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. The required 8.5 mL is under the 3-5% of TBV guideline.

### 5.2.2 Benefits

The size of the test dose (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to <17, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2) is designed to provide adequate analgesia for moderate to severe pain in substituting for the routinely prescribed postoperative pain regimen according to the custom of the attending physician and the institutional standard of care (SOC).

No other benefit is anticipated or expected for subjects participating in this study.

## 6. OBJECTIVE

The objective of this study is to characterize the pharmacokinetics and to evaluate the safety of single and multiple doses of Oxycodone Oral Solution in pediatric and adolescent subjects.

## 7. STUDY DESIGN

### 7.1 Overall Study Design and Plan

This is a Phase IV study to characterize the pharmacokinetics and to evaluate the safety of Oxycodone Oral Solution administered to pediatric and adolescent subjects following a surgical procedure. It is an open-label, multicenter study conducted at up to 10 sites. Subjects may be enrolled preoperatively, up to 14 days before surgery, or postoperatively with the expectation that they will require IV access after the surgery and postoperative analgesia with an opiate-level medication. After dosing with Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, 0.07 mg/kg for ages 13 to <17, and a dose to be determined based on PK modeling from the interim analyses for subjects under age 2), subjects will be carefully monitored for safety. A total of 110 pediatric and adolescent male or female subjects will be enrolled, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years. Subjects within each age group will be evenly distributed by age and gender.

An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 6 months to <2 years will receive will be based on an evaluation of the safety and PK observed from this interim analysis.

An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on an evaluation of the safety and PK observed from this interim analysis.

The study will consist of a Screening period (preoperatively, up to 14 days before surgery, or postoperatively); a predose check-in (Predose); a treatment period after surgery (Day 1, Time Zero); and an End-of-Study assessment. The total duration of the study, excluding Screening, will be approximately 1 full day.

Eligible subjects who provide assent (according to local standard of care or IRB directive) and whose parent(s) or legal guardian(s) provide consent as required will have study assessments performed at Screening. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone

medication that will not interfere with the measurement or metabolism of oxycodone. At this time (Predose), they will have a predose check-in to have eligibility confirmed.

After subjects ages 2 to <17 years have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

Water, Gatorade, Powerade, Pedialite, or Popsicles will be allowed for the first hour (1 hour) following dosing, but subjects must avoid fruit juice (excluding apple and grape), including fruit-containing popsicles, throughout the course of the study.

Subjects will undergo an End-of-Study assessment at least 24 hours after dosing with Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study. Subjects who discontinue the study for any reason will not be replaced.

Safety will be assessed, between time 0 and 24 hours post first study medication administration, by monitoring AEs, clinical laboratory test results, vital sign measurements, temperature, pulse oximetry, and physical examination findings.

The FLACC will be used to measure pain prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution in subjects under 2 years of age. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl or other rescue pain medication.

For subjects 2 to <17 years of age, serial blood samples for PK analysis will be collected for the determination of plasma concentrations of oxycodone at the predose time point (within 15 minutes of dosing); 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of

dosing); 30 (between 25-35 min) and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing.

### 7.2 Discussion of Study Design

This is an open-label, nonrandomized, multicenter study designed to assess the pharmacokinetics and safety of the product oxycodone hydrochloride USP oral solution, 5 mg per 5 mL, in pediatric and adolescent subjects <17 years of age following a surgical procedure and expected to require postoperative opioid analgesia and an indwelling IV catheter after being cleared for oral intake. Target enrollment will be 110 subjects, including a minimum of 20 subjects under age 2 (5 subjects ages 0 to <2 months, 5 subjects ages 2 to <6 months, and 10 subjects ages 6 months to <2 years), 30 ages 2 to 6 years, 30 ages 7 to 12 years and 30 ages 13 to <17 years, to evaluate safety in the population. Subjects within each age group will be evenly distributed by age and gender. In addition, this sample size will allow for an adequate evaluable population according to published population PK studies in children[21] and unofficial FDA guidance on sample size calculations based on estimates of clearance and volume of distribution.[27] Recruitment projections are based on a review of recent reports of adolescent scoliosis surgery showing that major specialty surgical centers average 10 to 20 patients per year in this age group.[28-32]

### 7.3 Study Sites

The study will take place at up to 10 sites in the US.

### 7.4 Point of Contact

A point of contact will be identified to provide subjects with information on the study, subject rights, and whom to contact in case of study-related injury. This information will be provided in the subject information and informed assent and consent forms.

## 8. SUBJECT POPULATION

### 8.1 Selection of Study Population

#### 8.1.1 Inclusion Criteria

A subject will be eligible for inclusion in the study if he or she meets the following criteria:

1 Is male or female <17 years of age at the time of dosing.

2 Subject 2 to <17 years of age, be in at least the 25% for weight according to the Center for Disease Control pediatric growth charts and weighs at least 28 lb at the time of dosing with study drug.

3 Is generally healthy defined as American Society of Anesthesiologists (ASA) Physical Status classification grade I or II (except for the condition for which the procedure is being performed), documented by medical history; physical examination

(including, but not limited to, the cardiovascular, gastrointestinal, respiratory, and central nervous systems); vital sign assessments; electrocardiogram (ECG); clinical laboratory assessments; and general observations.

4 Has a negative urine pregnancy test predose (for females of childbearing potential).

5 Is an outpatient prior to admission for a surgical procedure and is expected to remain hospitalized for at least 24 hours after dosing with study drug.

6 Is anticipated to have postsurgical pain requiring a parenteral analgesic regimen by using a short-acting opioid analgesic and is anticipated to be switched to an oral opioid for at least 1 dose (according to institution standard of care).

7 Has an indwelling access catheter for blood sampling.

8 Agrees to comply with all protocol requirements. If not old enough, the legally responsible parent(s) or legal guardian(s) must agree to comply with all protocol requirements.

9 Has been informed of the nature of the study, and informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, in accordance with institutional review board requirements.

### 8.1.2 Exclusion Criteria

A subject will be excluded from the study if he or she meets the following criteria:

1 Has the presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (except for the condition for which the procedure is being performed) greater than grade II on ASA Physical Status classification as determined by the clinical investigator.

2 Has any clinical laboratory test result documented as “alert”, “critical”, or “panic” per institution laboratory ranges or has aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2.0 x the upper limit of normal (ULN); total bilirubin > 1.5 x ULN; serum creatinine > 1.5 x ULN; or blood urea nitrogen > 1.5 x ULN.

3 Has a clinically significant illness (ASA Physical Status classification > II), except for the condition for which the procedure is being performed, in the 28 days before dosing with study drug as determined by the clinical investigator.

4 Is a lactating or breastfeeding female.

5 Uses any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug. Use of any monoamine oxidase inhibitor or St. John’s wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.

6 Consumes alcohol- or xanthine-containing products within 8 hours before dosing and during periods when blood samples are collected.

7 Consumes grapefruit, grapefruit products, Seville oranges, or pomelo-containing products within 5 days of dosing. Fruit juices, with the exception of apple and grape, will be prohibited during the study.

8 Is a smoker or has used nicotine or nicotine-containing products within 30 days of dosing.

9 Has a history of alcohol or drug addiction or abuse within the last year.

10 Temperature >100°F at time of initial administration of study medication.

11 Donated blood within 28 days or plasma within 14 days of dosing or plans to donate them within 4 weeks after completing the study.

12 Has a history of relevant drug allergies, food allergies, or both (i.e., allergy to oxycodone, allergy to related drugs, or any significant food allergy that could interfere with the study).

13 Is intolerant to direct venipuncture.

14 Received an investigational drug within 28 days of dosing.

15 Has taken oxycodone or oxymorphone within the 48 hours before anticipated dosing with study drug.

16 Is not suitable for entry into the study in the opinion of the investigator.

## 8.2 Removal of Subjects from Therapy or Assessment

All subjects are free to withdraw from participation in this study at any time for any reason and without prejudice.

The investigator may terminate a subject from the study at any time for lack of therapeutic effect that is intolerable to the subject or otherwise considered unacceptable, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or unsuitability for the study in the investigator's opinion to protect the subject's best interest.

If a subject is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate case report form (CRF). Whenever possible and reasonable, evaluations that were scheduled for study completion should be performed at the time of premature discontinuation.

Subjects who discontinue from the study will not be replaced.

# 9. STUDY TREATMENTS

## 9.1 Method of Assigning Subjects to Treatment Groups

### 9.1.1 Under Age 2

Subjects under age 2 who meet all eligibility criteria will receive a single dose of Oxycodone Oral Solution. This will be an open-label study and does not require randomization.

### 9.1.2 Ages 2 to <17

Subjects ages 2 to <17 who meet all eligibility criteria will be scheduled to receive single or multiple doses of Oxycodone Oral Solution. This will be an open-label study and does not require randomization.

## 9.2 Identification of Investigational Products

The study drug is Oxycodone Oral Solution (5 mg/5 mL) manufactured by VistaPharm (Largo, FL). Oxycodone Oral Solution is a red solution intended for oral administration.

Oxycodone Oral Solution will be supplied in 500-mL bottles. Oxycodone Oral Solution contains 4.5 mg of oxycodone free base per 5 mL (5 mg oxycodone HCl/5 ml) and the following inactive ingredients: poloxamer 188 NF, sodium benzoate NF, citric acid anhydrous USP, glycerin natural USP, sorbitol solution 70% USP, FD&C Red #40, raspberry flavor, and water.

VistaPharm will provide an adequate supply of study drug to the sites.

Ketorolac for injection (15 mg/mL or 30 mg/mL), Morphine Sulfate for injection (2 mg/mL), and Fentanyl via NCA for use as a rescue medication will be provided by the study site pharmacy. Should other rescue medication be required they will be provided by the study site pharmacy.

## 9.3 Treatment Administered

The study drug will be administered only to eligible subjects under the supervision of the investigator or identified subinvestigator(s).

### 9.3.1 Under Age 2

Each subject will receive a single dose of Oxycodone Oral Solution in place of the standard analgesic dose after being postoperatively cleared to transition to oral pain medication. The dose will be determined based on an evaluation of the safety and PK observed from the interim analyses. Oxycodone Oral Solution will be administered with an oral medication syringe.

### 9.3.2 Ages 2 to <17

Each subject will receive a dose of Oxycodone Oral Solution (0.1 mg/kg for children ages 2 to 6, 0.08 mg/kg for ages 7 to 12, and 0.07 mg/kg for ages 13 to <17) in place of

the standard analgesic dose after being postoperatively cleared to transition to oral pain medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. Oxycodone Oral Solution will be administered with an oral medication syringe.

## 9.4 Storage

Oxycodone Oral Solution will be stored in a locked facility with restricted access. This may be a locked cabinet or room for which the number of keys is limited and in compliance with standards of the Drug Enforcement Administration for Schedule II narcotics. Chain of custody of the study drug will be followed in accordance with the individual site's standard procedures, which will be documented by the site and provided to the sponsor. The study drug will be stored at controlled room temperature between 20°C and 25°C (68°F-77°F). The sponsor will provide to the site personnel instructions for the storage and return of used and unused study drug.

## 9.5 Labeling

Each container of study drug will be labeled with study-specific information that meets all applicable regulatory requirements.

## 9.6 Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of study drug, including the date, quantity, batch or code number, and identification of subjects (subject number and initials) who received study drug. The investigator will not supply study drug to any person except those named as subinvestigators on the FDA 1572, designated staff, and subjects in this study. The investigator will not dispense study drug from any sites other than those listed on the FDA 1572. Study drug may not be relabeled or reassigned for use by other subjects.

Upon completion of the study, unused supplies of study drug will be reconciled by the investigator and returned to the sponsor as directed.

## 9.7 Blinding and Unblinding Treatment Assignment

Not applicable.

## 9.8 Selection of Dose in the Study

The published literature on treatment of pediatric pain with oxycodone reports doses ranging from 0.125 to 0.2 mg/kg, up to a maximum of 15 mg, for treatment of acute musculoskeletal pain, including suspected fractures in emergency room settings, for treatment of undifferentiated abdominal pain, and for pediatric burn wound care in outpatient clinics.[33-36] A PK modeling has been conducted using the data derived from the 4 studies conducted in the adult population. Based on these population data, the test dose chosen for subjects ages 2 to 6 is 0.1 mg/kg, ages 7 to 12 is 0.08 mg/kg, ages 13 to <17 is 0.07 mg/kg, and a dose to be determined based on PK modeling from the interim

analyses for subjects under age 2, given when the subjects have been cleared for oral intake and in place of the analgesic regimen (nonoxycodone and nonoxymorphone) prescribed postoperatively for subjects by their attending physicians according to institutional SOCs. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed.

The dose for subjects under age 2 will be determined based on an evaluation of the safety and PK observed from the interim analyses.

## 9.9 Selection of Timing of Dose for Each Subject

The design of the study and the timing of dosing were selected to provide the appropriate basis for assessing the PK parameters of oxycodone following administration of the first dose.

## 9.10 Treatment Compliance

All study drugs will be administered in the hospital by study personnel and recorded in the CRF. Study personnel will confirm that the subject ingests the entire dose of study drug.

The date and time of study drug administration will be recorded on the appropriate page of the CRF. If a subject does not receive the study drug, the reason for the missed dose will be recorded.

## 9.11 Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate CRF. The medication name, dose, including frequency, date, and indication for use must be recorded. Time of rescue medication will also be recorded. The medical monitor should be notified in advance of (or as soon as possible after) any instances in which prohibited therapies or rescue medications are administered. Medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the study medication may be given at the discretion of the investigator.

### 9.11.1 Permitted Therapies

Concomitant medications (with the exceptions described in Section 9.11.2) are allowed, but should be limited to only those medications considered necessary.

Nausea and vomiting are common opioid-induced AEs for which subjects do develop a tolerance. Subjects who undergo surgery requiring opioid analgesia for an extended period of time may develop these AEs. Therefore, it is expected that some subjects will need to be given an antiemetic. Any antiemetic used during treatment with study drug should be recorded as a concomitant medication.

### 9.11.2 Prohibited Therapies

Use of any medication known to be an inhibitor or inducer of CYP3A4 within 14 days (for inhibitors such as the azole-antifungal agents voriconazole and ketoconazole, macrolide antibiotics such as erythromycin, and protease inhibitors such as ritonavir) or 28 days (for inducers such as rifampin, carbamazepine, and phenytoin) of dosing with study drug through the end of the study is prohibited.

Use of any monoamine oxidase inhibitor or St. John's wort is prohibited from 28 days before dosing until 14 days after dosing. Standard daily dose multivitamins (nontherapeutic doses) may be taken until enrollment into the study but will be restricted during the study.

Restrictions:

Females of childbearing potential must be practicing abstinence or using a medically acceptable form of contraception (e.g., intrauterine device, hormonal birth control, or double-barrier method). For the purpose of this study, all females who are menstruating will be considered to be of childbearing potential unless they are biologically sterile or surgically sterile for more than 1 year.

Consumption of alcohol- or xanthine-containing products within 8 hours before dosing and during periods when blood samples are collected is prohibited. Consumption of grapefruit, grapefruit products, Seville oranges, or pomelo-containing products is prohibited within 5 days of dosing with study drug. All types of fruit juices, with the exception of apple and grape, and fruit-containing popsicles will be prohibited during the study.

Subjects who smoke or use nicotine or nicotine-containing products within 30 days of Screening will be excluded from study participation.

Subjects receiving excluded therapies will be ineligible for study enrollment or for continuation in the study at the discretion of the sponsor, investigator, medical monitor, or other authority.

## 9.12 Rescue Medication

In subjects ages 2 to <17 years, if pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

In subjects under age 2, if pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the FLACC, the subject will be given Fentanyl via NCA. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy..

## 10. STUDY PROCEDURES

Subjects' legally responsible parent(s) or legal guardian(s) will provide written informed consent and subjects will provide written informed assent (as appropriate) before any study-related procedures are initiated, including the cessation of prohibited concomitant therapy.

Table 2 (Section 17) presents the schedule of events to be performed during the study.

### 10.1 Screening (Day –14 to Day 1)

Subjects must be screened within 14 days before enrollment in the study. The following procedures will be performed at Screening:

- Obtain written informed consent and assent (as appropriate).
- Review inclusion and exclusion criteria.
- Collect demographic information.
- Record medical history, including prior and current therapies (e.g. prescription and nonprescription medications).
- Perform a physical examination including weight, height, body mass index, and vital signs (blood pressure, heart rate, respiratory rate, and temperature).
- Perform urine pregnancy test for all females of childbearing potential.
- Perform ECG. This may occur at the screening visit or at any time prior to study medication dosing.
- Collect blood and urine samples for clinical laboratory tests (complete blood count with differential, clinical chemistry, serology, and urinalysis) (Section 11.2.2).

### 10.2 Predose Check-in (Predose)

The predose check-in (Predose) can be performed the same day as surgery (Day 1) at which time eligibility and prior medications will be reviewed and updated as needed. Medical history will be recorded, if it was not completed at Screening, and vital signs will be obtained. Following surgery, subjects will receive standard care, including parenteral analgesia with a nonoxycodone, nonoxymorphone medication that will not interfere with the measurement or metabolism of oxycodone. Screening and Predose procedures may overlap and, if so, do not need to be repeated.

### 10.3 Open-Label Treatment (Day 1, After Surgery)

The following procedures will be performed on Day 1:

- Measure heart rate, and respiratory rate before dosing (within 90 minutes) with Oxycodone Oral Solution and every 15 minutes for 4 hours after dosing, then every 2 hours until 24 hours after the first dose of Oxycodone Oral Solution.
- Measure blood pressure before dosing (within 90 minutes) with Oxycodone Oral Solution and every 15 minutes for 4 hours after dosing, every 2 hours until 8 hours

after the first dose of Oxycodone Oral Solution, and 4 hours until 24 hours after the first dose of Oxycodone Oral Solution.

- Measure temperature predose and every 2 hours for 24 hours after the first dose of Oxycodone Oral Solution.
- Continuous pulse oximetry beginning minimally 1 hour prior to transition to oral pain medication through 8 hours after the last study dose of Oxycodone Oral Solution. The following timepoints will be captured in the CRF: predose, 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last study dose of Oxycodone Oral Solution.
- Assess pain in subjects under 2 years of age by using the FLACC prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the first dose of Oxycodone Oral Solution. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl or other rescue pain medication**.**
- Record concomitant medication use.
- Assess and record AEs prior to dosing and throughout the remainder of Day 1.
- For subjects 2 to <17 years of age, collect serial blood samples for PK analysis at the predose time point (within 15 minutes of dosing); 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 30 (between 25-35 min) and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing.
- After subjects ages 2 to <17 have been postoperatively cleared to transition to oral pain medication, Oxycodone Oral Solution will be administered at Time Zero of Day 1 in place of the standard analgesic medication. The first 10 subjects in each of the 2 to 6, 7 to 12 and 13 to <17 age groups, who will be included in the first interim analysis, will only receive 1 dose of Oxycodone Oral Solution. Subjects in these age groups enrolled in the study after the interim analysis is completed may receive additional doses every 4-6 hours as needed. If pain control is inadequate with Oxycodone Oral Solution, the investigator may administer an IV dose of ketorolac (0.5 mg/kg) every 6 hours or an IV dose of Morphine Sulfate (0.1 mg/kg) every 4 hours as rescue medication for breakthrough pain after dosing. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care.
- After subjects under age 2 have been postoperatively cleared to transition to oral pain medication, they will receive a single dose of Oxycodone Oral Solution at Time Zero of Day 1 in place of the standard analgesic medication. The dose will be determined based on PK modeling from the interim analyses. If pain control is inadequate with Oxycodone Oral Solution, as indicated by a score of moderate to severe (4-10) on the

FLACC, the subject will be given Fentanyl via NCA. Use of other rescue pain medication is permissible in accordance with hospital pain management guidelines or facilities standard of care. Any rescue medications used will be provided by the study site pharmacy.

Water, Gatorade, Powerade, and Popsicles will be allowed for the first hour (1 hour) following dosing, but subjects must avoid fruit juice (excluding apple and grape), including fruit-containing popsicles, throughout the course of the study.

## 10.4 **End-of-Study/Early Discontinuation**

Subjects will undergo an End-of-Study/Early Discontinuation assessment at least 24 hours after dosing with Oxycodone Oral Solution.

The following procedures will be performed at the End-of-Study/ Early Discontinuation visit:

- Measure vital signs (blood pressure, heart rate, and respiratory rate).
- Clinical laboratory testing (complete blood count with differential and clinical chemistry).
- Record concomitant medications.
- Record AEs.

After these procedures are performed, the study staff will determine whether it is safe for the subject to be discharged from the study.

# 11. STUDY ASSESSMENTS

## 11.1 Pharmacokinetics

Blood samples for PK assessments in the subjects 2 to <17 years of age will be collected at the predose time point (within 15 minutes of the first dose of Oxycodone Oral Solution); 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 4 (between 3-5 hrs), 6 (between 4-7 hrs), 8 (between 6-10 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after the first dose of Oxycodone Oral Solution. For subjects under age 2, serial blood samples for PK analysis will be collected prior to the first dose (within 15 minutes of dosing); 30 (between 25-35 min), and 60 (between 50-70 min) minutes after dosing; and 2 (between 110-130 min), 6 (between 4-7 hrs), 12 (between 12-18 hrs), and 24 (between 22-24 hrs) hours after dosing. Time Zero is the time of the first dose of Oxycodone Oral Solution.

The following PK parameters will be calculated:

- Area under the plasma concentration versus time curve from Time Zero to the last measurable concentration ($AUC_{0-t}$)
- Area under the plasma concentration versus time curve from Time Zero to infinity ($AUC_{0-inf}$)
- Ratio of $AUC_{0-t}$ to $AUC_{0-inf}$ ($AUC_{0-t}/AUC_{0-inf}$)
- Maximum measured plasma concentration ($C_{max}$)
- Time of the maximum measured plasma concentration ($T_{max}$)
- Apparent first-order terminal elimination rate constant ($K_{el}$)
- Apparent first-order terminal elimination half-life ($t_{1/2}$)
- Apparent clearance (CL/F)
- Volume of Distribution (V/F)

Other PK parameters may be calculated if deemed necessary.

### 11.1.1 Sample Collection

Blood collection will be performed using an existing indwelling access catheter (arterial or venous noted on CRF) at the start of the study (the use of Emla at the insertion site is permitted). All catheter lines should be appropriately flushed per institutional SOC before each blood draw. The 0.5-mL blood samples will be obtained and placed into 2.0-mL K3 ethylenediamine tetra-acetic acid tubes at each blood collection time point. The labels for all biological sample collection and storage containers will contain, at a minimum, the subject's number, protocol number, collection date, and scheduled collection time (study hour).

| Study Visit/Phase | Amount Collected (mL) | Number of Samples Collected | Total Amount Collected per Subject (mL) |
|---|---|---|---|
| Screening Serum Chemistry and Hematology[a] | 2.5 mL | 1 | 2.5 mL |
| Pharmacokinetics (2 to <17 years old) or | 0.5 mL | 9 | 4.5 mL |
| Pharmacokinetics (<2 years old) | 0.5 mL | 7 | 3.5 mL |
| End of Study Serum Chemistry and Hematology | 2.5 mL | 1 | 2.5 mL |
| Grand Total | -- | -- | 14.0 – 19.5 mL[b] |

[a] Where possible, results from clinical laboratory tests performed as part of the standard of care (SOC) will be used for study purposes. A separate blood draw for the clinical laboratory test portion of this protocol will occur only if the clinical laboratory tests as part of the SOC will not be available to coincide with the approximate time scheduled by the protocol. Preoperative or intraoperative (collected before the incision) test results must be available for review by the investigator before enrolling any subject into the study. Procedures for blood draws should follow institutional SOC.

[b] The total includes up to 10-mL discard volume for all 9 pharmacokinetic and laboratory testing samples, for the 2 to <17 year olds. Total blood volume drawn for research purposes must not exceed 3% of subject's total blood volume, which is assumed to be 75 mL/kg.

### 11.1.2 Blood Volumes

Existing blood draw guidelines for pediatric research suggest minimal risk is between 3% and 5% of total blood volume (TBV) over 24 hours or on a single draw, and TBV is generally estimated at 75-80 mL/kg. For the smallest child permitted per protocol from ages 2 to <17 years (weight: 28 lbs or 12.7 kg), the TBV would be estimated at 952.5 ml. The maximum safe volume drawn would therefore be between 28 and 47 mL, based on minimal risk at 3-5% TBV over 24 hours. The required 9.5 mL plus up to 10 mL of discard volume, or a cumulative volume of 19.5 mL, is well under the 3-5% of TBV guideline for the smallest eligible participant using the smallest estimation of TBV.[26] For the child less than 2 years of age, there is a maximum of 7 serial blood samples of 0.5 mL each for a total of 3.5 mL, plus 2.5 mL each for standard clinical chemistry and hematology tests at Screening and End of Study. The required 8.5 mL is under the 3-5% of TBV guideline.

### 11.1.3 Sample Processing

Immediately after collection, the tube will be gently inverted several times to mix the anticoagulant with the blood sample. The plasma fraction will be separated by placing the collection tube into a refrigerated centrifuge (4°C to 8°C) for 10 minutes at approximately 1500*g* or 3000 RPM. The plasma fraction will be withdrawn by pipette and placed into a polypropylene freezing tube. All sample collection and freezing tubes will be clearly labeled in a manner that identifies the subject and the collection time. Labels will be fixed to the freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be placed into a freezer at approximately –20°C (± 10°C) or below until transfer or shipment to the bioanalytical laboratory. The time between sample collection and freezer storage should not exceed 90 minutes. The additional blood draws for the purposes of pharmacokinetic assessment in this study do not pose more than a minor risk to the subjects.

### 11.1.4 Transport of Samples

The clinic staff will inventory the samples that are to be shipped to the bioanalytical laboratory. Each shipment will contain a complete set of samples. The second set of samples will not be shipped until receipt of the first shipment is confirmed. The inventory record will accompany the frozen plasma samples as per standard operating procedures.

For sample shipment requiring a third party courier, the samples will be packed in ample dry ice within a styrofoam container to ensure the samples will remain frozen for at least 72 hours and will be shipped via express delivery to the bioanalytical facility. Written notification of sample shipment will be communicated to the bioanalytical facility and the sponsor. The samples will be tracked to assure arrival in a safe and timely manner.

The shipment will be accompanied by logs showing the name of the study drug, protocol number, and the subject numbers and samples included in the shipment. Documentation noting what the condition of the samples upon arrival at the bioanalytical laboratory is and whether the amount of dry ice remaining is adequate or inadequate should be returned to the clinic.

The samples will be shipped frozen to PPD at the address provided in the laboratory manual.

### 11.1.5 Analytical Procedures

#### 11.1.5.1 Bioanalytical Sample Analyses

Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be measured using a validated liquid chromatography–mass spectrometry assay method. The validated detection range for oxycodone is 0.2 to 125 ng/mL in human plasma.

Samples from subjects who withdraw consent/assent or are dropped from the study will not be analyzed unless otherwise requested by the sponsor.

Samples from subjects who have been dropped from the study because of emesis according to PPD's standard operating procedures will not be analyzed.

#### 11.1.5.2 Bioanalytical Methodology

The bioanalytical method, assay validation, and bioanalytical report for this study will be provided by the bioanalytical investigator. Full validation of a sensitive assay for the appropriate analytes in biological fluid, including precision, accuracy, reproducibility, and selectivity will be included in the final report. The bioanalytical report will include the stability of the frozen samples, limit of quantitation, recovery, and a summary of the standard curves.

## 11.2 **Safety**

Safety will be assessed during the study by the monitoring and recording of AEs, clinical laboratory test results (hematology, biochemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, heart rate, and respiratory rate), temperature, pulse oximetry, and physical examination findings.

### 11.2.1 Adverse Events

#### 11.2.1.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence in a subject or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease temporally associated with the product, whether or not it is related to the product.

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a preexisting condition is considered an AE.

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For an investigational drug, the known information is contained in the investigator brochure. For a marketed drug, the known information is in the current package insert.

An unexpected AE is one for which the specificity or severity is not consistent with the current investigator brochure or package insert. For example, hepatic necrosis would be unexpected (greater severity) if the investigator brochure or package insert only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the investigator brochure or package insert only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected AEs. Examples include acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis and hepatitis with a first occurrence of fulminate hepatitis.

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be used in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent another of the outcomes listed in the definition previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the study drug or a hospital admission for a diagnostic evaluation of an AE does not qualify the condition or event as an SAE. A newly diagnosed pregnancy in a subject who has received a study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method and led to the pregnancy; however, the medical monitor should be made aware of a newly diagnosed pregnancy as soon as possible after site notification. A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE.

#### 11.2.1.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 11.2.1.1) are recorded in the CRF and reported to the medical monitor (Section 11.2.1.3). Adverse events will be collected from the time of the first dose of Oxycodone Oral Solution through the End of Study or Early Discontinuation visit.

At each visit, subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications). In addition to subject observations, AEs will be documented from any data collected on the AE page of the CRF (e.g., clinical laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

#### 11.2.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the CRF. Information to be collected includes drug treatment, type of event, time of onset, dose, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The latest version of the Medical Dictionary of Regulatory Activities will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator or designee must report any AE that meets the criteria for an SAE (Section 11.2.1.1) to the medical monitor within 24 hours of first becoming aware of the event by telephone. At the time of first notification, the investigator or designee should provide at a minimum the following information if available:

- Protocol number
- Subject's study identification and initials
- Subject's date of birth
- Date of dose of study drug
- Time and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken

Within 24 hours of the initial telephone notification, the investigator must fax a written SAE report form to the medical monitor. Any missing or additional relevant information about the SAE should be provided in a written follow-up SAE report form. The investigator should also ensure that any additional information requested about the event (e.g., hospital reports, autopsy reports) is provided as soon as it is available.

The investigator is required to comply with applicable regulations (including local laws and guidances) regarding the notification of the institutional review board (IRB).

The following contact information is to be used for SAE reporting:

Thomas J. Hochadel, Pharm.D.
Cognitive Research Corporation
200 Central Ave, Suite 1230
Saint Petersburg, FL 33701
Telephone: 727-897-9000
Cell: 727-515-1334
Fax: 727-897-9000

#### 11.2.1.3.1 Assessment of Severity

The severity or intensity of an AE refers to the extent to which it affects the subject's daily activities. Severity will be rated as mild, moderate, or severe using the following criteria:

| | |
|---|---|
| Mild: | Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. |
| Moderate: | Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. |
| Severe: | Interrupts usual activities of daily living, significantly affects |

clinical status, or may require intensive therapeutic intervention

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

#### 11.2.1.3.2 Assessment of Relationship

The investigator's assessment of an AE's relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

| | |
|---|---|
| Not related: | An AE with sufficient evidence to accept that there is no causal relationship to administration of study drug (e.g., no temporal relationship because the study drug was administered after the onset of the event, an investigation shows that study drug was not administered, another cause was proven.) |
| Unlikely related: | An AE, including a clinical laboratory test abnormality, with a temporal relationship to administration of study drug that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations. |
| Possibly related: | An AE with a reasonable time sequence to administration of study drug but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear. |
| Related: | An AE occurring in a plausible time relationship to administration of study drug and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable. |

#### 11.2.1.3.3 Definition of Adverse Event Start Date, Stop Date, and Duration

| | |
|---|---|
| Start date: | The date at which the AE is first noted |
| Stop date: | The date at which the AE is known to be resolved. If it has not known to have stopped, then indicate "ongoing." |
| Duration: | A time in days, hours, or minutes |

#### 11.2.1.3.4 Action(s) Taken

Action(s) taken may consist of the following (as appropriate):

| | |
|---|---|
| None: | No actions taken. |
| Discontinued study drug: | Study drug was permanently discontinued because of the AE. |
| Treatment: | Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure. |
| Others: | Other actions, such as an operative procedure, were required because of the AE. |

#### 11.2.1.3.5 Definition of Adverse Event Outcome at the Time of Last Observation

The AE outcome at the time of last observation will be classified as "resolved," "resolved with sequelae," "ongoing," "death," "other," or "unknown."

"Death" should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE. Although "death" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

### 11.2.1.4 Follow-up of Adverse Events

Any AE will be followed (up to a maximum of 30 days after dosing with study drug) to a satisfactory resolution or until the investigator deems the event to be chronic or not clinically significant or the subject to be stable. All findings relevant to the final outcome of an AE must be reported in the subject's medical record and recorded on the appropriate CRF.

### 11.2.2 Laboratory Safety Assessments

Samples for the following laboratory tests will be collected at the time points specified in the Schedule of Events (Section 17).

| | |
|---|---|
| Hematology: | Consists of complete blood count (hemoglobin, hematocrit, white blood cell count with differential, red blood cell count, and platelet count) |
| Serum chemistry: | Includes blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase), alanine aminotransferase (serum glutamic pyruvic transaminase), glucose (fasting), albumin, and total protein |
| Urinalysis: | Includes pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrites, leukocytes, urobilinogen, microscopic urine analysis if dipstick positive |
| Urine pregnancy test: | Conducted for females of childbearing potential only |

Each safety laboratory assessment blood sample will be 2.5 mL in volume. The total amount of blood to be drawn will be a maximum of 19.5 mL per subject, including 9 samples for PK assessments (0.5 mL each).

### 11.2.3 Vital Signs

Vital signs, including heart rate, respiratory rate, and blood pressure will be measured at the time points specified in the schedule of events (Section 17) after the subject has been in a sitting or supine position for 5 minutes. Body temperature will also be measured.

### 11.2.4 Pulse Oximetry

Continuous pulse oximetry will begin minimally 1 hour prior to transition to oral pain medication and will continue until 8 hours after the last study dose of Oxycodone Oral Solution. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last study dose of Oxycodone Oral Solution.

### 11.2.5 Electrocardiogram

An ECG will be performed pre-dose. This may occur at Screening or any time pre-dose, including intra-op.

### 11.2.6 Physical Examination

A standard physical examination will be performed at Screening or any time pre-dose, including intra-op. The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. Interim physical examinations will be performed at

the investigator's discretion if necessary to evaluate AEs or clinical laboratory abnormalities.

### 11.3 Faces, Legs, Activity, Crying, Consolability Scale (FLACC)

The Faces, Legs, Activity, Crying, Consolability Scale (FLACC) (See Attachment 17.4) will be used to measure pain in subjects under age 2 prior to and 20, 40, 60, 90, 120, 180, and 240 minutes after the dose of Oxycodone Oral Solution. The FLACC will also be administered prior to the subject receiving each dose of Fentanyl or other rescue pain medication.

The FLACC provides a simple framework for quantifying pain behaviors in children who are unable to verbalize the presence or severity of pain.[37]

Additionally, time of rescue medication will also be evaluated.

## 12. STATISTICAL METHODS

### 12.1 General Considerations

Descriptive statistics will be provided for all demographic, safety, and PK parameters. No formal statistical testing will be performed for this study.

A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written before database lock.

### 12.2 Analysis Populations

The following analysis populations are planned for this study:

- PK Population: the PK population will consist of all subjects who receive the study drug and have at least 1 measureable plasma concentration.
- PK Parameter Population: all subjects who receive study drug and for which at least one PK parameter can be determined.
- Safety Population: the safety population will consist of all subjects who receive the study drug.

### 12.3 Statistical Analyses

#### 12.3.1 Subject Disposition and Demographic Characteristics

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized by using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum).

Baseline demographic and background variables will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, along with the reason for withdrawal or discontinuation, will also be summarized.

### 12.3.2 Pharmacokinetic Analyses

Oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) plasma concentrations will be listed and summarized. Each subject's oxycodone plasma concentrations will be graphed using both a normal scale y-axis and a logarithmic scale y-axis. Mean oxycodone plasma concentrations for each age group will also be graphed using scheduled elapsed sampling times for both the normal and logarithmic scale y-axis.

Pharmacokinetic parameters will be listed for each subject and summarized by group. Key PK parameters will be contrasted with adult values from the previously conducted PK studies.

Other PK analyses may be performed as appropriate.

### 12.3.3 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities and will be summarized overall. Adverse events will also be summarized by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be summarized.

Actual values and changes from Baseline for clinical laboratory results, vital sign measurements, temperature, and pulse oximetry will be summarized at each time point using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or shift tables where appropriate. Physical examination findings will be presented in a listing.

### 12.3.4 Exploratory Analyses

The change from baseline in total FLACC Score will be summarized at each time point. The total amount of Fentanyl or other rescue pain medication will also be evaluated.

### 12.3.5 Interim Analyses

An interim analysis will be run after 10 subjects ages 2 to 6 years, 10 ages 7 to 12 years and 10 ages 13 to <17 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, adverse events (AEs) and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 6 months to <2 years will receive will be based on an evaluation of the safety and PK observed from this interim analysis.

An additional interim analysis will be run after at least half of the subjects aged 6 months to <2 years have completed the study. The interim analysis will include PK, pulse oximetry readings, vital sign measurements, AEs and concomitant medications. The dose of Oxycodone Oral Solution that the subjects ages 0 to <2 months and 2 months to <6 months will receive will be based on an evaluation of the safety and PK observed from this interim analysis.

### 12.4 Sample Size Determination

The evaluable sample size for this study is powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for oxycodone with at least 80% power.

Estimates of the coefficient of variation for the clearance and volume of distribution of oxycodone were 25.72% and 71.12%, respectively, and were based on estimated standard deviations of (log-transformed) clearance and volume as provided in a June 28, 2012 PK modeling technical report. The above mentioned values for % coefficient of variation (*%CV*) are derived using the approximation:

$$\%CV = \sqrt{e^{SD^2} - 1},$$

where *SD* are the standard deviations given in the technical report, with values of 0.2531 and 0.6398 for clearance and volume, respectively. The methodology for samples size calculation is as given in Wang, et al.[27]

Because of an anticipated dropout rate of 33%, a recruited sample size of 30 subjects is considered sufficient to ensure 20 evaluable subjects to assess the PK profiles of Oxycodone Oral Solution.

While the PK analysis will require a recruited sample size of 30 subjects, the trial will enroll 110 subjects to gather adequate safety information.

## 13. STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

### 13.1 Sponsor and Investigator Responsibilities

#### 13.1.1 Sponsor Responsibilities

The sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The sponsor reserves the right to withdraw a subject from the study (Section 8.2), to terminate participation of a study site at any time (Section 13.7), or to discontinue the study (Section 13.6.2).

The sponsor agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study according to the study protocol.

#### 13.1.2 Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.3), the investigator indicates that he or she has carefully read the protocol, fully understands the requirements, and agrees to

conduct the study in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 Good Clinical Practice (GCP) and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and his or her specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, study drugs, and their specific duties within the context of the study. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study will be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

### 13.2 **Site Initiation**

Study personnel may not screen or enroll subjects into the study until after receiving notification from the sponsor or its designee that the study can be initiated at the study site. The study site will not be authorized for study initiation until:

1. The study site has received the appropriate IRB approval for the protocol and the appropriate informed assent and consent.
2. All GCP documents have been submitted to and approved by the sponsor or its designee.
3. The study site has a Clinical Trial Agreement in place.
4. Study site personnel, including the investigator, have participated in a study initiation meeting.

## 13.3 Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study. Subjects may only be rescreened once 30 days or more after the original Screening visit. If a subject is eligible to enter the study after having previously failed screening, he or she will be assigned a new subject identification number.

## 13.4 Study Documents

All documentation and material provided by the sponsor for this study are to be retained in a secure location and treated as confidential material.

### 13.4.1 Good Clinical Practice Documents

The GCP documents are listed below.

- Signed original protocol; (i.e., Investigator's Agreement)
- Curricula vitae of all investigators and sub-investigators
- Name and address of the laboratories
- List of laboratory reference ranges, and if available, a quality certificate
- Form *Signature Log/Delegation of Study-related Duties*
- FDA Form 1572
- Any other relevant GCP documents

The GCP documents must be received from the investigator and reviewed and approved by the sponsor or designee before the study site can initiate the study and before the sponsor will authorize shipment of study drug to the study site. Copies of the investigator's GCP documents must be retained at the study site in a secure location. Additional documents, including a copy of the protocol and applicable amendment(s), the study drug, CRF completion guidelines, copies of regulatory references, copies of IRB correspondence, and study drug accountability records should also be retained as part of the investigator's GCP documents. It is the investigator's responsibility to ensure that copies of all required GCP documents are organized, current, and available for inspection.

### 13.4.2 Case Report Forms

By signing the Investigator's Agreement (Section 17.3), the investigator agrees to maintain accurate CRFs and source documentation as part of the case histories for all subjects whose legally responsible parent(s) or legal guardian(s) sign an informed consent form and subjects who sign assent (as appropriate).

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific CRF system used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, CRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the electronic data capture (EDC) system, if applicable, according to the completion guidelines provided by the sponsor or its designee.

The CRFs may be signed by the investigator or a subinvestigator. These signatures serve to attest that the information contained in the CRF is accurate and true.

### 13.4.3 Source Documents

All information recorded in the EDC system must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

During the study, select CRF data may be used as original data collection tools as long as a description of this documentation process is maintained in the investigator's study files. Before the study starts, a list identifying any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data) and considered to be source data will be provided.

Clinical laboratory data required by the protocol will be electronically transferred from the central laboratory to the sponsor or its designee. A paper copy of the laboratory results will be provided to the study site and should be retained with each subject's source data.

## 13.5 Data Quality Control

The sponsor and its designees will perform quality control checks on this clinical study.

### 13.5.1 Monitoring Procedures

The sponsor or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The assigned clinical research associate(s) (CRA[s]) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized sponsor personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review:

- Regulatory documents, directly comparing entries in the EDC system with the source documents
- Consenting procedures
- AE procedures
- Storage and accountability of study drug and study materials

The CRA will ask for clarification or correction of any noted inconsistencies. Procedures for correcting CRFs are described in the study manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.3), the investigator agrees to meet with the CRA(s) during study site visits; to ensure that study staff is available to the CRA(s) as needed; to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

### 13.5.2 • ata Management

he sponsor or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the sponsor's or CRO's standard operating procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the study manual.

### 13.5.3 Quality Assurance/Audit

This study will be subject to audit by the sponsor or designee. The audits will be undertaken to check compliance with GCP guidelines and will include a minimum of:

- In-house study file audit
- Audit of computer database quality control
- Audit of clinical report quality control

The sponsor or designee may conduct additional audits on a selection of study sites, requiring access to subject notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify the sponsor immediately.

## 13.6 Study Termination

The study may be terminated at the sponsor's discretion at any time and for any reason.

### 13.6.1 Regular Study Termination

The end of this study is defined as the date of the last visit of the last subject (last subject out or last subject last visit) participating in the study. Within 90 days of the end of the clinical study, the sponsor or designee will notify the IRB and regulatory authorities about the regular termination of the study as required.

### 13.6.2 Premature Study Termination

The study may be terminated prematurely for any reason and at any time by the sponsor, IRB, regulatory authorities, or the coordinating investigator. A decision to prematurely terminate the study is binding to all investigators of all study sites.

Within 15 days of premature termination of a clinical study, the sponsor or designee will notify the IRB and regulatory authorities as required. The sponsor or designee must clearly explain the reasons for premature termination.

If the study is terminated prematurely, all investigators must inform their subjects and take care of appropriate follow-up and further treatment of subjects to ensure protection of the subjects' interests. Study sites may be asked to have all subjects currently participating in the study complete all of the assessments for the Early Termination visit.

## 13.7 Study Site Closure

At the end of the study, all study sites will be closed. The sponsor may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol, applicable regulations and guidelines, or both
- Inadequate subject enrollment

### 13.7.1 Record Retention

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential until at least 2 years after the notification of submission of the final study report to regulatory authorities by the sponsor.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After completing the study, the sponsor will be provided with the original CRFs or at least a legible copy and retain the documents at least 5 years after the completion of the study.

One copy will remain with the investigator. The investigator shall arrange for the retention of the subject identification codes, subject files, and other source data until at least 5 years after notification of submission of the final study report to the regulatory authorities by the sponsor. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Copies of these study records (and all study-related documents, including source data) shall be kept by the investigator for the maximum period of time permitted by the hospital, institution, or private practice.

### 13.7.2 Sample Retention

Samples may be used for purposes related to this research. The samples will be stored until the sponsor has determined that specimens are no longer needed and the decision has been made that none of the samples needs to be reanalyzed. In addition, identifiable samples can be destroyed at any time at the request of the subject.

## 13.8 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval by the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency.

## 13.9 Use of Information and Publication

All information about the study drug, the sponsor's operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of study execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this study will be used by the sponsor in connection with the continued development of the study drug and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of the sponsor. Publication or other public presentation of study drug data resulting from this study requires prior review and written approval of the sponsor. Abstracts, manuscripts, and presentation

materials should be provided to the sponsor for review and approval at least 30 days prior to the relevant submission deadline. Data from individual study sites must not be published separately.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the investigator until the sponsor has reviewed, commented on, and authorized such a presentation or manuscript for publication.

## 14. FINAL CLINICAL STUDY REPORT

The sponsor will retain ownership of the data from this study.

The final CSR will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints.

The final CSR will be submitted to the regulatory authorities.

## 15. ETHICAL AND LEGAL CONSIDERATIONS

### 15.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents) and the 1996 Version of the Declaration of Helsinki.

### 15.2 Subject Information and Informed Consent

A properly constituted, valid IRB must review and approve the protocol, the investigator's informed assent and consent documents, and related subject information and recruitment materials before the start of the study.

It is the responsibility of the investigator to ensure that informed consent and assent (as appropriate) have been obtained from the legally responsible parent(s) or legal guardian(s) and the subject, respectively, before any activity or procedure is undertaken that is not part of routine care.

### 15.3 Approval by Institutional Review Board

A valid IRB must review and approve this protocol before study initiation. Written notification of approval is to be submitted by the investigator to the sponsor monitor before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor IRB Approval Form or written documentation from the IRB containing the same information.

Until written approval by the IRB has been received by the investigator, no subject may undergo any procedure solely for determining eligibility for this study.

Protocol amendments must also be reviewed and approved by the IRB. Written approval from the IRB, or a designee, must be received by the sponsor before implementation.

This written approval will consist of a completed IRB Approval form or written documentation from the IRB containing the same information.

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# 17. ATTACHMENTS

## 17.1 Schedule of Events

### Table 2: Schedule of Events

| STUDY PROCEDURES | Screening (Day –14 to 1) | OUTPATIENT HOSPITALIZATION | | End of Study/Early Discontinuation[b] |
|---|---|---|---|---|
| | | Predose Check-in (Predose) [a] | Treatment (Day 1, Time Zero) | |
| Informed consent/assent | X | | | |
| Eligibility (inclusion/exclusion) | X | X | | |
| Prior medication assessment | X | X | | |
| Medical history | X | X | | |
| Vital signs | X | X | X | X |
| Temperature | X | | X | |
| Pulse Oximetry | | | X | |
| FLACC | | | X | |
| Physical examination[c] | X | | | |
| Clinical laboratory tests[d] | X | | | X |
| Urine pregnancy test (females) | X | X | | |
| Safety electrocardiogram | X or | X | | |
| Study drug administration | | | X | |
| Pharmacokinetic sampling | | | X | |
| Adverse event assessment | | | X[e] | X |
| Concomitant medication assessment | X | X | X | X |

[a] The predose check-in (Predose) can be performed the same day as surgery (Day 1). At the predose check-in, eligibility and prior medications will be reviewed and updated as needed. Medical history will be recorded if it was not completed at Screening.

[b] Subjects will undergo an End-of-Study/Early Discontinuation assessment at least 24 hours after dosing with Oxycodone Oral Solution. At that time, if the study staff determines that it is safe to do so, subjects will be discharged from the study.

[c] The physical examination will include measurements of height, weight, and body mass index.

[d] Complete blood count with differential and clinical chemistry will be performed at Screening and End of Study/Early Discontinuation. Urinalysis will be performed at Screening only.

[e] During the study, subjects will be asked about adverse events. If an adverse event occurs, clinic staff may advise the subject to remain at the hospital until a decision is made that it is safe for the subject to be discharged.

## 17.2 **Treatment Day Procedures**

### Table 3: Treatment Day Procedures

| **Time, related to 1st dose of Oxycodone Oral Solution** | **Pre-dose** | **0 min** | **5 min** | **10 min** | **15 min** | **30 min** | **45 min** | **60 min** | **1 hr 15 min** | **1 hr 30 min** | **1 hr 45 min** | **2 hr** | **2 hr 15 min** | **2 hr 30 min** | **2 hr 45 min** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vital signs (BP, HR, Resp.) | X | | | | X | X | X | X | X | X | X | X | X | X | X |
| Temperature | X | | | | | | | | | | | X | | | |
| Pulse oximetry[a] | X | | X | X | | X | | X | | | | X | | | |
| PK sampling (Under age 2) | X[b] | | | | | X | | X | | | | X | | | |
| PK sampling (2 to <17) | X[b] | | | | | X | | X | | | | X | | | |
| Study drug administration[c] | | X | | | | | | | | | | | | | |
| FLACC[d] | X | | | | | | | | | | | | | | |
| AE evaluation[e] | | | | | | | | | | | | | | | |
| Con meds query[e] | | | | | | | | | | | | | | | |

| **Time, related to 1st dose of Oxycodone Oral Solution** | **3 hr** | **3 hr 15 min** | **3 hr 30 min** | **3 hr 45 min** | **4 hr** | **6 hr** | **8 hr** | **10 hr** | **12 hr** | **14 hr** | **16 hr** | **18 hr** | **20 hr** | **22 hr** | **24 hr** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HR, Resp.[a] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood Pressure (BP) | X | X | X | X | X | X | X | | X | | X | | X | | X |
| Temperature | | | | | X | X | X | X | X | X | X | X | X | X | X |
| Pulse oximetry[a] | | | | | X | X | X | | | | | | | | |
| PK sampling (Under age 2) | | | | | | X | | | X | | | | | | X |
| PK sampling (2 to <17) | | | | | X | X | X | | X | | | | | | X |
| Study drug administration[c] | | | | | | X | | | | | | | | | |
| FLACC[d] | | | | | X | | | | | | | | | | |
| AE evaluation[e] | | | | | | | | | | | | | | | |
| Con meds query[e] | | | | | | | | | | | | | | | |

a Pulse oximetry will begin minimally 1 hour prior to transition to oral pain medication and will continue until 8 hours after the last study dose. The following timepoints will be captured in the CRF: 5, 10, 30 and 60 minutes, 2 hours, then every 2 hours until 8 hours after the last dose of Oxycodone Oral Solution.
b Blood samples for pharmacokinetic assessment will be collected at the predose time point (within 15 minutes of dosing);
c The study drug will be administered after the surgery when subjects have been postoperatively cleared to transition to oral pain medication in place of the standard analgesic medication. If pain control is inadequate with study drug, the investigator may administer rescue medication for breakthrough pain after dosing.
d The FLACC will also be administered prior to the subject receiving each rescue dose of Fentanyl or other rescue pain medication.
e AEs and Con Meds will be monitored throughout the course of the study.

## 17.3 **Investigator's Agreement**

| | |
|---|---|
| PROTOCOL NUMBER: | 2012O004 |
| PROTOCOL TITLE: | A PHASE IV STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS |
| FINAL PROTOCOL: | AMENDMENT #1; 11 July 2013<br>AMENDMENT #2; 18 September 2013 |

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with VistaPharm, Inc. and Lehigh Technologies, Inc., or designee during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an investigational product during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

## 17.4 **Faces, Legs, Activity, Cry, Consolability Scale (FLACC)**

| **Categories** | **Scoring** | | |
|---|---|---|---|
| | **0** | **1** | **2** |
| **Face** | No particular expression or smile | Occasional grimace or frown, withdrawn, disinterested | Frequent to constant quivering chin, clenched jaw |
| **Legs** | Normal position or relaxed | Uneasy, restless, tense | Kicking, or legs drawn up |
| **Activity** | Lying quietly, normal position, moves easily | Squirming, shifting back and forth, tense | Arched, rigid or jerking |
| **Cry** | No cry, (awake or asleep) | Moans or whimpers; occasional complaint | Crying steadily, screams or sob, frequent complaints |
| **Consolability** | Content, relaxed | Reassured by occasional touching, hugging or being talked to, distractible | Difficult to console or comfort |

## 18. APPENDICES

A. Address List
B. OXYCODONE HYDROCHLORIDE USP ORAL SOLUTION, Approved Label and Full Prescribing Information

## A. Address List

### 18.1.1 Sponsors

| | |
|---|---|
| Name: | VistaPharm, Inc. |
| Address: | 7256 Ulmerton Road<br>Largo, FL 33771 |
| Phone: | (727) 530-1633 |
| Fax: | (727) 531-5427 |
| Project Manager: | Melissa L. Goodhead, MSc, RAC<br>President<br>Pharmaceutical Project Solutions, Inc. |

| | |
|---|---|
| Name: | Lehigh Valley Technologies, Inc. |
| Address: | 514 North 12th Street<br>Allentown, PA 18102 |
| Phone: | (610) 782-9780 |
| Project Manager: | Melissa L. Goodhead, MSc, RAC<br>President<br>Pharmaceutical Project Solutions, Inc. |

### 18.1.2 Clinical Research Organization

| | |
|---|---|
| Name: | Cognitive Research Corporation |
| Address: | 200 Central Avenue, Suite 1230<br>Saint Petersburg, FL 33703 |
| Phone: | (727) 897-9000 |
| Fax: | (727) 897-9009 |
| Project Manager: | Eva M. Kemper, MSHS<br>Director, Clinical Projects |

# B. OXYCODONE HYDROCHLORIDE USP ORAL SOLUTION, Approved Label and Full Prescribing Information

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Oxycodone Hydrochloride Oral Solution safely and effectively. See full prescribing information for Oxycodone Hydrochloride Oral Solution.**
**Oxycodone Hydrochloride Oral Solution CII**
**Initial U.S. Approval: 1950**

**WARNING: RISK OF MEDICATION ERRORS**

**Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution 5 mg per 5 mL to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.**

**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.**

**INDICATIONS AND USAGE**

Oxycodone Hydrochloride Oral Solution is an opioid agonist indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. (1)

**DOSAGE AND ADMINISTRATION**

- Dosage should be individualized based on the severity of pain, and patient response. (2.1)
- Patients who have not been receiving opioid analgesics should be started in dosing range of 5 to 15 mg every 4 to 6 hours as needed. (2.2)
- When converting from a fixed ratio opioid/non-opioid regimen, the dose should be titrated in response to the level of analgesia and adverse effects and depending on continuation or non-continuation of the non-opioid component. (2.3)
- In patients with hepatic impairment or end-stage renal failure, dose initiation should follow a conservative approach. (2.7)

**DOSAGE FORMS AND STRENGTHS**

- Oral Solution containing 5 mg per 5 mL oxycodone hydrochloride, available in 500 mL bottle and 5 mL unit dose cup. (3)

**CONTRAINDICATIONS**

- Respiratory depression in the absence of resuscitative equipment. (4)
- Suspected or confirmed paralytic ileus. (4)
- Acute or severe bronchial asthma or hypercarbia. (4)
- Known hypersensitivity to oxycodone. (4)

**WARNINGS AND PRECAUTIONS**

- Use caution when prescribing, dispensing, and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between different concentrations and between mg and mL, which could result in accidental overdose and death. (5.1)
- Increased risk or respiratory depression in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnea, or upper airway obstruction. (5.2)
- Oxycodone hydrochloride is a Schedule II controlled substance with an abuse liability similar to other opioids. (5.3)
- Assess patients for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. (5.3)
- Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.4)
- Increased risk of respiratory depression and of elevation of cerebrospinal fluid pressure in patients with head injury, intracranial lesions or pre-existing increase in intracranial pressure. (5.5)
- Risk of severe hypotension in patients with compromised ability to maintain blood pressure. (5.6)
- May obscure the diagnosis or clinical course in patients with acute abdominal conditions. (5.7)
- Use with caution in patients with biliary tract disease and acute pancreatitis. (5.8)
- The mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery may be impaired. (5.10)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.11)

**ADVERSE REACTIONS**

- The most common adverse reactions are nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence. (6)

**To report SUSPECTED ADVERSE REACTIONS CONTACT FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

**To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

**DRUG INTERACTIONS**

- Skeletal muscle relaxants: Enhance action of and increased degree of respiratory depression (7.2)
- Drugs that inhibit CYP3A4 activity may decrease clearance of oxycodone and lead to an increase in oxycodone plasma concentrations. (7.4)

**USE IN SPECIFIC POPULATIONS**

- Safety and efficacy in pediatric patients below the age of 18 have not been established. (8.4)
- Geriatric patients, Renal Impairment, and Hepatic impairment: Use caution during dose selection, starting at the low end of the dosing range while carefully monitoring for side effects. (8.5, 8.6, 8.7)

**See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide**

**Revised: 03/2012**

**FULL PRESCRIBING INFORMATION: CONTENTS ***



*** Sections or subsections omitted from the full prescribing information are not listed**

## FULL PRESCRIBING INFORMATION

### WARNING: RISK OF MEDICATION ERRORS

**Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution 5 mg per 5 mL to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed.**
**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.**

### 1 INDICATIONS AND USAGE

Oxycodone Hydrochloride Oral Solution is an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate.

### 2 DOSAGE AND ADMINISTRATION

Take care when prescribing and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume. Always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately.
Selection of patients for treatment with oxycodone hydrochloride should be governed by the same principles that apply to the use of similar opioid analgesics. Individualize treatment in every case, using non-opioid analgesics, opioids on as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality, and the American Pain Society.

#### 2.1 Individualization of Dosage

As with any opioid drug product, adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. In the selection of the initial dose of oxycodone hydrochloride, give attention to the following:
• the total daily dose, potency and specific characteristics of the opioid the patient has been taking previously;

- the reliability of the relative potency estimate used to calculate the equivalent oxycodone hydrochloride dose needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medications;
- the type and severity of the patient's pain;
- risk factors for abuse, addiction or diversion, including a prior history of abuse, addiction or diversion.

The following dosing recommendations, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.
Continual re-evaluation of the patient receiving oxycodone hydrochloride is important, with special attention to the maintenance of pain management and the relative incidence of side effects associated with therapy. During chronic therapy, especially for non-cancer-related pain, periodically re-assess the continued need for the use of opioid analgesics.
During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient, and the caregiver/family.

**2.2 Initiation of Therapy**
Start patients who have not been receiving opioid analgesics on Oxycodone Hydrochloride Oral Solution in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain.
Titrate the dose based upon the individual patient's response to their initial dose of Oxycodone Hydrochloride Oral Solution. Adjust the dose to an acceptable level of analgesia taking into account the improvement in pain intensity and the tolerability of the oxycodone by the patient.

**2.3 Conversion to Oral Oxycodone Oral Solution**
There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dose of Oxycodone Hydrochloride. It is better to underestimate a patient's 24-hour oral Oxycodone Hydrochloride dose and make available rescue medication than to overestimate the 24-hour oral Oxycodone Hydrochloride dose and manage an adverse experience of overdose.
**2.3.1 Conversion from Fixed-Ratio Opioid/Acetaminophen, Opioid/Aspirin, or Opioid/Nonsteroidal Combination Drugs**

When converting patients from fixed ratio opioid/non-opioid drug regimens it may be necessary to titrate the dose of Oxycodone Hydrochloride Oral Solution in response to the level of analgesia and adverse effects.

**2.3.2 Conversion from Non-Oxycodone Opioids**

In converting patients from other opioids to oxycodone hydrochloride, close observation and adjustment of dosage based upon the patient's response to oxycodone hydrochloride is imperative. Physicians and other healthcare professionals are advised to refer to published relative potency information, keeping in mind that conversion ratios are only approximate.

**2.4 Conversion from Oral Oxycodone Hydrochloride to Controlled-Release Oral Oxycodone**
The relative bioavailability of Oxycodone Hydrochloride Oral Solution compared to controlled-release oxycodone is unknown, so conversion to controlled-release tablets must be accompanied by close observation for signs of excessive sedation.

**2.5 Maintenance of Therapy**
Continual re-evaluation of the patient receiving Oxycodone Hydrochloride Oral Solution is important, with special attention to the maintenance of pain management and the relative incidence of side effects associated with therapy. If the level of pain increases, effort should be made to identify the source of increased pain, while adjusting the dose as described above to decrease the level of pain.
During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), the continued need for the use of opioid analgesics should be re-assessed as appropriate.

**2.6 Cessation of Therapy**
When a patient no longer requires therapy with Oxycodone Hydrochloride Oral Solution for the treatment of their pain, it is important that therapy be gradually discontinued over time to prevent the development of an opioid abstinence syndrome (narcotic withdrawal). In general, therapy can be decreased by 25% to 50% per day with careful monitoring for signs and symptoms of withdrawal [see *Drug Abuse and Dependence (9.3) section for description of the signs and symptoms of withdrawal*]. If the patient develops these signs or symptoms, the dose should be raised to the previous level and titrated down more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. It is not known at what dose of Oxycodone Hydrochloride Oral Solution that treatment may be discontinued without risk of the opioid abstinence syndrome.

**2.7 Dosage in patients with Hepatic or Renal Impairment**
Follow a conservative approach to dose initiation in patients with hepatic or renal impairment. Monitor patients closely and adjust dose based on clinical response.

**3 DOSAGE FORMS AND STRENGTHS**
Oxycodone Hydrochloride Oral Solution, 5 mg per 5 mL is available in a 500 mL bottle and 5 mL unit dose cup.

**4 CONTRAINDICATIONS**
Oxycodone Hydrochloride Oral Solution is contraindicated in
- patients with respiratory depression in the absence of resuscitative equipment.
- any patient who has or is suspected of having paralytic ileus.
- patients with acute or severe bronchial asthma or hypercarbia.
- patients with known hypersensitivity to oxycodone, oxycodone salts, or any component of this product

**5 WARNINGS AND PRECAUTIONS**

**5.1 Risk of Medication Errors**
Use caution when prescribing, dispensing, and administering Oxycodone Hydrochloride Oral Solution to avoid dosing errors due to confusion between mg and mL, and other oxycodone solutions with different concentrations, which could result in accidental overdose and death. Use caution to ensure the dose is communicated clearly and dispensed accurately. Always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution to ensure the dose is measured and administered accurately.

**5.2 Respiratory Depression**
Respiratory depression is the primary risk of Oxycodone Hydrochloride Oral Solution. Respiratory depression occurs most frequently in elderly or debilitated patients, and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation, or following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.
Use Oxycodone Hydrochloride Oral Solution with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of Oxycodone Hydrochloride Oral Solution may increase airway resistance and decrease respiratory drive to the point of apnea. Consider alternative non-opioid analgesics, and use Oxycodone Hydrochloride Oral Solution only under careful medical supervision at the lowest effective dose in such patients.

**5.3 Misuse and Abuse of Opioids**
Oxycodone Hydrochloride Oral Solution is a Schedule II controlled substance with an abuse liability similar to other opioids. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.
Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids.
Oxycodone Hydrochloride Oral Solution can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Oxycodone Hydrochloride Oral Solution in situations where the physician or pharmacist is concerned about an increased risk of misuse or abuse.
Oxycodone Hydrochloride Oral Solution may be abused by injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence (9.2) and Overdosage (10)]*.
Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

**5.4 Interactions with Alcohol and Drugs of Abuse**
Oxycodone Hydrochloride Oral Solution may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, profound sedation, coma or death may result *[see Drug Interactions (7.1)]*.

**5.5 Use in Head Injury and Increased Intracranial Pressure**
In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of Oxycodone Hydrochloride Oral Solution and its potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following $CO_2$ retention) may be markedly exaggerated. Furthermore, Oxycodone Hydrochloride Oral Solution can produce effects on

pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients w head injuries.

**5.6 Hypotensive Effect**
Oxycodone Hydrochloride Oral Solution may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or general anesthetics or other agents which compromise vasomotor tone. Oxycodone Hydrochloride Oral Solution may produce orthostatic hypotension in ambulatory patients. Administer Oxycodone Hydrochloride Oral Solution with caution in hypovolemic patients, sucl as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Administer Oxycodone Hydrochloride Oral Solution with caution to patients in circulatory shock, since vasodilatation produced by the drug ma further reduce cardiac output and blood pressure.

**5.7 Gastrointestinal Effects**
Do not administer Oxycodone Hydrochloride Oral Solution to patients with gastrointestinal obstruction, especially paralytic ileus because oxycodone hydrochloride diminishes propulsive peristaltic waves in the gastrointestinal tract and may prolong the obstruction.
The administration of Oxycodone Hydrochloride Oral Solution may obscure the diagnosis or clinical course in patients with acute abdominal condition.

**5.8 Use in Pancreatic/Biliary Tract Disease**
Use Oxycodone Hydrochloride Oral Solution with caution in patients with biliary tract disease, including acute pancreatitis, as oxycodone hydrochloride may cause spasm of the sphincter of Oddi and diminish biliary and pancreatic secretions.

**5.9 Special Risk Groups**
Use Oxycodone Hydrochloride Oral Solution with caution and in reduced dosages in patients with severe renal or hepatic impairmer Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients *[see Use in Specific Populations (8.5)]* .
Exercise caution in the administration of Oxycodone Hydrochloride Oral Solution to patients with CNS depression, toxic psychosis, acute alcoholism and delirium tremens. All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.
Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. In case of accidental ingestion, seek emergency medical help immediately.

**5.10 Driving and Operating Machinery**
Caution patients that oxycodone hydrochloride could impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.
Caution patients about the potential combined effects of Oxycodone Hydrochloride Oral Solution with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol *[see Drug Interactions (7.)]*.

**5.11 Cytochrome P450 3A4 Inhibitors and Inducers**
Since the CYP3A4 isoenzyme plays a major role in the metabolism of oxycodone, drugs that alter CYP3A4 activity may cause changes in clearance of oxycodone which could lead to changes in oxycodone plasma concentrations. The expected clinical results with CYP3A4 inhibitors would be an increase in oxycodone plasma concentrations and possibly increased or prolonged opioid effec The expected clinical results with CYP3A4 inducers would be a decrease in oxycodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone.
If co-administration is necessary, caution is advised when initiating Oxycodone Hydrochloride Oral Solution treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.4) and Clinical Pharmacology (12.3)]*.

**5.12 Seizures**
Oxycodone Hydrochloride Oral Solution may aggravate convulsions in patients with convulsive disorders, and all opioids may indu or aggravate seizures in some clinical settings.

**6 ADVERSE REACTIONS**
The following serious adverse reactions are described, or described in greater detail, in other sections:
- Respiratory depression [see *Warnings and Precautions (5.2)*]
- Seizures [see *Warnings and Precautions (5.12)*]
- Hypotension [see *Warnings and Precautions (5.6)*]

• Spasm of the sphincter of Oddi and increases in the serum amylase level [see *Warnings and Precautions (5.8)*]

Serious adverse reactions that may be associated with oxycodone therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock [see *Overdose (10.1) and Warnings and Precautions (5.1, 5.3)*].
The less severe adverse events seen on initiation of therapy with oxycodone are also typical opioid side effects. These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include nausea, constipation, vomiting, headache, and pruritus.
In many cases the frequency of adverse events during initiation of opioid therapy may be minimized by careful individualization of starting dosage, slow titration and the avoidance of large rapid swings in plasma concentration of the opioid. Many of these adverse events will abate as therapy is continued and some degree of tolerance is developed, but others may be expected to remain throughout therapy.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In all patients for whom dosing information was available (n=191) from the open-label and double-blind studies involving immediate-release oxycodone, the following adverse events were recorded in oxycodone treated patients with an incidence ≥ 3%. In descending order of frequency they were: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.
The following adverse experiences occurred in less than 3% of patients involved in clinical trials with oxycodone:
*Body as a Whole:* abdominal pain, accidental injury, allergic reaction, back pain, chills and fever, fever, flu syndrome, infection, neck pain, pain, photosensitivity reaction, and sepsis.
*Cardiovascular:* deep thrombophlebitis, heart failure, hemorrhage, hypotension, migraine, palpitation, and tachycardia.
*Digestive:* anorexia, diarrhea, dyspepsia, dysphagia, gingivitis, glossitis, and nausea and vomiting.
*Hemic and Lymphatic:* anemia and leukopenia.
*Metabolic and Nutritional:* edema, gout, hyperglycemia, iron deficiency anemia and peripheral edema.
*Musculoskeletal:* arthralgia, arthritis, bone pain, myalgia and pathological fracture.
*Nervous:* agitation, anxiety, confusion, dry mouth, hypertonia, hypesthesia, nervousness, neuralgia, personality disorder, tremor, and vasodilation.
*Respiratory:* bronchitis, cough increased, dyspnea, epistaxis, laryngismus, lung disorder, pharyngitis, rhinitis, and sinusitis.
*Skin and Appendages:* herpes simplex, rash, sweating, and urticaria.
*Special Senses:* amblyopia.
*Urogenital:* urinary tract infection

## 7 DRUG INTERACTIONS

### 7.1 CNS Depressants
Patients receiving narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Oxycodone Hydrochloride Oral Solution may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dosage of Oxycodone Hydrochloride Oral Solution. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

### 7.2 Neuromuscular Blocking Agents
Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

### 7.3 Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as Oxycodone Hydrochloride Oral Solution. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of Oxycodone Hydrochloride Oral Solution and/or may precipitate withdrawal symptoms in these patients.

### 7.4 Agents Affecting Cytochrome P450 Enzymes
CYP3A4 Inhibitors

A published study showed that the co-administration with voriconazole, a CYP3A4 inhibitor, significantly increased the plasma concentrations of oxycodone. Inhibition of CYP3A4 activity by its inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, significantly decreased plasma oxycodone concentrations. Induction of CYP3A4 activity by its inducers, such as rifampin, carbamazepine, and phenytoin, may lead to a lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to oxycodone. If co-administration is necessary, caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via the Cytochrome P450 Isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. However, clinicians should be aware of this possible interaction.

**7.5 Monoamine Oxidase Inhibitors (MAOIs)**
MAOIs have been reported to intensify the effects of at least one opioid drug, causing anxiety, confusion and significant depression of respiration or coma. The use of Oxycodone Hydrochloride Oral Solution is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

**7.6 Anticholinergics**
Anticholinergics or other medications with anticholinergic activity, when used concurrently with opioid analgesics including oxycodone hydrochloride, may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**
Pregnancy Category B: There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during pregnancy only if clearly needed.

Teratogenic Effects

Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that oxycodone administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a $mg/m^2$ basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a $mg/m^2$ basis), respectively was not teratogenic or embryo-fetal toxic.

Nonteratogenic Effects

Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

**8.2 Labor and Delivery**
Oxycodone Hydrochloride Oral Solution is not recommended for use in women during or immediately prior to labor. Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. Neonates, whose mothers received opioid analgesics during labor, should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

**8.3 Nursing Mothers**
Low levels of oxycodone have been detected in maternal milk. The amount of oxycodone hydrochloride delivered to the infant depends on the plasma concentration of the mother, the amount of milk ingested by the infant, and the extent of first-pass metabolism. Because of the potential for serious adverse reactions in nursing infants from oxycodone hydrochloride including respiratory depression, sedation and possibly withdrawal symptoms, upon cessation of oxycodone hydrochloride administration to the mother, decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**8.4 Pediatric Use**
The safety and efficacy of Oxycodone Hydrochloride Oral Solution in pediatric patients below the age of 18 have not been established.

**8.5 Geriatric Use**
Elderly patients (aged 65 years or older) may have increased sensitivity to oxycodone hydrochloride. In general, use caution when selecting a dose for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

**8.6 Hepatic Impairment**
Since oxycodone is extensively metabolized, its clearance may decrease in hepatic failure patients. Follow a conservative approach to dose initiation in patients with hepatic impairment, monitor patients closely and adjust the dose based on clinical response.

**8.7 Renal Impairment**
Information from oxycodone tablets indicate that patients with renal impairment (defined as a creatinine clearance <60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function. Use a conservative approach to dose initiation in patients with renal impairment, monitor patients closely and adjust the dose based on clinical response.

**9 DRUG ABUSE AND DEPENDENCE**

**9.1 Controlled Substance**
**Oxycodone hydrochloride is a mu-agonist opioid of the morphine type and is a Schedule II controlled substance. Oxycodone Hydrochloride Oral Solution, like other opioids used in analgesia, can be abused and is subject to criminal diversion.**

**9.2 Abuse**
Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.
"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.
The risks of misuse and abuse should be considered when prescribing or dispensing Oxycodone Hydrochloride Oral Solution. Concerns about abuse and addiction, should not prevent the proper management of pain, however. Treatment of pain should be individualized, balancing the potential benefits and risks for each patient.
Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.
**Oxycodone Hydrochloride Oral Solution is intended for oral use only. Abuse of Oxycodone Hydrochloride Oral Solution poses a risk of overdose and death. The risk is increased with concurrent abuse of alcohol and other substances. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.**
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.
**Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms** *[see Use in Specific Populations (8.2)].*

**9.3 Dependence**
Tolerance to opioids is demonstrated by the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). If tolerance develops, or if pain severity increases, a gradual increase in dose may be required. The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the effect is desirable (e.g., analgesia) or undesirable (e.g., nausea). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are frequent during chronic opioid therapy.
Patients using Oxycodone Hydrochloride Oral Solution chronically (for several weeks) should be instructed that they should contact their health care providers if they notice the need to increase dosing to treat symptoms of pain or they experience symptoms of withdrawal upon abrupt cessation of dosing.
The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.
In general, taper opioids rather than abruptly discontinue *[see Dosage and Administration (2.6)].*

## 10 OVERDOSAGE

### 10.1 Signs and Symptoms

Acute overdose with Oxycodone Hydrochloride Oral Solution can be manifested by respiratory depression (a decrease in respiratory rate and/or end tidal volume. Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, pulmonary edema, cardiac arrest, and death. Oxycodone Hydrochloride Oral Solution may cause miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12)]* .

### 10.2 Treatment

Give primary attention to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures including oxygen and vasopressors should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of oxycodone hydrochloride, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to opioid antagonists is suboptimal or only brief in nature, administer additional antagonist as directed by the manufacturer of the product.

Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. Administer such agents cautiously to persons who are known, or suspected to be physically dependent on oxycodone. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome.

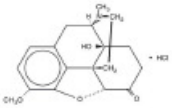
In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. Reserve use of an opioid antagonist for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, initiate administration of the antagonist with care and titrate with smaller than usual doses.

## 11 DESCRIPTION

Oxycodone Hydrochloride Oral Solution, USP, 5mg/5mL: Each 5 mL's is for oral administration and contains 5 mg of oxycodone hydrochloride USP.

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula:



$C_{18}H_{21}NO_4$•HCl MW 351.82

The 5 mg per 5 mL Oxycodone Hydrochloride Oral Solution contains equivalent of 4.5 mg of oxycodone free base per 5 mL's and contains the following inactive ingredients: Poloxamer 188 NF, Sodium Benzoate NF, Citric Acid Anhydrous USP, Glycerin Natural USP, Sorbitol Solution 70% USP, FD&C Red #40 , Raspberry Flavor and Water.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Oxycodone, as the hydrochloride salt, is a full opioid agonist whose principal therapeutic action is analgesia.

### 12.2 Pharmacodynamics

Effects on Central Nervous System

Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. A significant feature of opioid-induced analgesia is that it occurs without loss of consciousness. The relief of pain by morphine-like opioids is relatively selective, in that other sensory modalities, (e.g., touch, vibrations, vision, hearing, etc.) are not obtunded.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on Gastrointestinal Tract and Other Smooth Muscle

Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla. The frequency and severity of emesis gradually diminishes with time.

Oxycodone may cause a decrease in the secretion of hydrochloric acid in the stomach that reduces motility while increasing the tone of the antrum, stomach, and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone, in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown.

**12.3 Pharmacokinetics**
The activity of Oxycodone Hydrochloride Oral Solution is primarily due to the parent drug oxycodone.
Absorption

The oral bioavailability of oxycodone is 60 - 87%. This high oral bioavailability (compared to other oral opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone.

Food Effect

Presence of food may slightly delay the rate ($C_{max}$ and $T_{max}$) and enhance the extent of absorption (AUC) of oxycodone from Oxycodone Hydrochloride Oral Solution. Overall, food is not expected to have a clinically significant impact on the absorption of Oxycodone Hydrochloride Oral Solution.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.3)]*.

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, noroxymorphone, which are subsequently glucuronidated. CYP3A4 mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a less contribution from CYP2D6 mediated O-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that

of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of Oxycodone Hydrochloride Oral Solution was approximately 3.5 hours.

Special Populations

*Geriatric*

Information obtained from oxycodone tablets indicate that the plasma concentrations of oxycodone did not appear to be increased in patients over of the age of 65.

*Gender*

Information obtained from oxycodone tablets support the lack of gender effect on the pharmacokinetics of oxycodone.

*Hepatic Impairment*

Since oxycodone is extensively metabolized, its clearance may be decreased in hepatic failure patients *[see Use in Special Populations (8.6)]*.

*Renal Impairment*

Information obtained from oxycodone tablets indicate that patients with renal impairment (defined as creatinine clearance < 60 mL/min) had higher plasma concentrations of oxycodone than subjects with normal renal function *[see Use in Special Populations (8.7)]*.

*Drug-Drug Interactions*

*CYP3A4 Inhibitors*

CYP3A4 is the major enzyme involved in noroxycodone formation. A published study showed that the co-administration of voriconazole, a CYP3A4 inhibitor, increased oxycodone AUC and $C_{max}$ by 3.6 and 1.7 fold, respectively.

*CYP3A4 Inducers*

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and $C_{max}$ values by 86% and 63%, respectively.

*CYP2D6 Inhibitors*

Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone hydrochloride was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay *(Salmonella typhimurium* and *Escherichia coli)* or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

Impairment of Fertility

The potential effects of oxycodone on male and female fertility have not been evaluated.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**
Oxycodone Hydrochloride Oral Solution, USP, 5 mg per 5 mL is available as follows:
NDC 66689-403-16: 500 mL bottle packaged with calibrated measuring cup
NDC 66689-401-01: 5 mL unit dose cup
NDC 66689-401-50: Case contains 50 unit dose cups of 5 mL (NDC 66689-401-01), packaged in 5 trays of 10 unit dose cups each

**16.2 Storage and Handling**
All opioids, including Oxycodone Hydrochloride Oral Solution, are liable to diversion and misuse both by the general public and healthcare workers and should be handled accordingly.
Dispense in a tight, light-resistant container as defined in the USP/NF.
Keep in secured area and protect from diversion.
Store at controlled room temperature 20°-25°C (68°- 77°F).

**17 PATIENT COUNSELING INFORMATION**
***See Medication Guide***
Provide the following information to patients receiving Oxycodone Hydrochloride Oral Solution or their caregivers:

- Advise patients that Oxycodone Hydrochloride Oral Solution is a narcotic pain medication, and should be taken only as directed.
- Advise patients that sharing oxycodone can result in fatal overdose and death.
- Advise patients that Oxycodone Hydrochloride Oral Solution is a potential drug of abuse. They must protect it from theft. It should never be given to anyone other than the individual for whom it was prescribed.
- Advise patients to keep Oxycodone Hydrochloride Oral Solution in a secure place out of the reach of children. When Oxycodone Hydrochloride Oral Solution is no longer needed, the unused solution should be destroyed by flushing down the toilet.
- Advise patients how to measure and take the correct dose of Oxycodone Hydrochloride Oral Solution, and to always use the enclosed calibrated measuring cup when administering Oxycodone Hydrochloride Oral Solution, to ensure the dose is measured and administered accurately.
- Advise patients whenever the prescribed concentration is changed to avoid dosing errors which could result in accidental overdose and death.
- Advise patients not to adjust the dose of Oxycodone Hydrochloride Oral Solution without consulting with a physician or other healthcare professional.
- Advise patients that Oxycodone Hydrochloride Oral Solution may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Advise patients started on Oxycodone Hydrochloride Oral Solution or patients whose dose has been adjusted to refrain from any potentially dangerous activity until it is established that they are not adversely affected.
- Advise patients that Oxycodone Hydrochloride Oral Solution will add to the effect of alcohol and other CNS depressants (such as antihistamines, sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and monoamine oxidase [MAO] inhibitors).
- Advise patients not to combine Oxycodone Hydrochloride Oral Solution with central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, and not to combine with alcohol because dangerous additive effects may occur, resulting in serious injury or death.
- Advise women of childbearing potential who become or are planning to become pregnant to consult a physician prior to initiating or continuing therapy with Oxycodone Hydrochloride Oral Solution.

- Advise patients that safe use in pregnancy has not been established and that prolonged use of opioid analgesics including Oxycodone Hydrochloride Oral Solution during pregnancy may cause fetal-neonatal physical dependence, and neonatal withdrawal may occur.
- If patients have been receiving treatment with Oxycodone Hydrochloride Oral Solution for more than a few weeks and cessation of therapy is indicated, counsel them on the importance of safely tapering the dose and that abruptly discontinuing the medication could precipitate withdrawal symptoms. Provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Advise patients taking Oxycodone Hydrochloride Oral Solution of the potential for severe constipation; appropriate laxatives and/or stool softeners as well as other appropriate treatments should be initiated from the onset of opioid therapy.
- Advise patients of the most common adverse events that may occur while taking Oxycodone Hydrochloride Oral Solution: constipation, nausea, somnolence, lightheadedness, dizziness, sedation, vomiting, and sweating.
- Advise patients to call 911 or the local Poison Control center, and get emergency help immediately if they take more Oxycodone Hydrochloride Oral Solution than prescribed, or overdose.
- Advise patients, that if they miss a dose, to take the missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and go back to their regular dosing schedule. Do not take two doses at once unless instructed by their healthcare provider.

**DEA Order Form Required**
Manufactured by:
*VistaPharm®*
Largo, FL 33771
VP 2013R1
01/12
To request medical information contact VistaPharm, Inc. at 1-727-530-1633.

**MEDICATION GUIDE**
**Oxycodone Hydrochloride**
**(ox-ee-CO-dohn) (CII)**
**Oral Solution**
Rx Only

**IMPORTANT: Keep Oxycodone Hydrochloride Oral Solution in a safe place away from children. Accidental use by a child is a medical emergency and can cause death. If a child accidentally takes Oxycodone Hydrochloride Oral Solution, get emergency help right away.**

Read the Medication Guide that comes with Oxycodone Hydrochloride Oral Solution before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

**What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Oral Solution?**
**Oxycodone Hydrochloride Oral Solution can cause serious side effects, including death.**
- **Take Oxycodone Hydrochloride Oral Solution exactly as prescribed by your healthcare provider.** If you take the wrong dose or strength of Oxycodone Hydrochloride Oral Solution, you could overdose and die.
- **It is especially important when you take Oxycodone Hydrochloride Oral Solution that you know exactly what dose and strength to take, and the right way to measure your medicine.** Your healthcare provider or pharmacist should show you the right way to measure your medicine. Always use the dosing cup provided with Oxycodone Hydrochloride Oral Solution to help make sure you measure the right amount.
- **Do not drink alcohol.** Using alcohol with Oxycodone Hydrochloride Oral Solution may increase your risk of dangerous side effects, including death.

**What is Oxycodone Hydrochloride Oral Solution?**
Oxycodone Hydrochloride Oral Solution is in a group of drugs called narcotic pain medicine. Oxycodone Hydrochloride Oral Solution is only for adults who have moderate to severe pain.
- A prescription medicine that is used to manage moderate to severe pain that is expected to last a short period of time (acute), and pain that continues around-the-clock and is expected to last for a long period of time (chronic).

- Oxycodone Hydrochloride Oral Solution is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.
- Prevent theft, misuse or abuse. Keep Oxycodone Hydrochloride Oral Solution in a safe place to keep it from being stolen. Oxycodone Hydrochloride Oral Solution can be a target for people who misuse or abuse prescription medicines or street drugs.
- Never give Oxycodone Hydrochloride Oral Solution to anyone else, even if they have the same symptoms you have. It may harm them or even cause death.
- Selling or giving away this medicine is against the law.
- It is not known if Oxycodone Hydrochloride Oral Solution is safe and effective in children under age 18 years of age.

**Who Should Not Take Oxycodone Oral Solution?**
**Do not take Oxycodone if you:**
- are having breathing problems and there is no emergency medical equipment nearby
- have a bowel blockage called paralytic ileus
- are having an asthma attack or have severe asthma, trouble breathing, or lung problems
- are allergic to oxycodone or any of the ingredients in Oxycodone Hydrochloride Oral Solution. See the end of this Medication Guide for a complete list of ingredients in Oxycodone Hydrochloride Oral Solution

**What should I tell my healthcare provider before taking Oxycodone Hydrochloride Oral Solution?**
**Before taking Oxycodone Hydrochloride Oral Solution, tell your healthcare provider if you:**
- have trouble breathing or lung problems
- have had a head injury
- have liver or kidney problems
- have adrenal gland problems, such as Addison's disease
- have severe scoliosis that affects your breathing
- have thyroid problems
- have problems urinating or enlargement of your prostate
- have or had convulsions or seizures
- have a past or present drinking problem or alcoholism
- have hallucinations (seeing or hearing things that are not really there) or other severe mental problems
- have constipation or other bowel problems
- have problems with your pancreas or gallbladder
- have past or present substance abuse or drug addiction
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if Oxycodone Hydrochloride Oral Solution will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
  If you take Oxycodone Hydrochloride Oral Solution regularly before your baby is born, your newborn baby may have signs of withdrawal because their body has become used to the medicine. Signs of withdrawal in a newborn baby can include:

| | |
|---|---|
| • irritability | • vomiting |
| • being very active | • diarrhea or more stools than normal |
| • problems sleeping | • weight loss |
| • high pitched cry | • shaking (tremors) |

If you are taking Oxycodone Hydrochloride Oral Solution right before your baby is born, your baby could have breathing problems.

- are breast-feeding or plan to breastfeed. Some Oxycodone Hydrochloride Oral Solution passes into your breast milk. A nursing baby could become very sleepy or have difficulty breathing or feeding well. If you stop breastfeeding, your baby may have withdrawal symptoms. See the list of withdrawal symptoms above. You and your healthcare provider should decide if you will take Oxycodone Hydrochloride Oral Solution or breastfeed.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Sometimes the doses of medicines that you take with Oxycodone Hydrochloride Oral Solution may need to be changed if used together. Be especially careful about taking other medicines that make you sleepy such as:

- sleeping pills
- other pain medicines
- anti-nausea medicines
- tranquilizers
- muscle relaxants
- anti-anxiety medicines
- antihistamines
- anti-depressants
- monoamine oxidase inhibitors (MAOIs): Do not take Oxycodone Hydrochloride Oral Solution if you already take an MAOI or within 14 days after you stop taking an MAOI medicine

Ask your healthcare provider if you are not sure if your medicine is one listed above.
Do not take other medicines while using Oxycodone Hydrochloride Oral Solution until you have talked with your healthcare provider or pharmacist. They will tell you if it is safe to take other medicines with Oxycodone Hydrochloride Oral Solution.
**Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.**

**How Should I Take Oxycodone?**

- See **"What is the most important information I should know about Oxycodone Hydrochloride Oral Solution?"**
- **Take Oxycodone Hydrochloride Oral Solution exactly as prescribed**. Do not change your dose unless your healthcare provider tells you to. Your healthcare provider may change your dose after seeing how the medicine affects you. Call your healthcare provider if your pain is not well controlled with your prescribed dose of Oxycodone Hydrochloride Oral Solution.
- **Make sure you understand exactly how to measure your dose**. Always use the dosing cup provided with our Oxycodone Hydrochloride Oral Solution to help make sure you measure the right amount. See the Patient Instructions for Use at the end of this Medication Guide for information about how to measure your dose the right way. Ask your healthcare provider or pharmacist if you are not sure what dose of Oxycodone Hydrochloride Oral Solution you should take or if you are not sure how to use the dosing cup.
- **Do not stop taking Oxycodone Hydrochloride Oral Solution suddenly**. If you have been taking Oxycodone Hydrochloride Oral Solution for more than a few weeks, stopping it suddenly can make you sick with withdrawal symptoms (for example, nausea, vomiting, diarrhea, anxiety, and shivering). If your healthcare provider decides you no longer need Oxycodone Hydrochloride Oral Solution, ask how to slowly reduce this medicine. Do not stop taking Oxycodone Hydrochloride Oral Solution without talking to your healthcare provider.
- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at one time unless your healthcare provider tells you to.
- If you take too much Oxycodone Hydrochloride Oral Solution call your healthcare provider or your local Poison Control Center right away or go to the nearest hospital emergency room right away.
- Talk with your healthcare provider regularly about your pain to see if you still need to take Oxycodone Hydrochloride Oral Solution.

**What Should I Avoid While Taking Oxycodone?**

- **You should not drink alcohol while using Oxycodone Hydrochloride Oral Solution. Drinking alcohol with Oxycodone Hydrochloride Oral Solution may increase your risk of having dangerous side effects or death.**

- **Do not drive, operate heavy machinery, or do other dangerous activities,** especially when you start taking Oxycodone Hydrochloride Oral Solution and when your dose is changed, until you know how Oxycodone Hydrochloride Oral Solution affects you. Oxycodone can make you sleepy. Ask your healthcare provider to tell you when it is okay to do these activities.

**What are the Possible Side Effects of Oxycodone?**

**Oxycodone Hydrochloride Oral Solution can cause serious side effects, including:**

- See **"What is the most important information I should know about Oxycodone Hydrochloride Oral Solution?"**

- **Oxycodone can cause serious breathing problems that can become life-threatening, especially if Oxycodone Hydrochloride Oral Solution is used the wrong way.** Call your healthcare provider or get help right away if:
- your breathing slows down
- you have shallow breathing (little chest movement with breathing)
- you feel faint, dizzy, confused, or
- you have any other unusual symptoms

  These can be symptoms that you have taken too much Oxycodone Hydrochloride Oral Solution (overdose) or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away.**

- **Oxycodone Hydrochloride Oral Solution can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down. Low blood pressure is also more likely to happen if you take other medicines that can also lower your blood pressure. Severe low blood pressure can happen if you lose blood or take certain other medicines.

- **Oxycodone can cause physical dependence.** Do not stop taking Oxycodone or any other opioid without talking to your healthcare provider about how to slowly stop your medicine. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction. Tell your healthcare provider if you have any of these symptoms of withdrawal while slowly stopping Oxycodone:

| | |
|---|---|
| • feel restless | • trouble sleeping |
| • tearing eyes | • runny nose |
| • sweating | • yawning |
| • chills or hair on your arms "stand up" | • nausea, loss of appetite, vomiting |
| • muscle aches, backache | • diarrhea, stomach area (abdominal) cramps |
| • dilated pupils of your eyes | • increase in your blood pressure |
| • feel irritable or anxious | • breathing faster, or your heart beats faster |

- **There is a chance of abuse or addiction with Oxycodone Hydrochloride Oral Solution.** The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

- **Seizures: Oxycodone Hydrochloride Oral Solution may cause seizures or make seizures that you already have worse.**

**Call your healthcare provider if you have any of the symptoms listed above.**

**Common side effects of Oxycodone Hydrochloride Oral Solution include:**

| | |
|---|---|
| • nausea | • dizziness |
| • constipation | • weakness |
| • vomiting | • drowsiness |
| • headache | • sweating |
| • itching | • lightheadedness |
| • trouble sleeping | |

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including Oxycodone Hydrochloride Oral Solution. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking Oxycodone Hydrochloride Oral Solution.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of Oxycodone Hydrochloride Oral Solution. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Oxycodone Hydrochloride Oral Solution?**

- Store Oxycodone Hydrochloride Oral Solution at controlled room temperature between 68°F - 77°F (20°C - 25°C).
- Protect Oxycodone Hydrochloride Oral Solution from moisture and light.
- When Oxycodone Hydrochloride Oral Solution is no longer needed, the unused solution should be destroyed by flushing down the toilet.

**Keep Oxycodone Hydrochloride Oral Solution out of the reach of children. Accidental overdose by a child is a medical emergency and can lead to death.**

**General information about Oxycodone Hydrochloride Oral Solution**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Oxycodone Hydrochloride Oral Solution for a condition for which it was not prescribed.
**Do not give your Oxycodone Hydrochloride Oral Solution to other people, even if they have the same symptoms you have. Selling or giving away Oxycodone Hydrochloride Oral Solution may harm others, may cause death, and is against the law.**
This Medication Guide summarizes the most important information about Oxycodone Hydrochloride Oral Solution. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Oxycodone Hydrochloride Oral Solution that is written for healthcare professionals.
For more information about Oxycodone Hydrochloride Oral Solution, contact VistaPharm, Inc. at (727) 530-1633.

**What are the ingredients in Oxycodone Hydrochloride Oral Solution?**

**Active ingredient: oxycodone hydrochloride**
**Inactive ingredients:** anhydrous citric acid, FD&C red #40, glycerin, poloxamer 188, purified water, raspberry flavor, sodium benzoate and sorbitol solution.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

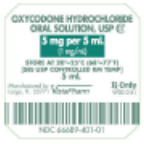
**Manufactured by:**

*VistaPharm®*
Largo, FL 33771
VP2100
01/12

**Rx Only**

**PRINCIPAL DISPLAY PANEL - 5 mL Cup Label**

**OXYCODONE HYDROCHLORIDE**
**ORAL SOLUTION, USP CII**
**5 mg per 5 mL**
(1 mg/mL)
**STORE AT 20°-25°C (68°-77°F)**
**[SEE USP CONTROLLED RM TEMP]**
**5 mL**
Manufactured by VistaPharm® Largo, FL 33771
**Rx Only**
VP2012 R1
NDC 66689-401-01




**PRINCIPAL DISPLAY PANEL - 500 mL Bottle Carton**

**NDC 66689-403-16**
**Oxycodone Hydrochloride**
**Oral Solution, USP CII**
**5 mg per 5 mL**
(1 mg/mL)
Each 5 mL Contains:
**Oxycodone Hydrochloride — 5 mg**
**USUAL DOSAGE:** See Package Insert for Complete Prescribing Information.
**PHARMACIST: Dispense the enclosed Medication Guide to each patient.**
**500 mL**
VistaPharm, Inc., Largo, FL 33771
**Rx**
**only**
**VP 2089**
*VistaPharm*®
66689-403-16


Revised: 03/2012

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page 18 of 18

# A PHASE IV STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF OXYCODONE ORAL SOLUTION IN PEDIATRIC AND ADOLESCENT SUBJECTS

| | |
|---|---|
| PROTOCOL DATE: | Version 7.1, Final 25 April 2013<br>Amendment #1, 11 July 2013<br>Amendment #2, 18 September 2013<br>Amendment #3, 8 April 2014 |
| SPONSORED BY: | VistaPharm, Inc.<br>7256 Ulmerton Road<br>Largo, FL 33771<br>Phone: (727) 530-1633<br><br>Lehigh Valley Technologies, Inc.<br>514 North 12th Street<br>Allentown, PA 18102<br>Phone: (610) 782-9780 |
| CONTRACT RESEARCH ORGANIZATION: | Cognitive Research Corporation<br>200 Central Avenue, Suite 1230<br>St. Petersburg, FL 33701<br>Phone: (727) 897-9000<br>Fax: (727) 897-9009 |