1 TITLE PAGE

PROTOCOL NUMBER:	**DLP-114-03 Revision E**
STUDY TITLE:	Open-Label Study in Stable Schizophrenia Patients to Evaluate the Safety, Tolerability, and Pharmacokinetics of Switching from Oral Risperidone to Risperidone Implant (DLP-114)
INVESTIGATIONAL AGENT/DEVICE:	DLP-114 (Risperidone Implant)
ROUTE OF ADMINISTRATION:	Subcutaneous implantation of the DLP-114 device
STUDY DESIGN:	Open-label, parallel group study to demonstrate a comparable PK profile between the marketed oral form of risperidone and risperidone administered subcutaneously with the DLP-114 device.
SPONSOR:	Delpor, Inc 150 North Hill Drive, Suite 25 Brisbane, CA 94005
PRINCIPAL INVESTIGATOR (PI):	Dr. David Walling, CEO, CNS Network, LLC
SPONSOR REPRESENTATIVE	Dr Frank Martin Chief Science Officer, Delpor, Inc.
STUDY CENTER:	CNS Network, LLC 12772 Valley View Street, Suite #3 Garden Grove, CA, 92845

CONFIDENTIALITY STATEMENT
Information contained in this protocol should not be disclosed, other than to those directly involved in the execution or ethical review of the study, without written authorisation from Delpor Inc. It is, however, permissible to provide information to a volunteer in order to obtain consent.

COVID-19
Due to recent developments related to the COVID-19 pandemic, Collaborative Neuroscience Research (the clinical research unit [CRU]) has implemented several procedures in accordance with the current CDC, WHO, FDA and other public regulatory guidance in order to ensure the safety of patients and CRU staff. These new measures include ensuring that trial participants test negative (or only IgG positive) for COVID-19 before they are admitted to the CRU, and practicing symptom recognition and monitoring for patients before each CRU visit. Additional COVID-19 testing may be conducted during the study at the PI's discretion. COVID-19 testing and other related assessments are not listed in this protocol as they are not specific to this study. Additional information on the CRU's COVID-19 policies can be found here: Policy on Research During the COVID-19 Pandemic

EMERGENCY CONTACT INFORMATION

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In case of a serious adverse event (See Section 16.5), the investigator will send a report within 24 hours of notification to:

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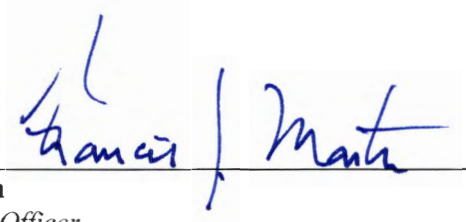
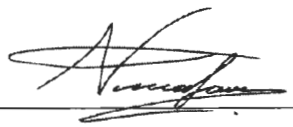
2 SPONSOR SIGNATURE PAGE

Study Title: Open-Label Study in Stable Schizophrenia Patients to Evaluate the Safety, Tolerability, and Pharmacokinetics of Switching from Oral Risperidone to Risperidone Implant (DLP-114).

By my signature, I confirm that I have reviewed this protocol and find its content to be acceptable.

Signature:  ***Date:*** 7/12/21

Frank Martin
Chief Science Officer

Signature:  ***Date:*** 07/12/2021

Tassos Nicolaou
President & Chief Executive Officer

3 PRINCIPAL INVESTIGATOR DECLARATION

Study Title: Open-Label Study in Stable Schizophrenia Patients to Evaluate the Safety, Tolerability, and Pharmacokinetics of Switching from Oral Risperidone to Risperidone Implant (DLP-114).

DECLARATION
By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, *Institutional Review Board (IRB)* procedures, instructions from Delpor Inc representatives, the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and local regulations governing the conduct of clinical studies.

Signature of Site Principal Investigator ***Date***

Printed Name of Site Principal Investigator

Institution Name:

4 PROTOCOL SYNOPSIS

Study Title:	Open-Label Study in Stable Schizophrenia Patients to Evaluate the Safety, Tolerability, and Pharmacokinetics of Switching from Oral Risperidone to Risperidone Implant (DLP-114).
Study Number:	DLP-114-03
Phase:	Phase Ib
Number of Clinical Centers:	Up to 3 centers in the US
Study Objective (*Primary*):	To evaluate the safety and tolerability of DLP-114: 1) Determine the number and percent of patients experiencing a treatment-emergent adverse event; 2) Evaluate the incidence of local site reactions; 3) Assess the tolerability of implantation and explantation procedures.
Study Objectives (*Secondary*):	1) Measure the plasma concentration of risperidone and 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) following repeated oral administrations. 2) Measure the plasma concentration of risperidone and 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) following switch from oral risperidone to subcutaneous implantation of two DLP-114 devices. 3) Measure exploratory treatment outcomes using 2 psychiatric rating scales: the Clinical Global Impression (CGI-I) rating scale and the PANSS. 4) Measure the amount of risperidone drug substance remaining in the DLP-114 reservoir following its removal, in order to estimate average daily output and duration. 5) Determine average depth of device placement and any potential migration.
Study Population:	Adult male and female patients between 18 and 70 years of age with a diagnosis of schizophrenia and stable for at least 2 weeks on 2-3 mg/day of oral risperidone will be enrolled.
Patient Number:	Two groups of 12-15 schizophrenia patients who are currently on oral risperidone therapy (2-3 mg/day), or who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) but complete the conversion phase, will receive two DLP-114 implants, either the 6-month version (Gr 1) or the 12-month version (Gr 2). Therefore, the total number of patients enrolled in the study is estimated to be approximately 24-30.
Study Treatments & Route of	• Risperdal® (risperidone) - oral administration • DLP-114 (Risperidone Implant - Subcutaneous implantation in a

Administration:	quadrant of the abdomen)
Number of Administrations per Treatment:	Risperdal® (risperidone) – During the conversion phase, subjects who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) will be tapered off their current antipsychotic and titrated, at the PI's discretion, to oral Risperidone 3 mg/day starting a minimum of 2 weeks before implantation. Oral risperidone 1 mg to 3 mg/day will be administered at the investigator's discretion in the conversion phase. Risperdal® (risperidone) – Unsupervised administrations of 3 mg/day, for 3-6 days (starting 7-10 days before implantation and until 4 days before implantation) for subjects who are currently on oral risperidone therapy (2-3 mg/day). Risperdal® (risperidone) – Supervised administrations of 3 mg/day, for six days (4 days before implantation, the day of implantation and the day after implantation). DLP-114-α4 Implant - Subcutaneous implantation of 2 devices per patient for 183 (± 7) days. DLP-114-α7 Implant - Subcutaneous implantation of 2 devices per patient for 364 (± 7) days.
Study Duration:	The study duration for each patient in the study will be up to 236 days plus the conversion phase, if applicable, for patients assigned to Group 1 and 417 days plus the conversion phase, if applicable, for those in Group 2. This includes the following: • Screening period (up to 28 days) • Conversion phase- Cross-titrating, at the PI's discretion, from other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks to achieve an oral risperidone dose of 3 mg by Day -14; • Unsupervised oral risperidone (3 mg/day) (3-6 days); • Supervised oral risperidone (3 mg/day) (4 days); • DLP-114 implant treatment, Gr 1 183 [± 7] days; Gr 2 (364 [± 7] days); • Follow-up (7 (± 1) days).
Study Confinement Periods:	All patients will be confined to the clinical facility at different stages for an overall total of up to 9 days. Patients will be confined to the clinical facility overnight on Day -1. The implantation is scheduled to take place on Day 1 without a washout period. The patient will continue to stay confined in the clinical facility until Day 7 (a total of 7 days). All patients will be confined to the clinical facility for 2 days at the time of implant removal.
Study Outpatient Visits:	Patients will be required to attend the clinical facility for at least 20 outpatient visits (Gr 1) and at least 33 outpatient visits (Gr 2) in

	addition to the screening visit.
Blood Sample Collection:	An approximate 3 mL of blood will be collected for each PK sampling timepoint.

Enrollment Criteria:

Inclusion Criteria:

To be eligible for enrolment, patients must meet the following criteria:

1. Adult patients 18-70 years of age of both sexes diagnosed with schizophrenia or schizoaffective disorder according to DSM-V who have been stable on oral risperidone (2mg-3mg) for at least 2 weeks.
   Note: Patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) and complete the conversion phase may be enrolled.
2. Patient (and/or a patient's authorized legal representative) has provided written informed consent
3. Patient meets the following criteria:
   a. Outpatient status
   b. PANSS Total Score ≤ 80 at screening.
   c. A score of ≤ 4 on the following PANSS items:
      i. Conceptual disorganization
      ii. Suspiciousness
      iii. Hallucinatory behavior
      iv. Unusual thought content
      v. Hostility
   d. CGI-S ≤ 4 (moderately ill)\Lack of clinically significant suicidal ideation or behavior; C-SSRS score type of 4-5 require evaluation by mental health professional to ensure patient safety in study
4. Body Mass Index (BMI) within the range of 18.5 to 40.0 kg/m^2 (inclusive);
5. Ability to understand the nature and objectives of the trial, including risks and adverse events, and be able to read, review and sign the informed consent document prior to conduct of any study procedures;
6. Willing and able to comply with the requirements of the study protocol; including willingness to visit the clinical facility for all outpatient visits and confinement periods;
7. Have suitable venous access for blood sampling.
8. Patient is assessed by the Investigator to be symptomatically stable with regard to pre-existing medical conditions as evidenced by medical history, non-clinically significant findings on physical examination, vital signs, clinical laboratory evaluations (hematology, serum chemistries, and urinalysis) or 12-lead electrocardiogram (ECG). Subjects may continue on their current prescribed medication regimens to control pre-existing medical and psychiatric conditions (other than schizophrenia) including the use of prescribed PRN medications.

Exclusion Criteria:

1. PANSS score at baseline is ≥ 20% change from screening.

2. Hospitalized or required acute crisis intervention for symptom exacerbation in the 60 days prior to admission as determined by the Investigator
3. Patient has a history of suicide attempt in the last year, or in the opinion of the investigator is currently at imminent risk of suicide.
4. Patient experiencing acute depressive symptoms within the past 30 days, according to the Investigator's opinion, that required treatment with an antidepressant
5. Has a current or recent (within 12 months) DSM-V diagnosis of moderate or severe substance use disorder (except for tobacco use disorder) or has a positive urine drug screen for prohibited substances at screening.
6. Have impaired hepatic (ALT/AST >1.5 times higher than the upper limit of normal) or renal function (eGFR<50 mL/min)
7. Previously defined hypersensitivity to Risperidone
8. History of neuroleptic malignant syndrome (NMS)
9. Electroconvulsive therapy within 6 months of admission
10. Requires current use of agents that are strong inhibitors and inducers of cytochrome P450;
11. Known hypersensitivity or allergy to lidocaine or any local anesthetic agent of the amide type (local anesthetic used during implant and explant procedures);
12. Presence of clinically significant skin disorders (such as, but not limited to, skin cancer, psoriasis, eczema, or atopic dermatitis), evidence of recent sunburn, scar tissue, tattoo, open sore, body piercing or branding at the intended implantation site that would interfere with the implantation procedure or interfere with implant site assessments as determined by the investigator;
13. History of clinically significant hypersensitivity or allergic reactions;
14. Known allergy or hypersensitivity to PABA;
15. Known allergy or hypersensitivity to parabens, local anesthetics of the ester type, and sulfa drugs including antibiotics and thiazide diuretics;
16. Known hypersensitivity to titanium, implant materials or procedure;
17. Administration of an investigational drug or device within 1 month prior to first dosing;
18. Positive result for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibody, or HIV antibody;
19. Pregnant or lactating patients. Positive pregnancy test;
20. Positive drug test for Methamphetamines, Opiates, Cocaine, Phencyclidine, Benzodiazepines, Barbiturates, Methadone, Antidepressants and Amphetamines or positive alcohol test at screening or prior to first dose;
21. Poor CYP2D6 metabolizer;
22. History of skin picking or delusional parasitosis;
23. Known history of abnormal scar formation or family history of keloid formation

Study Design/Methods:
This study is a Phase 1b clinical study of DLP-114, a Risperidone Implant product. The study is an open-label, parallel group design aimed at assessing the safety, tolerability and PK profile of two versions of the DLP-114 drug product, alpha 4, designed to operate for at least 6 months, and alpha 7 designed to operate for 12 months. Eligible patients will be assigned to one of two groups following completion of the conversion phase, if applicable, and supervised oral risperidone dosing (3mg for 4 days). Both groups will be switched to 2 DLP-114 devices on

Day 1 and safety and PK assessed in parallel for 6 months (Group 1, alpha 4) or 12 months (Group 2, alpha 7). The study also aims to evaluate the utility of DLP-114 in achieving a PK profile that is comparable to the marketed oral form of risperidone for either 6 months (DLP-114-α4) or 12 months (DLP-114-α7).

Subjects receiving an antipsychotic other than oral risperidone (2-3 mg/day) will be required to enter the conversion phase. During the weekly visits in the conversion phase, subjects will cross-titrate, at the PI's discretion, from other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks. The objective of the oral conversion phase is for all subjects to achieve an oral risperidone dose of 3 mg by Day -14.

The study will be conducted in four sequential periods for both groups (subjects will either enter the conversion phase or the unsupervised oral risperidone [3 mg/day] period) following Screening:

1. Conversion phase (Cross-titration, at the PI's discretion, from other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks to achieve an oral risperidone dose of 3 mg by Day -14)
2. Unsupervised oral risperidone (3 mg/day)
3. Supervised oral risperidone (3 mg/day)
4. DLP-114 implant treatment with oral supplement
5. DLP-114 implant treatment;
6. Follow-up.

Each patient enrolled in this study will commence unsupervised dosing with 3 mg/day oral risperidone for 3-6 consecutive days, followed by supervised dosing with 3 mg/day oral risperidone for 4 consecutive days. Patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) will enter the conversion phase and cross-titrate, at the PI's discretion, from the other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks prior to commencing the supervised 3 mg/day oral risperidone for 4 consecutive days. Following the conversion, patients will need to be stable on oral risperidone 2-3 mg/day for at least 2 weeks prior to being implanted. PK analysis will be conducted following the fourth dose of supervised oral risperidone. Two additional oral doses will be administered, one on the day immediately prior to implant administration, and another one 24 hours after implant administration.

Following the completion of the oral phase of the study, each patient in Group 1 will be implanted with two DLP-114 alpha 4 devices for 183 (± 7) days and each Group 2 patients will receive 2 DLP-114 alpha 7 devices for 364 (± 7) days. 24 hours after implant administration an additional oral dose will be administered. PK analysis will be conducted during the first 72 hours after implant administration and then daily during the confinement period. During the implant treatment period, patients will return to the clinical facility for outpatient visits for safety assessments and sampling for PK. Assessments will include vital signs, physical examination, inspection of the site of DLP-114 implantation, ECG, safety laboratory tests, CGI-I, PANSS, C-SSRS, BARS, SAS, AIMS, assessment of AEs and implant/device events (IDEs), including migrations, spontaneous expulsions, and other device-related events, and measurement of body weight.

Pregnancy tests will be conducted (female patients only) to monitor and confirm absence of pregnancies. Compliance to study restrictions relating to drugs of abuse will also be monitored throughout the dosing and implant periods. If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping.

For detailed description of schedule of assessments refer to **Section 14** (Study Conduct Schedules and Guidelines) and **Appendix 1** (Overall Schedule of Assessments).

For detailed description of PK blood collection times (including time point windows) refer to **Appendix 2** (Pharmacokinetic Sample Collection Schedule).

Dose Administration Stopping Rules for an Individual Subject:

The Investigator and/or Sponsor may suspend or terminate dose administration upon any of the following events:

- One occurrence of a Serious Adverse Event (SAE) assessed to be probably or possibly related to dosing with the investigational product;
- Two or more severe Adverse Events (AEs) of the same character that are determined to be clinically significant by the investigator or sponsor and are assessed as probably or possibly related to dosing with the investigational product;
- Signs of impending relapse

Study Procedures and Assessments:

Informed Consent. The Patient Information and Consent Form (PICF) will be provided to the study participants at screening, prior to any study procedures being performed.

Medical History. Medical history and demographic data, including name, gender, age, race, Body Mass Index (BMI) will be recorded at screening.

Safety Assessments. This study will assess the safety and tolerability of DLP-114. Safety will be determined by evaluating physical examinations, vital signs, ECGs, clinical laboratory parameters, clinical ratings (e.g. C-SSRS) and adverse events. Local tolerance at the implantation site will be examined and scored for severity of visible signs of irritation/inflammation. If deemed necessary, additional safety measurements will be performed at the discretion of the investigator (or delegate). If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping. The following assessments will be completed at selected time points (see Section 14 and **Appendix 1** for details)

- Physical Examination. Complete physical examination performed at screening will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.
- Implantation site inspection will be by visual and physical examination at each assessment visit. The physician will palpate the device to determine whether it has migrated by noting a change in distance from the incision site to the proximal end of the device. Healing of the incision will be monitored. Dermal reactions will be scored on a Skin Irritation Scoring System (**Appendix 3)** [1] recommended for transdermal dosage forms that describes the amount of erythema, edema, and other features indicative of irritation.
- Electrocardiogram. Single 12-lead ECG will be performed at selected time points. The following variables will be provided automatically: RR, PR, QRS, QT and QTcF intervals and pulse rate. In case of evident bad quality (muscle tremor) of the tracing, the ECG will be repeated. All ECGs should be obtained prior to vital signs and blood

sampling when applicable.

- Vital Signs. Vital signs will be performed at selected time points. Assessments will include systolic and diastolic blood pressure, pulse, body temperature, respiratory rate and orthostatic blood pressure and pulse at selected timepoints.
- Safety Laboratory Tests. The following clinical laboratory safety tests will be performed:
  - Hematology. Leukocytes, erythrocytes, haemoglobin, haematocrit, thrombocytes; (partial automated differentiation): lymphocytes, monocytes, eosinophils, basophils, neutrophils.
  - Serum Chemistry. Sodium, potassium, calcium, phosphate, blood urea nitrogen (BUN), serum creatinine, glucose, lactic acid dehydrogenase (LDH), alanine transferase (ALT), aspartate transferase (AST), total bilirubin, alkaline phosphatase, gamma glutamyl transferase (GGT), total proteins, albumin and urates. Lipid profile: total cholesterol, LDL, HDL, non-HDL and triglycerides.
  - Coagulation. Prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT).
  - Urinalysis. Urine sample for urinalysis will be collected at specified time points. The following urinalysis parameters will be assessed: hemoglobin, urobilinogen, ketones, bilirubin, glucose, protein, nitrite, leukocytes, pH, specific gravity.
- Ultrasound. To determine depth of device placement.
- CYP2D6 genotyping
- Viral Serology. Hepatitis B surface antigen, hepatitis C antibody and HIV screen.
- Pregnancy Test (Females only): serum human chorionic gonadotropin (hCG) at the screening visit and urine hCG test at all subsequent visits.
- Alcohol and Drugs of Abuse Screen. Alcohol breath test will be conducted at screening and prior to first dose. Urine drug test will include screen for: Methamphetamines, Opiates, Cocaine, Phencyclidine, Benzodiazepines, Barbiturates, Methadone, Tricyclic Antidepressants and Amphetamines.
- C-SSRS will be administered each visit; additional evaluation by a mental health professional may follow
- EPS (Bars, SAS and AIMS)
- CGI-I will be administered at least every 4 weeks
- PANSS will be administered at least every 3 months. If CGI-I worsens, PANSS will be administered more frequently

Pharmacokinetics. Determination of plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) on the last day of oral risperidone treatment, throughout the duration of the DLP-114 implant treatment and following removal of the DLP-114 implants.

Study Endpoints:

Safety endpoints include:

- Incidence and severity of AEs;
- Local tolerance at the implantation site will be examined and scored for severity of visible signs of irritation/inflammation;
- Tolerability of the implantation and explantation procedures;
- Vital signs parameters;

- Physical examination findings;
- Electrocardiogram parameters;
- Safety laboratory test parameters (serum chemistry, hematology, urinalysis);
- Exploratory treatment outcomes will be assessed using 2 psychiatric rating scales: the Clinical Global Impression (CGI-I) rating scale and the PANSS.

Pharmacokinetic Endpoints include the evaluation of plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone).

PK parameters to be calculated for oral risperidone treatment period include:

- Maximum concentration (C_{max});
- Minimum concentration (C_{min})
- Time to maximum concentration (T_{max});
- Time to minimum concentration (T_{min})
- Average concentration (C_{ave})
- Area under the plasma concentration vs. time curve (AUC)

PK parameters to be calculated for implant treatment period include:

- Maximum concentration (C_{max});
- Minimum concentration (C_{min})
- Time to maximum concentration (T_{max});
- Time to minimum concentration (T_{min});
- Average concentration (C_{ave})
- Area under the plasma concentration vs. time curve (AUC)

Device Endpoints include:

- Implant spontaneous migration away from the initial subcutaneous implantation area during the implant treatment period.
- Amount of unreleased drug substance remaining in the DLP-114 implant following its removal in order to estimate average daily output.
- Average depth of device placement

Statistics and Data Analyses:

Sample Size Considerations. The maximum sample size is 24-30. The primary objective of this study is to determine safety and tolerability of two versions of the DLP-114 implant (one designed for 6 months and the other designed to operate for 1 year) and as such the sample size for this study was based upon qualitative considerations. No formal sample size calculations were performed.

Demographic Data. For all patients who received at least 1 dose of study treatment, descriptive statistics (mean, standard deviation, median, minimum, maximum) will be performed for age, gender, body mass index, weight, and height.

Safety/Tolerability Data. All patients who receive at least 1 dose of study treatment will be included in the safety and tolerability analysis. Baseline for all vital signs, 12-lead ECG measurements, and clinical laboratory assessments will be defined as the last evaluation done before the start of study treatment administration on Day -5. Safety evaluations will be based on the incidence, intensity and type of AE and clinically significant changes in the patient's physical examination findings, vital signs, 12-lead ECGs, and clinical laboratory results. Safety

variables will be tabulated and presented for all patients who receive study treatment. Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by study treatment showing patient counts and percentages. The original terms used in the CRF by investigators to identify AEs will be coded using the current version of the Medical Dictionary of Regulatory Activities (MedDRA). The percentage of patients with treatment-emergent AEs will be summarized for each treatment. Laboratory data will be summarized by the type of laboratory test. Normal reference ranges and markedly abnormal results will be used in the summary of laboratory data. Raw data and change from baseline in clinical laboratory parameters will be summarized using descriptive statistics. A listing of patients with any laboratory results outside the reference ranges that are deemed clinically significant will be provided.

Pharmacokinetic Data. Plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) determined at specified time points will be used to calculate PK parameters. Data will be listed for all patients with available plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone). Pharmacokinetic parameters for risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) will be calculated using non-compartmental analysis. Listing of individual patient plasma concentrations, actual blood sampling times, and PK parameters and graphs of concentration vs. time will be prepared by study treatment. Plasma concentrations and PK parameters will be summarized by and compared between study treatments using descriptive statistics. Statistical analysis will be performed on the pharmacokinetic parameters using validated statistical software. If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping.

5 TABLE OF CONTENTS

6 LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
ADL	Activities of daily living
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BARS	Barnes Akathesia Rating Scale
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C_{ave}	Average concentration
C_{max}	Concentration maximum (peak)
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression Scale – Improvement
CGI-S	Clinical Global Impression Scale – Severity
CNS	Central Nervous System
C-SSRS	Columbia-Suicide Severity Rating Scale
DCF	Data Correction Forms
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
EIU	Exposure In Utero
CRF	Case Report Form
EOS	End of Study
EPS	Extrapyramidal Symptoms
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C antibodies
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonization
IDE	Implant/Device Event
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
LDH	Lactic Acid Dehydrogenase
LDL	Low Density Lipoprotein
LOQ	Limit of Quantification
MAOI	Monoamine oxidase inhibitors

MedDRA	Medical Dictionary of Regulatory Activities
NHANES	National Health and Nutrition Examination Survey
PABA	Para-aminobenzoate
PANSS	Positive and Negative Syndrome Scale
PBS	Phosphate-buffered saline
PICF	Patient Information and Consent Form
PK	Pharmacokinetic
PT	Prothrombin Time
PVDF	Polyvinylidene difluoride
PVP40	Polyvinylpyrrolidone
QTcF	QT interval corrected for heart rate using Fridericia's formula
RSQ	Risperidone Symptom Questionnaire
SAE	Serious Adverse Event
SAS	Simpson-Angus Scale
SUSAR	Suspected Unexpected Adverse Reaction
THC	Tetrahydrocannabinol
T_{max}	Time at which the C_{max} is observed

7 INTRODUCTION

7.1 Background Information

Risperidone is an antipsychotic whose primary therapeutic activity is postulated to be mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) antagonism. Risperidone is currently marketed as immediate-release tablets, orally disintegrating tablets, an oral solution and as a long-acting intramuscular injection.

DLP-114 is a Risperidone Implant that is a combination drug-device product designed to continuously elute the equivalent of a daily 1-2 mg oral dose of risperidone following subcutaneous implantation. The device is implanted in a quadrant of the abdomen at least 5cm from midline and 5 cm below the ribs, using a sterile disposable implanter tool and local anesthesia in a minimally invasive procedure.

Each DLP-114 device consists of a hollow cylindrical titanium reservoir (similar in materials, size and shape, to other approved implants) that is fitted on each end with a cap containing a 0.1 micron membrane and filled with tablets of a homogenous powder form of risperidone plus a two-time molar excess of para-aminobenzoic acid (PABA). To aid with tableting the formulation, PVP40 and stearic acid are added. Drug release is achieved by a novel passive diffusion mechanism initiated by the introduction of sterile saline. Two versions of the DLP-114 device will be tested in the IND study. The devices are loaded with the same risperidone formulation (RISP/PABA 1:2), are the same diameter, have the same membrane diffusive surface area, but differ in the length of the reservoir and in vivo operating period. DLP-114-α4 is 44 mm in length and designed to operate for 6 months. DLP-114-α7 is 50 mm long and designed to operate for 12 months.

7.2 Proposed Clinical Application

Risperidone, is currently approved for acute and maintenance therapy of schizophrenia and, as monotherapy or adjunctively, in the acute treatment of Bipolar Disorder I. It is also approved for the management of irritability in pediatric and adolescent patients with autistic disorder. The DLP-114 drug-device is appropriate for maintenance therapy rather than acute therapy and thus it is being developed as a maintenance treatment for schizophrenia in adults.

7.3 Non-clinical Safety, Toxicology and Pharmacokinetics

The PK and local tolerance of DLP-114 has been tested preclinically in two species, rat and rabbit. A total of 7 non-clinical studies have been completed testing the Pharmacokinetics, Toxicity and Tissue Compatibility of DLP-114. **Table 1** below provides a summary of the studies conducted.

Table 1: Summary of *in vivo* Non-Clinical Studies with DLP-114

Animal Study	GLP?	Group Number	Formulation	Device Type	Length of Implant (days)	Output Rate *in vivo* (mg/day)	Observations
		7	RISP/PABA 1:3	1-ended α2	119 (n=5)	0.29	No to mild local tissue reactivity; no adverse

							treatment-related clinical observations
		8	RISP/PABA 1:2	α3	119 (n=4)	0.80	No to mild local tissue reactivity; no adverse treatment-related clinical observations
		9	RISP/PABA 1:2	α2	119 (n=1) 183 (n=5)	0.70	No to mild local tissue reactivity; no adverse treatment-related clinical observations
		10	RISP/PABA 1:2	α1	119 (n=4) 183 (n=6)	0.46	No to mild local tissue reactivity; one self-explant, otherwise no adverse treatment-related clinical observations
12	No	11	RISP/PABA 1:2	1-ended α2	183 (n=5)	0.42	No to mild local tissue reactivity; no adverse treatment-related clinical observations
		1	PLGA Mix C	α2	124 (n=5)	0.86	No to mild local tissue reactivity; no adverse treatment-related clinical observations
		2	PLGA Mix C	α3	124 (n=5)	0.79	No to mild local tissue reactivity; no adverse treatment-

							related clinical observations
		3	RISP/PABA 1:2	α2	278 (n=5)	0.68	No to mild local tissue reactivity; no adverse treatment-related clinical observations other than one spontantaneous explantation
13	No	4	Sebacic Acid	α3	180 (n=5)	0.98	No to mild local tissue reactivity; no adverse treatment-related clinical observations
		5	Risperidone Acetate	ALZET pump	31 (n=5)	N/A	No to mild local tissue reactivity; no adverse treatment-related clinical observations
		1	RISP/PABA 1:2	2 α2	92 (n=5)	0.98	No to moderate local tissue reactivity; animals appeared lethargic for 12 days post implant, normal afterwards; animal 1001partially explanted a device multiple times
		2	RISP/PABA 1:2	2 α2	92 (n=5)	0.97	No to moderate local tissue

14	No						reactivity; animal 2003 partially explanted a device, and then fully explanted it the following day after re-insertion; animal 2005 was discovered moribund and subject to euthanasia, it is unclear if this is related to test article
15	Yes	1	Placebo	α2	30 (n=2)	N/A	No local tissue reactivity; no adverse treatment-related clinical observations
		2	RISP/PABA 1:2	α2	30 (n=8)	1.58	No to moderate local tissue reactivity; no adverse treatment-related clinical observations
16	No	1	RISP/PABA 1:2	α2	273 (n=5)	0.58	No to mild local tissue reactivity; no adverse treatment-related clinical observations
		2	RISP/PABA 1:2	α2	273 (n=5)	0.51	No to moderate local tissue reactivity; no adverse treatment-related clinical

							observations
19	No	1	RISP/PABA 1:2 (12%PVP)	α2	183 (n=5)	0.56	No local tissue reactivity; no adverse treatment-related clinical observations
		2	RISP/PABA 1:2 (5%PVP)	α2	364 (n=5)	0.37	No to mild local tissue reactivity; no adverse treatment-related clinical observations other than one spontaneous explant
		1	RISP/PABA 1:2	α2	182 (n=6)	0.65	No to moderate local tissue reactivity; no adverse treatment-related clinical observations other than one spontaneous explantation
		2	RISP/PABA 1:2	α4	182 (n=12)	0.72	No local tissue reactivity; one animal (2003) was found dead on day 20, otherwise no adverse treatment-related clinical observations
		3	RISP/PABA 1:3	α4	182 (n=12)	0.57	No to moderate local tissue reactivity; no adverse treatment-related clinical

20	Yes						observations other than one spontaneous explantation
		4	Placebo	α4	182 (=12)	N/A	No local tissue reactivity; no adverse treatment-related clinical observations

DLP-ASR-0012: This study was proposed to compare different formulations, mechanisms, and devices in order to optimize risperidone output. It compared 3 types of devices (α1, α2, and α3), as well as the pre-clinical prototype device for comparison. Formulations included risperidone hexanoate salts mixed with PLGA copolymers, and risperidone free based mixed with molar excesses of 2 or 3 time para-aminobenzoic acid (PABA). The devices were implanted for 119 or 183 days, and evaluated by plasma concentration over time, clinal observations, and post-explant tissue necropsy and histopathology. From the PK it can be concluded that the output from single ended devices is not optimal, and that a double-ended device is likely needed to achieve sufficient output for a clinical device. The risperidone PABA output from the double-ended devices had a burst effect in groups 8-10, but the output achieved steady state by week 2, at about 3 times below the C_{max}. The plasma concentration remained fairly flat for the remainder of the implant period. The average plasma concentrations of groups 8 and 9 were, and both were higher than that of group 10. Taken together, these results indicate the best clinical product for risperidone using this technology would be risperidone with a 2-fold molar excess of PABA. It was also noted that the device was well tolerated in rats, with one self explantation (Group 10, α1 device), but otherwise no adverse treatment-related clinical observations and no (score of 1 out of 5) to mild (score of 2 out of 5) local tissue reactivity at necropsy.

DLP-ASR-0013: This study was proposed to study the viability of a risperidone PABA 2 times molar excess formulation over a 9 month period in rats, as well as to compare that formulation with a previously used formulation, “Mix C”, and to a formulation that involved a diprotic acid, sebacic acid. This study also included the use of an ALZET pump configured to released risperidone acetate at a rate equivalent to 1mg of risperidone base/day for 30 days. The ALZET group was mainly used to correlate plasma concentrations of risperidone active moiety to a known control. The devices were implanted for 124, 180, or 278 days, and evaluated by plasma concentration over time, clinal observations, and post-explant tissue necropsy and histopathology. Based on the PK profile, it was estimate that the lifespan of the risperidone PABA device (α2 device loaded with 480mg of risperidone PABA 1:2) was 8 months before it dipped below the 50 ng/ml threshold. This study again reiterated that the device is well tolerated with minimal discomfort and no test-article related clinical observations or adverse body weight effects. One animal self-explanted on Day 231. Necropsy findings found no to mild inflammation in the tissue surrounding the implant site.

DLP-ASR-0014: This study was proposed to study whether implanting additional devices resulted in a linear increase in plasma concentration *in vivo.* This study also compared devices made by Delpor, and those made by a CMO, Hantel, to determine if manufacturing transfer was successful. The devices were implanted for 92 days, and evaluated by plasma concentration over time, clinal observations, and post-explant tissue necropsy and histopathology. Based off the results of this study comparing devices prepared by Delpor and those prepared by the CMO, the transfer of the production process to the CMO was successful. This study demonstrated that the doses of DLP-114 can be additive; by comparing the plasma concentrations of this study against those of group 9 from DLP-ASR-0012, we can see that animals implanted with two devices had approximately double the plasma concentration of those implanted with one device. It was also noted that rats may not be an appropriate species for studying the implantation of two devices, given the one complete and two partial explantations during the study in the double implant groups. Local tissue reactivity ranged from no reactivity to moderate reactivity (score of 3 out of 5). One animal (2005) was discovered moribund and subject to euthanasia per veterinary guidelines; it is unclear whether this adverse event was related to the implant device. Otherwise, there were no adverse treatment-related clinical observations.

DLP-ASR-0015: This GLP study was proposed in order to study the pharmacokinetics, safety, and tissue compatibility of DLP-114 in female New Zealand White (NZW) rabbits. Two rabbits were implanted with an empty placebo device, while eight were implanted with a single DLP-114 device. The devices were implanted for 30 days, and evaluated by plasma concentration over time, clinal observations, and post-explant tissue necropsy and histopathology. Based on the results of this study, surgical subcutaneous implantation of a single α2 device containing the placebo (1X PBS) or the test article (RISP/PABA 1:2, ~250 mg of active drug/device) in the inter scapular region of the New Zealand White rabbits was well tolerated and did not result in evidence of overt toxicity (animal observation or body weight changes) or evidence that the device caused physical irritation or discomfort (control or test device). In fact, there were no visible indications that the animals were aware of the presence of the device. Gross necropsies conducted 30 days post-implantation revealed either no visual inflammatory response in the tissues surrounding the device (both control animals and 2 of 7 risperidone treated animals), or a slight to moderate tissue response (remaining 5 of 7 risperidone treated animals). Capsule formation surrounding the implant in each animal was clear and thin. Histopathology was conducted on the tissues taken directly adjacent to the test or placebo device. The pathologist concluded that the slow-release risperidone implants (RISP/PABA 1:2, 250 mg of active drug) produced significantly more inflammation in the subcutis of the test rabbits than was evident in the control rabbits. The lesions were consistent with persistent irritation resulting in necrosis of the adipocytes, pyogranulomatous inflammation and healing by fibrosis. However, it is important to note that the microscopic findings are for tissue taken directly adjacent to the test or control device. As is evidenced in the photos, the areas of inflammation were visibly very small and sometimes not visible at all (control and test animals). In addition, the clinical observations did not reveal any evidence that the devices caused physical irritation or discomfort to any animals (control or test device). One animal broke its back on day 1 during a restrained blood draw, was euthanized and therefore excluded from PK analysis.

DLP-ASR-0016: This non-GLP study was proposed in order to investigate whether a change in hydration medium from 1X PBS to 0.9% saline affected device performance. This

study also utilized the same lot of DLP-114 that was used in the first-in-man study of DLP-114 in Australia. The devices were implanted for 273 days, and evaluated by plasma concentration over time, clinal observations, and post-explant tissue necropsy and histopathology. The results of this study indicate that there is no difference in PK profile between devices hydrated with PBS or with saline, and that all devices were well tolerated. These devices were the same devices used in a clinical trial, allowing for an important comparison between output in rats and output in humans. The average tissue reactivity score was between no inflammation and mild inflammation (1.6), and output was 0.5-0.6 mg/device/day. No adverse treatment-related clinical observations were reported, again demonstrating tolerance of extended implantation with the DLP-114 device.

DLP-ASR-0019: The purpose of this study was to investigate whether lowering the percentage of PVP used in the formulation as a binder influenced device performance. A lower amount of PVP would leave more room for risperidone to be loaded in the final product, allowing for a longer effective life of the product. The wt% of PVP was investigated at 12% in one group and 5% in another. The devices were implanted for 183 (group 1) or 364 (group 2) days, and evaluated by plasma concentration over time, clinal observations, and post-explant tissue necropsy and histopathology. The results of this study indicate there was no difference between devices filled with a drug formulation composed of 12% PVP and one composed of 5% PVP. This allows for a longer life of the device, reflecting the longer implant lengths of group 2. The devices were again well tolerated (average necropsy score 1.5), with implantation lasting up to 364 days. There was one spontaneous explantation in group 2. There were no adverse treatment-related clinical observations otherwise.

DLP-ASR-0020: This GLP study compared the device used in Delpor's first-in-man clinical trial, α2, with the same formulation in a longer device with a larger exposed membrane area, α4, and a formulation with a 3 fold molar excess of PABA (RISP/PABA 1:3) in the larger α4 device. This study also included a placebo α4 group. The purpose of this study was to determine whether the larger α4 device is well tolerated, and whether an increase in the ratio of risperidone to PABA influenced device performance. It had been previously noted from clinical data that PABA was leaving the device faster than risperidone, so by increasing PABA the longevity of the device might be increased. The devices were implanted for 182 days, and evaluated by plasma concentration over time, clinal observations, and post-explant tissue necropsy and histopathology. The release rates based on mass balance between the two RISP/PABA 1:2 groups was similar, 0.64mg/day and 0.72mg/day respectively for α2 and α4. The release rate was lower for the RISP/PABA 1:3 formulation in the α4 device, at 0.57mg/day. It can be concluded that drug release rate is approximately 10% higher for α4 devices compared with α2, and that RISP/PABA 1:2 in an α4 device is the best option for developing a long-acting, effective clinical product. RISP/PABA 1:3 resulted in a depressed output of risperidone, making it a suboptimal formulation.

Table 2: Summary of Biocompatibility Studies with DLP-114

Test Article	Species or Strain	ISO or USP Standard	GLP Compliance	Testing Facility	Study Number	Results
Subcutaneous Implant Study, 13-week and 26-week						
DLP-114 Implant	New Zealand White Rabbits	ISO 10993-6	Yes	NAMSA	TI249_826/S	Well tolerated, little to no local tissue reaction
DLP-114 Implanter Tool	ND	ND	ND	ND	ND	ND
Cytotoxicity						
DLP-114 Implant	L-929 mouse fibroblast cells	ISO 10993-5	Yes	NAMSA	V0014_130	No observed cytotoxic effects
DLP-114 Implanter Tool	L-929 mouse fibroblast cells	ISO 10993-5	Yes	NAMSA	V0014_130	No observed cytotoxic effects
Irritation Testing						
DLP-114 Implant	New Zealand White Rabbits	ISO 10993-10	Yes	NAMSA	TI251_800	Well tolerated in terms of intracutaneous irritability
DLP-114 Implanter Tool	New Zealand White Rabbits	ISO 10993-10	Yes	NAMSA	TI251_800	Well tolerated in terms of intracutaneous irritability
Pyrogen Testing						
DLP-114 Implant	New Zealand White Rabbits	ISO 10993-11	Yes	NAMSA	TU010_807	Nonpyrogenic
DLP-114 Implanter Tool	New Zealand White Rabbits	ISO 10993-11	Yes	NAMSA	TU010_807	Nonpyrogenic
Sensitization Testing						

DLP-114 Implant	Hartley Albino Guinea Pigs	ISO 10993-10	Yes	NAMSA	TI261_300	No delayed dermal contact sensitization
DLP-114 Implanter Tool	Hartley Albino Guinea Pigs	ISO 10993-10	Yes	NAMSA	TI261_300	No delayed dermal contact sensitization
Acute System Toxicity						
DLP-114 Implant	ND	ND	ND	ND	ND	ND
DLP-114 Implanter Tool	Mice (*Mus musculus*)	ISO 10993-11	Yes	NAMSA	T0625_500	No evidence of systemic toxicity
Extractables and Leachables						
DLP-114 Implant	N/A	ISO 10993-18	No	NAMSA	C0839_002/s	Discovered substances do not pose a risk to a patient with lifetime exposure
DLP-114 Implanter Tool	ND	ND	ND	ND	ND	ND

ISO Subcutaneous Implantation Study in Rabbits, 13 Week and 26 Week Implantation Report – Implant Device

Testing was completed with seven New Zealand White Rabbits (*Oryctolagus cuniculus*), 3-3.3kg at selection. Each animal was implanted with four DLP-114 devices using the Delpor implanter tool and four negative control articles. At 13 week, three rabbits were euthanized and the tissue surrounding the implant and control devices was examined. At 26 weeks, the remaining animals were euthanized and the tissue surrounding the implant and control devices was examined. Clinical observations were recorded throughout the duration of the study. The negative control article was USP high density polyethylene (HDPE). Tissues were macroscopically studied and scored from 0 (lowest) to 4 (highest) on encapsulation and irritation.

No major clinical observations were reported. Two animals had small amounts of alopecia, two had reduced feces, and one had a dry, red, scaly lesion on the left rear foot for two days. Macroscopic observations showed no visible reaction at any test or control site in either the 13-week group or the 26-week group. Microscopic observation caused a minimal or no reaction as compared to the negative control article in both the 13-week group and the 26-week group. See the NAMSA GLP report TI249_826/S for detailed results.

Cytotoxicity Study Using the ISO Elution Method – Implant Device

Testing was completed on the DLP-114 device prepared in single strength Minimum Essential Medium (IX MEM) at 37°C for 72 hours. The negative control, reagent control, and positive control were similarly extracted (see Delpor internal report RPT-1151 for more detail on extraction). Triplicate monolayers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% CO2 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration.

The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity). See the NAMSA GLP report V0014_130 for detailed results.

Cytotoxicity Study Using the ISO Elution Method – Implanter tool

Testing was completed on the DLP-114 implanter tool prepared in single strength Minimum Essential Medium (IX MEM) at 37°C for 72 hours. The negative control, reagent control, and positive control were similarly extracted (see RPT-1151 for more detail on extraction). One test article (cannula and rod) were included in each preparation. Triplicate monolayers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% CO2 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration.

The test article extract showed no evidence of causing cell lysis or toxicity. The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity). See the NAMSA GLP report V0014_130 for detailed results.

ISO Intracutaneous Study in Rabbits – Implant Device

Test articles were extracted with 0.9% sodium chloride USP (SC) or sesame oil, NF (SO). Seven devices were cut in half and extracted with each extraction vehicle, continuously agitated for the extraction period. See RPT-1151 for more detail on extraction.

Testing was completed with three New Zealand White Rabbits (*Oryctolagus cuniculus*), 2.4-2.8kg at selection. A 0.2 mL dose of the appropriate test article extract was injected by the intracutaneous route into five separate sites on the right side of the back of each animal. Similarly, the corresponding control (the extraction vehicle alone) was injected on the left side of the back of each animal. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. Reactions were scored on a 0 to 4 basis.

All animals appeared normal throughout the study. See the NAMSA GLP report TI251_800 for detailed results.

ISO Intracutaneous Study in Rabbits – Implanter Tool

Test articles were extracted with 0.9% sodium chloride USP (SC) or sesame oil, NF (SO). Two articles (cannula and rod) were subdivided and extracted with each extraction vehicle, continuously agitated for the extraction period. See RPT-1151 for more detail on extraction.

Testing was completed with three New Zealand White Rabbits (*Oryctolagus cuniculus*), 2.6-2.7kg at selection. A 0.2 mL dose of the appropriate test article extract was injected by the intracutaneous route into five separate sites on the right side of the back of each animal. Similarly, the corresponding control (the extraction vehicle alone) was injected on the left side of the back of each animal. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection. Reactions were scored on a 0 to 4 basis.

All animals appeared normal throughout the study. See the NAMSA GLP report TI251_800 for detailed results.

USP Rabbit Pyrogen Study, Material Mediated – Implant Device

Test articles were extracted with sterile, nonpyrogenic 0.9% sodium chloride solution (SNPS). Sixty-four devices were cut in half and extracted with the extraction vehicle, with an extraction ratio of 900 cm^2:150 mL, 790.2 cm^2 of article amount, and 132 mL of vehicle. The extraction process was continuously agitated at 70° C for 24 hours.

Testing was completed with three New Zealand White Rabbits (*Oryctolagus cuniculus*), 3.4-3.9kg at selection. Temperatures were obtained rectally, with control temperatures recorded no more than 30 minutes prior to injection, and recordings taken at 30-minute intervals between 1 and 3 hours after injection. Injection was delivered intravenously via the marginal ear vein with the test extract at 10 mL/kg of body weight.

No single animal showed a temperature rise of 0.5° C or more above its baseline temperature. The total rise of the rabbits' temperature throughout the 3 hours was 0.4° C. See the NAMSA GLP report TU010_807 for detailed results.

USP Rabbit Pyrogen Study, Material Mediated – Implanter Tool

Test articles were extracted with sterile, nonpyrogenic 0.9% sodium chloride solution (SNPS). Sixteen test articles (cannula and rod) were subdivided and extracted with the extraction vehicle, with an extraction ratio of 900 cm^2:150 mL, 920 cm^2 of article amount, and 153 mL of vehicle. The extraction process was continuously agitated at 70° C for 24 hours.

Testing was completed with three New Zealand White Rabbits (*Oryctolagus cuniculus*), 3.5-3.7kg at selection. Temperatures were obtained rectally, with control temperatures recorded no more than 30 minutes prior to injection, and recordings taken at 30-minute intervals between 1 and 3 hours after injection. Injection was delivered intravenously via the marginal ear vein with the test extract at 10 mL/kg of body weight.

No single animal showed a temperature rise of 0.5° C or more above its baseline temperature. The total rise of the rabbits' temperature throughout the 3 hours was 0.2° C. See the NAMSA GLP report TU010_807 for detailed results.

ISO Guinea Pig Maximization Sensitization Test – Implant Device

Test articles were extracted with 0.9% sodium chloride USP (SC) or sesame oil, NF (SO). Seven test articles were included in each Induction I preparation and four test articles were included in each Induction II and Challenge preparation. Devices were cut in half and extracted with the extraction vehicle. The control is the extraction vehicle without the test article. See RPT-1151 for

extraction details.

Testing was completed with thirty Hartley Albino Guinea Pigs (*Cavia porcellus*), 302g to 450g at selection. Ten animals were assigned to each test group (SC and SO extractions), and five were assigned to each control group (SC and SO vehicle alone). On the first day, during the Induction I phase, the animals were injected with their assigned extract or control. At day 6 (Induction II), the animals were treated with a 10% SLS suspension to provoke mild inflammation, and 24 hours later were applied topically with a filter paper saturated in their assigned extracted or control. This was removed at 48 hours. 14 days after the completion of Induction II, cotton disks were saturated with extract or control, and applied to the animals, removed after 24 hours.

Clinical observations were noted daily, observations for dermal reactions were conducted 24 and 48 hours after challenge patch removal, and dermal reactions were scored from 0 (no visible change) to 3 (intense erythema and swelling).

No major clinical observations were observed. Two animals had some significant self-inducted trauma to the skin at Induction I injection sites, and were treated with an analgesic (see report). No evidence of sensitization was noted at 24 or 48 hours. The raw data can be found in appendix 2 of the RPT-1151. See the NAMSA GLP report TI261_300 for detailed results.

ISO Guinea Pig Maximization Sensitization Test – Implanter Tool

Test articles were extracted with 0.9% sodium chloride USP (SC) or sesame oil, NF (SO). One test article (only the cannula and rod) was included in each preparation. Devices were subdivided and extracted with the extraction vehicle. The control is the extraction vehicle without the test article. See RPT-1151 for extraction details.

Testing was completed with thirty Hartley Albino Guinea Pigs (*Cavia porcellus*), 301g to 445g at selection. Ten animals were assigned to each test group (SC and SO extractions), and five were assigned to each control group (SC and SO vehicle alone). On the first day, during the Induction I phase, the animals were injected with their assigned extract or control. At day 6 (Induction II), the animals were treated with a 10% SLS suspension to provoke mild inflammation, and 24 hours later were applied topically with a filter paper saturated in their assigned extracted or control. This was removed at 48 hours. 14 days after the completion of Induction II, cotton disks were saturated with extract or control, and applied to the animals, removed after 24 hours.

Clinical observations were noted daily, observations for dermal reactions were conducted 24 and 48 hours after challenge patch removal, and dermal reactions were scored from 0 (no visible change) to 3 (intense erythema and swelling).

No major clinical observations were observed. No evidence of sensitization was noted at 24 or 48 hours. The raw data can be found in appendix 2 of the report. See the NAMSA GLP report TI261_300 for detailed results.

ISO Acute Systemic Toxicity Study in Mice – Implanter tool

Test articles were extracted with 0.9% sodium chloride USP (SC) or sesame oil, NF (SO). Two test articles were included in each preparation. The control is the extraction vehicle without the test article. See RPT-1151 for extraction details.

Testing was completed with twenty mice (*Mus musculus*), 19g to 22g at selection. 10 animals were used per extraction vehicle, with 5 assigned to be injected with extract and 5 to be injected with a control. The SC injections were intravenous, while the SO injections were intraperitoneal. Animals were observed for clinical reactions at 0, 4, 24, 48, and 72 hours.

All animals were clinically normal throughout the study. Clinical observations can be found in the corresponding report. See the NAMSA GLP report T0625_500 for detailed results.

Extractables and Leachables Chemical Characterization – Implant Device

The test article, Delpor Device, was extracted (exhaustively) in Purified Water, Acidified Water, Isopropanol, and Hexane. The resulting extracts were analyzed by Gas Chromatography – Mass Spectrometry (GC-MS) for Semi-Volatile Organic Compounds (SVOC), Headspace – Gas Chromatography - Mass Spectrometry (HS-GC-MS) for Volatile Organic Compounds (VOC) and Ultra Performance Liquid Chromatography - Ultraviolet Spectrometry - Mass Spectrometry (UPLC-UV-MS) for Non-Volatile Organic Compounds (NVOC). The Purified Water (PW) test article extract was analyzed by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) for ions and metals/elements. A breakdown of the extraction method can be seen in RPT-1151 and in NAMSA report C0839_002/s.

Eleven characterized substances or groups of substances were identified as extractables from the DLP-114 implantable device at levels above the detection limit. An independent consultant (Gad Consulting Services) reviewed the results of the chemical characterization, and came to the determination that the substances listed should not present a potential risk to patients for any duration of implantation to include lifetime exposure. Please see Appendix A of RPT-1151 for the full report on the safety of the results from extractables and leachables testing.

7.4 Clinical Experience

Delpor has completed a first-in-man ex-US PK/safety study of the DLP-114 device in Australia. This was a pilot 4-month trial of the α2 RISP/PABA 1:2 device in healthy subjects implanted in the arm with a single device using the clinical implanter tool. After twelve subjects completed the study, an extension of the study (n=5) was added to bridge the alpha-2 RISP/PABA 1:2 and alpha-4 RISP/PABA 1:3.

A total of seventeen subjects were dosed with the DLP-114 (12 with the α2 RISP/PABA 1:2 and 5 with α4 RISP/PABA 1:3). PK analysis shows the average plasma levels are more variable in the first few weeks but settle into a steady state of about 6-7 ng/mL after Day 40 until the end of the dosing period at Day 123.

The DLP-114 plasma values are in line with the exposure seen following a single 1 mg oral dose; the observed average C_{max} is lower for the DLP-114-α2 device relative to the 1.0 mg oral dose. Conversely, the C_{min} is higher for the DLP-114-α2 than for the oral dose. Mass balance analysis on devices removed from first 12 subjects who have completed the implant period indicate the average output is 1.01 ± 0.10 mg/day. Plasma levels fall below the LLOQ within 12-24 hours after device removal.

The insertion procedure was well-tolerated and incisions healed within a week or two. No device-related serious AEs were reported. Mild to moderate AEs at the implantation site included bruising, itching and pain in some subjects. Risperidone effects included weight gain and prolactinemia. Punch biopsies of the implantation site in the first two subjects after device removal revealed no clinically significant inflammation. One subject developed cellulitis two months into the implant phase of the study. Although the reaction was not rated as serious and responded to antibiotics, the PI felt the reaction was related to the device and to observe maximum caution in a volunteer study, the device was removed on Day 70. It was noted for this participant, who had a relatively low BMI, that the implanted device formed a prominent bulge under the skin of the arm that the participant reported “touching” during the study. It is believed that the lack of subcutaneous fat tissue and the relatively thin superficial fascia in the arm rendered the site problematic in as much as the layer between the skin and muscle was not sufficiently thick to comfortably accommodate the 5 mm OD device in this low BMI individual. This observation has prompted switching the implant site for this IND study to the abdomen where the subcutaneous fat/superficial fascia layer is generally thicker and the surface area available for implantation is greater.

7.5 Risk/Benefit Assessment and Guidance for Investigators

Eligible schizophrenia patients will be stable on 2-3 mg/day oral risperidone for at least 2 weeks, or will be stable on an antipsychotic other than oral risperidone (2-3 mg/day) but complete the conversion phase. Patients stable on 2-3 mg/day oral risperidone will be instructed to take oral risperidone (3 mg/day, unsupervised dosing) starting on Day -7. At the PI’s discretion, if patient has been screened, patient can commence oral dosing of risperidone (3 mg/day, unsupervised) as early as Day -10. Patients stable on an antipsychotic other than oral risperidone (2-3 mg/day) will be required to complete the conversion phase prior to beginning the unsupervised dosing on Day -7. During the conversion phase, subjects will cross-titrate, at the PI’s discretion, from other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks. Starting on Day -4, all patients will continue taking oral risperidone under supervision. Implantation of DLP-114 will follow the oral risperidone treatment. Exposure following implantation of two DLP-114 is

expected to be comparable to that of a 2-3 mg/day oral risperidone dose for 6 or 12 months. Rat PK studies suggests exposure may be greater the first few weeks following implantation. Also, following implantation in rats, a "burst" effect has been observed, with the highest plasma level observed 2 days following implantation (~3 x higher than the steady state reached in the first week of implantation). This initial burst is not seen in rabbits or human subjects.

Dose dumping is considered unlikely. The total amount of risperidone loaded into each DLP-114 device is ~360 mg in an alpha-4 device and ~435 mg in an alpha-7 device. The device has a robust design and functional testing regimen, and there have been no PK or mass balance signals suggestive of dose dumping in preclinical *in vivo* studies or clinical studies to date. Examination of devices removed from animals and human subjects after 4-12 months showed no evidence of in vivo membrane rupture or compromised reservoir or seals.

Premarketing experience with oral risperidone includes eight reports of acute overdose with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms resulting from an overdose were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia, hypotension and extrapyramidal symptoms.

All components of the DLP-114 device that are directly exposed to tissues have been shown to be biocompatible. The mechanism of release from DLP-114 is passive diffusion. The device permits diffusion of water-soluble forms of risperidone across its membranes (driven by the concentration gradient created between the reservoir volume and the interstitial fluid), while retaining the insoluble suspension within the reservoir. The reservoir dimensions, housing material, finish and shape are modeled directly after Viadur, an FDA-approved osmotic implant. [1] The system is designed for subcutaneous implantation using a sterile disposable implanter tool and a minimally invasive procedure similar to that used for Viadur and Vantas [1, 2]. DLP-114 is implanted subcutaneously with local anesthesia in a quadrant of the abdomen. Implant removal is straightforward; the polished titanium surface has low tissue binding.

Some local inflammation observed at the site of implantation in rats and more prominently in rabbits was only observed at histopathology and did not result in any visible swelling or erythema on the skin surface. Subcutaneous inflammation is common among injectable sustained release products with acidic formulations. These products are well-tolerated and such inflammation is reversible. Histopathology conducted on two sentinel subjects in Delpor's ex-US Phase 1 study showed no clinically significant inflammation following 4 months exposure.

Potential adverse events that may be observed in this study due to implantation of the device include the following:

- Pain at the site of implantation;
- Skin irritation at the site of implantation;
- Local tissue and blood vessel injuries;
- Hematoma;
- Local and/or systemic microbial infections;
- Seroma.

The distribution, metabolism, excretion, and systemic effects of risperidone are expected to be the same regardless of the route of administration (oral Risperdal, intramuscular Risperdal Consta or subcutaneous implant DLP-114). Several studies have reported risperidone-associated adverse effects such as hyperprolactinemia, weight gain, extrapyramidal symptoms, and other adverse effects in patients with schizophrenia.

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. These observations are the origin of the label warning of increased mortality among elderly patients taking risperidone. Elderly will be excluded from this clinical trial.

Para-aminobenzoic acid (4-amino benzoic acid, PABA), is an excipient in the DLP-114 drug/device product. PABA is an intermediate in the synthesis of folate by bacteria, plants, and fungi [3, 4] . Many bacteria, including those found in the human intestinal tract such as *E. coli*, generate PABA. PABA has been used as a component of sunscreens, and, given orally, as a diagnostic marker. It is a food additive. Clinical evidence suggest oral PABA provides benefit as an antifibrotic. Small amounts of PABA are found in cereal, eggs, milk and meats. Detectable amounts are normally present in human blood, spinal fluid, urine, and sweat [5]. The total amount of PABA loaded into a single DLP-114 implant is 240 mg for the α4 and 290 mg for the α7 device. The α4 implant is expected to operate for at least 6 months whereas the α7 is designed to operate for at least one year, eluting risperidone at a fairly constant rate throughout the period. PABA release from the DLP-114 implant parallels that of risperidone, in an apparent 2:1 stochiometric relationship. Assuming the PABA release is constant, exposure following implantation of a single DLP-114 implant is projected to be less than 1 mg/day. The projected daily exposure of PABA for each study patient is projected not to exceed that of one application of a 2% PABA sunscreen (3 mg becoming systemically bioavailable) or the consumption of seven servings of Brussel sprouts or peas (0.8 to 1.0 mg of total PABA). The exposure to the amount of PABA included in the DLP-114 is not expected to pose any significant safety risk to patients.

PVP is used as a binder to aid tableting of the DLP-114 risperidone drug formulation. Approximately 32 mg of PVP40 is included in each DLP-114 α4 implant and 40 mg in each α7 device. PVP is used in cosmetic formulations, food additives and pharmaceutics. PVP is approved as a food additive and clarifying agent for beverages and beer. PVP is added to wine up to 60ppm (21CFR173.55), so a 750 ml bottle of wine could contain up to 45 mg PVP. PVP is used as a binder to create tablets of a wide variety of oral drug products including acyclovir, ibuprofen, magaldrate, nystatin, phenytoin, trimethoprim, sulfonamides and antibiotics. PVP dissolved at a concentration of 3.5% in buffered saline has been used as a plasma substitute in emergency battlefield situations and surgery. A lower molecular weight PVP is included in intravenous formulations of antineoplastic drugs. The exposure to the amount of PVP included in the DLP-114 is not expected to pose any significant safety risk to patients.

A small amount of stearic acid is included in each DLP-114 device (~12 mg in the α4 device and ~16 mg for the α7 device) as a lubricant to aid tableting of the formulation. Stearic acid is a ubiquitous fatty acid found in food and tissues. It is used in food with no limitation other than current good manufacturing practice. This ingredient is generally recognized as safe as a direct human food ingredient (21CFR 184.1090). The average intake of stearic acid is 5.7 g/day (8.1% of total fat) for women and 8.2 g/day (8.4% of total fat) for men, according to data from NHANES (National Health and Nutrition Examination Survey) 2001-2002 [6]. The exposure to the amount of stearic acid included in the DLP-114 is not expected to pose any significant safety risk to patients.

The patients enrolled in this study are expected to benefit by maintaining plasma levels on the implant comparable to plasma levels achieved on their oral risperidone.

The study is being conducted with schizophrenia patients who are stable on oral risperidone (2-3 mg/day) for at least 2 weeks. Preclinical and clinical evidence indicate the operating lifetime of

the DLP-114 α4 will be at least 6 months and the α7 device will operate for at least 1 year, but this is not certain, the drug and/or the acid (which is needed to deploy the drug) may run out before 6 months for the alpha 4 device or 12 months for the alpha 7, and the patient may be underdosed, particularly in the later part of the dosing period. To safeguard an individual subject, stopping rules will include signs of impending relapse including:

- Hospitalization due to worsening of schizophrenia;
- Increase (worsening) of the PANSS of ⩾30% from baseline. $PANSS_T$ score confirmed at a second visit conducted within 1-7 days;
- Clinically significant emergent or worsening suicidal, homicidal, or aggressive behavior;
- A CGI-I Improvement (CGI-I) score of 6 (much worse) or 7 (very much worse) after start of study;
- A need for additional antipsychotic treatment following the conversion phase, with the exception of protocol-permitted short-term add-on therapy (in the instance that the investigator believes that the subject is not experiencing a true exacerbation of schizophrenia, a supplemental antipsychotic may be used for a maximum of 14 days upon consultation with the medical monitor.)

8 STUDY OBJECTIVES

8.1 Primary

To evaluate the safety and tolerability of DLP-114:

1) Determine the number and percent of patients experiencing a treatment-emergent adverse event;
2) Evaluate the incidence of local site reactions;
3) Assess the tolerability of implantation and explantation procedures.

8.2 Secondary

1) Measure the plasma concentration of risperidone and 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) following repeated oral administrations.
2) Measure the plasma concentration of risperidone and 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) following switch from oral risperidone to subcutaneous implantation of two DLP-114 devices.
3) Measure exploratory treatment outcomes using 2 psychiatric rating scales: the Clinical Global Impression (CGI-I) rating scale and the PANSS.
4) Measure the amount of risperidone drug substance remaining in the DLP-114 reservoir following its removal, in order to estimate average daily output and duration.
5) Determine average depth of device placement and any potential migration.

9 STUDY DESIGN

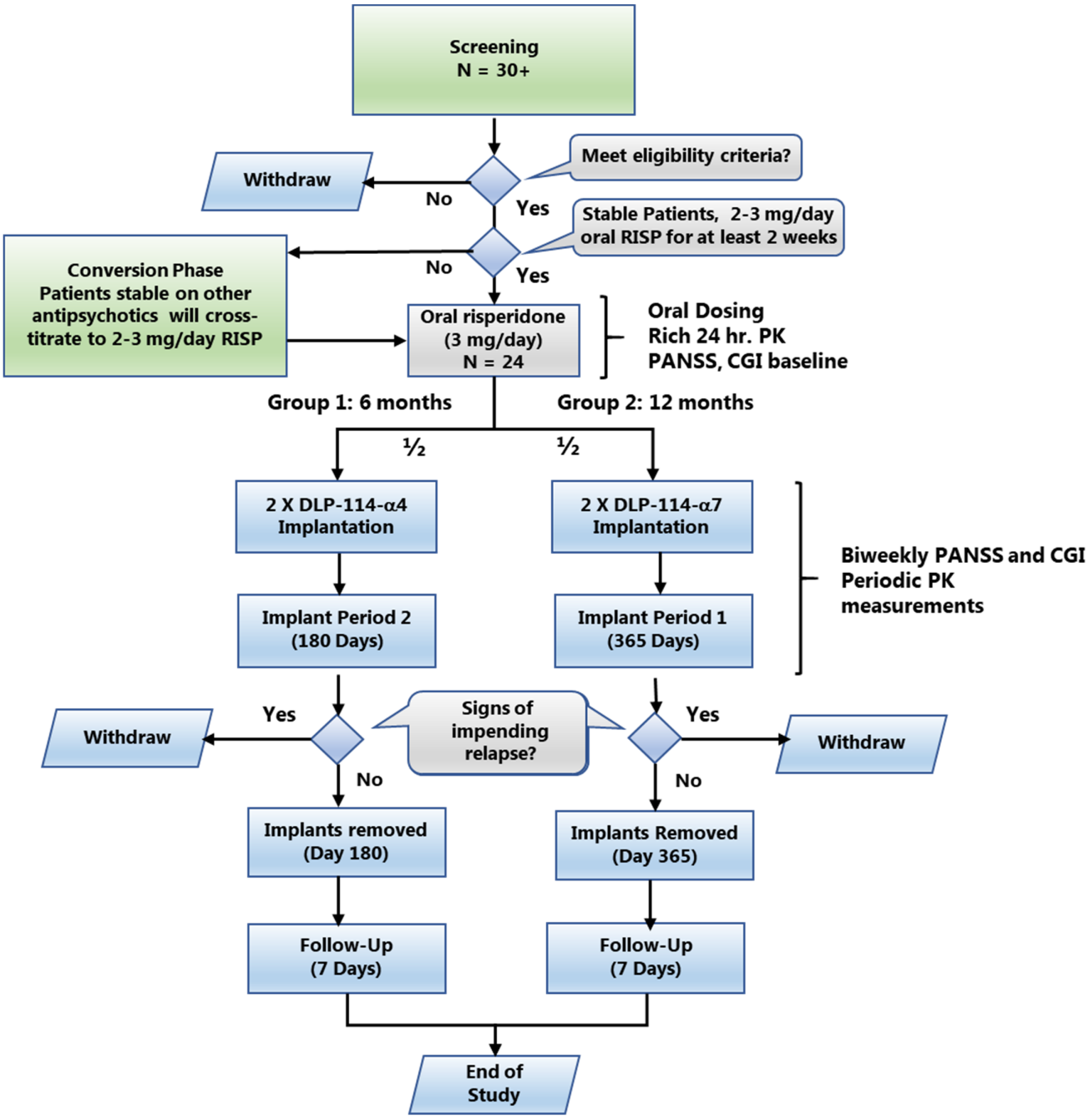
9.1 Design Type and Description

The study is an open-label, parallel group design aimed at assessing the safety and tolerability of DLP-114 and evaluating its utility in achieving a PK profile that is comparable to the marketed oral form of risperidone.

Treatment of each patient will be conducted in four sequential periods (subjects will either enter the conversion phase or the unsupervised oral risperidone [3 mg/day] period) following Screening (Error! Reference source not found.)

1. Conversion phase, if applicable (Cross-titration, at the PI's discretion, from other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks to achieve an oral risperidone dose of 3 mg by Day -14) - oral risperidone (3 mg/day)
2. Unsupervised oral risperidone (3 mg/day)
3. Supervised oral risperidone (3 mg/day)
4. DLP-114 implant treatment with oral supplement (1 day)
5. DLP-114 implant treatment;
6. Follow-up.

Figure 1: Flowchart of Study Design



For a detailed description of the schedule of assessments refer to **Section 14** (Study Conduct Schedules and Guidelines) and **Appendix 1** (Overall Schedule of Assessments).

For a detailed description of blood collection times (including time point windows) refer to **Appendix 2** (Pharmacokinetic Sample Collection Schedule).

9.1.1 *Unsupervised oral risperidone period (Day -7 to -5)*

Eligibility in the study requires that patients have been stable on 2-3 mg/day oral risperidone for at least 2 weeks. Starting on Day -7, and as early as Day -10 at the PI's discretion, patients who are currently on oral risperidone therapy (2-3 mg/day) will be instructed to take a dose of 3

mg/day oral risperidone (unsupervised), daily through Study Day -5.

9.1.2 *Oral risperidone conversion phase (minimum of 2 weeks prior to implant)*

Patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) will cross-titrate, at the PI's discretion, from the other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks. The objective of the oral conversion phase is for all subjects to achieve an oral risperidone dose of 3 mg by Day -14.

9.1.3 *Supervised oral risperidone period (days -4 to 1)*

On Days -4, -3 and -2 all patients will be required to attend the clinical facility for outpatient visits to receive a dose of 3 mg/day oral risperidone (under the supervision of the clinical facility staff) and safety assessments.

On the morning of Day -1 patients will be admitted and confined to the clinical facility overnight and for a period of 7 days. Following admission each patient will receive an additional supervised oral dose of risperidone (3 mg). PK samples will be collected pre-dose and at a number of time points following the fourth dose of oral risperidone. On the morning of Day 1 (immediately after the 24-hour PK sample, and immediately before the DLP-114 implantation), another oral dose will be administered (3 mg).

9.1.4 *DLP-114 implant treatment period with oral supplement (Days 1 to 2)*

Patients will be assigned to Group 1 (DLP-114-α4) or Group 2 (DLP-114-α7). On Day 1, following measurements of vital signs and collection of a pre-implantation blood samples (for PK), each Group 1 patient will be implanted with two DLP-114-α4 and each Group 2 patient with 2 DLP-114-α7 devices. Following implantation, vital signs will be monitored, an ECG will be administered and safety laboratory tests will be performed. PK samples will be collected at several time points after DLP-114 implantation. A final oral dose of risperidone (3mg) will be administered 24 hours after implantation

9.1.5 *DLP-114 implant treatment period (days 2-183 [± 7] for Gr 1, or days 2-365 [± 7] for Gr 2)*

Patients will remain in the clinical facility for 72 hours post-implantation and will be discharged no later than Day 7. PK samples will be collected each day during the confinement period and on the day of discharge.
Both groups will return to the clinical facility for outpatient visits once every week for safety assessments and PK sampling during the first 4 weeks after implantation (i.e., days 7, 14, and 28)

and bi-weekly after that. Safety assessments will include vital signs, measurement of body weight, assessment of AEs, C-SSRS, review of con meds, and inspection of DLP-114 implant site at every visit. Other safety assessments (performed less frequently) will include a urine drug test, urine pregnancy test (female subjects only), safety lab test (blood and urine), ECG, CGI-I, PANSS, BARS, SAS, and AIMS (see **Appendix 1**. Overall Schedule of Assessments).

An ultrasound will be conducted on day 14 and prior to implant removal in order to assess the depth of the implanted device and any possible vertical migration over time.

Assessments may be performed more frequently than what's stated in **Appendix 1** based on the PI's discretion. If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping.

On the morning of Day 183 [± 7 days] (α4 Group 1) or Day 364 [± 7 days] (α7 Group 2) patients will attend the clinical facility for the removal of the DLP-114 implants. Vital signs and body weight will be obtained and a PK sample collected prior to the removal of the implant. Following the removal of the implant, vital signs will be monitored, safety laboratory tests will be conducted and a number of PK samples collected. Patients will be confined to the clinical facility for 2 nights and will be discharged on the following day (Day 185 [± 7 days] for Group 1 or Day 366 [± 7 days] for Group 2) following inspection of the implant site, a complete physical exam, safety review and PK sampling. It may not be practical to schedule the exact explantation date at the time of patient enrollment (i.e., 6-12 months in advance). As a result, the target date of explantation may be adjusted [± 7 days] in order to accommodate potential scheduling conflicts with the physician responsible for the explantation procedure. In the event that the explantation date is adjusted, all the target dates following explantation will also be adjusted accordingly.

9.1.6 *Follow-up and End of Study Visits (7 days [±1] after device removal)*

Patients will return to the clinical facility 3 days post implant removal (Day 186 for Group 1 and Day 367 for Group 2) for safety assessments and collection of PK samples.

Each patient's participation in this study will conclude on Day 190 (Group 1, α4) or Day 371 Group 2, α7), 7 days post implant removal. Patients will attend the clinical facility for final safety assessments, including vital signs, an abbreviated physical examination, inspection of the implantation site, body weight, and AE assessment/review.

9.2 Dose Administration Stopping Rules for an Individual Subject

The PI and/or Sponsor may suspend or terminate dose administration upon any of the following events:

- One occurrence of a Serious Adverse Event (SAE) assessed to be probably or possibly related to dosing with the investigational product;
- Two or more severe Adverse Events (AEs) of the same character that are determined to be clinically significant by the investigator or sponsor and are assessed as probably or possibly related to dosing with the investigational product;
- If four or more patients experience the same or similar moderate intensity AE which is possibly or probably related to the investigational product (or device), the sponsor and the investigator will review all available safety data and will recommend if dosing should continue.
- Signs of impending relapse, including:
    - Hospitalization due to worsening of schizophrenia;

- Increase (worsening) of the PANSS of ⩾30% from baseline. $PANSS_T$ score confirmed at a second visit conducted within 1-7 days;
- Clinically significant emergent or worsening suicidal, homicidal, or aggressive behavior;
- A CGI-I Improvement (CGI-I) score of 6 (much worse) or 7 (very much worse) after start of study;
- A need for additional antipsychotic treatment

9.3 Suspension or Termination of Study at the Investigational Site

The sponsor reserves the right to terminate the investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- Unacceptable safety and tolerability;
- The incidence or severity of AEs or SAEs that are observed in this study indicates a potential health hazard to patients;
- Serious or persistent noncompliance by the investigator with the protocol, clinical research agreement, principles of the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), or applicable regulatory guidelines in conducting the study;
- IRB decision to terminate or suspend approval for the investigator;
- Investigator request to withdraw from participation;
- Volunteer enrollment rate is unsatisfactory.

9.4 Randomization and Blinding

Patients will be assigned to one of two groups that will be dosed in parallel. The dosing period for Group 1 is 183 (± 7) days and Group 2 364 (± 7) days. The study is open label.

9.5 Endpoints

9.5.1 *Safety Endpoints*

Safety endpoint evaluations will include the following:

- Incidence and severity of AEs;
- Local tolerance at the implantation site will be examined and scored for severity of visible signs of irritation/inflammation;
- Tolerability of the implantation and explantation procedures;
- Vital signs parameters;
- Physical examination findings;
- Electrocardiogram parameters;
- Safety laboratory test parameters (serum chemistry, hematology, urinalysis).
- C-SSRS
- EPS Assessments (BARS, SAS, AIMS)

9.5.2 *Pharmacokinetic Endpoints*

Evaluation of plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone).

PK parameters to be calculated for oral risperidone treatment period include:

- Maximum concentration (C_{max});
- Minimum concentration (C_{min})
- Time to maximum concentration (T_{max});

- Time to minimum concentration (T_{min})
- terminal half-life ($t_{1/2}$).

PK parameters to be calculated for implant treatment period include:

- Maximum concentration (C_{max});
- Minimum concentration (C_{min})
- Time to maximum concentration (T_{max});
- Time to minimum concentration (T_{min});
- Average concentration (C_{ave})

9.5.3 *Exploratory Treatment Outcomes*

Exploratory treatment outcomes will be assessed using 2 psychiatric rating scales: the Clinical Global Impression (CGI-I) rating scale and the PANSS.

9.5.4 *Device Endpoints*

- Implant spontaneous migration away from the initial subcutaneous implantation area during the implant treatment period.
- Amount of unreleased drug substance remaining in the DLP-114 implant following its removal.
- Depth of device placement

9.6 Duration of the Study

Group 1

The study duration for each Group 1 patient will be up to 236 days (up to 278 with the conversion phase, if applicable). This includes the following:

- Screening period (28 days)
- Conversion phase (minimum 2 weeks)
- Oral risperidone (3 mg/day, 3-6 days, unsupervised);
- Oral risperidone (3 mg/day, 4 days, supervised);
- DLP-114 α4 implant treatment (Group 1 183 days [± 7] days);
- Follow-up (7 (± 1) days).

Group 2

The study duration for each Group 2 patient will be up to 417 days (up to 459 with the conversion phase, if applicable). This includes the following:

- Screening period (28 days)
- Conversion phase (minimum of 2 weeks)
- Oral risperidone (3 mg/day, 3-6 days, unsupervised);
- Oral risperidone (3 mg/day, 4 days, supervised);
- DLP-114 α7 implant treatment (364 [± 7] days);
- Follow-up (7 (± 1) days).

If patients experience any clinically significant adverse events during the study, they may be required to remain in the clinical facility for further observation at the discretion of the investigator. If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping.

9.7 Study Design Rationale

This study design aims to establish the safety and tolerability of the DLP-114 implant and investigate the feasibility of switching from oral risperidone treatment to DLP-114 implant-based treatment.

The open-label, parallel group design is intended to show comparable plasma risperidone PK when patients switch from 3 mg oral Risperdal® to either 1) DLP-114-α4 for 6 months (Group 1) or 2) DLP-114-α7 for one year (Group 2).

Several safety assessments including vital signs, ECG, safety laboratory tests, regular inspections of the implantation site and AE monitoring are included in the design in order to minimize risk for the patients and obtain appropriate set of safety data to address the study primary objective.

Given the primary Central Nervous System (CNS) effects of risperidone, caution should be used when this drug is taken in combination with other centrally acting drugs. In order to minimize the risk of CNS acting drug interactions, prescription/non-prescription drugs and drugs of abuse restrictions have been included with appropriate tests conducted throughout the study to ensure compliance.

Risperidone has been classified in US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Given this classification, this study will aim to mitigate against Exposure In Utero Events (EIU). Inclusion/exclusion criteria and study restrictions relating to contraception, as well as pregnancy tests have been included in the study design.

10 PATIENT SELECTION

10.1 Number of Patients

Two groups of 12-15 schizophrenia patients (12-15 Group 1 and 12-15 Group 2) who have been stable on 2-3mg/day oral risperidone for at least 2 weeks, or who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) but complete the conversion phase, will receive the DLP-114 implants. Group 1 will receive 2 DLP-114-α4 devices and Group 2 will receive 2 DLP-114-α7 devices.

10.2 Inclusion Criteria

To be eligible for enrolment, patients must meet the following criteria:

1. Adult patients 18-70 years of age of both sexes diagnosed with schizophrenia or schizoaffective disorder according to DSM-V who have been stable on oral risperidone (2mg-3mg) for at least 2 weeks.
   Note: Patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) and complete the Conversion Phase may be enrolled.
2. Patient (and/or a patient's authorized legal representative) has provided written informed consent
3. Patient meets the following criteria:
   a. Outpatient status
   b. PANSS Total Score ≤ 80 at screening.
   c. A score of ≤ 4 on the following PANSS items:
      i. Conceptual disorganization

ii. Suspiciousness
iii. Hallucinatory behavior
iv. Unusual thought content
v. Hostility

d. CGI-S ≤ 4 (moderately ill)\Lack of clinically significant suicidal ideation or behavior in investigator's judgement; C-SSRS score type of 4-5 require evaluation by mental health professional to ensure patient safety in study

4. Body Mass Index (BMI) within the range of 18.5 to 40.0 kg/m^2 (inclusive);
5. Ability to understand the nature and objectives of the trial, including risks and adverse events, and be able to read, review and sign the informed consent document prior to conduct of any study procedures;
6. Willing and able to comply with the requirements of the study protocol; including willingness to visit the clinical facility for all outpatient visits and confinement periods;
7. Have suitable venous access for blood sampling.
8. Patient is assessed by the Investigator to be symptomatically stable with regard to pre-existing medical conditions as evidenced by medical history, non-clinically significant findings on physical examination, vital signs, clinical laboratory evaluations (hematology, serum chemistries, and urinalysis) or 12-lead electrocardiogram (ECG). Subjects may continue on their current prescribed medication regimens to control pre-existing medical and psychiatric conditions (other than schizophrenia) including the use of prescribed PRN medications.

10.3 Exclusion Criteria

Patients will be excluded from the study if *any* of the following criteria apply:

1. PANSS score at baseline is ≥ 20% change from screening.
2. Hospitalized or required acute crisis intervention for symptom exacerbation in the 60 days prior to admission as determined by the Investigator
3. Patient has a history of suicide attempt in the last year, or in the opinion of the investigator is currently at imminent risk of suicide
4. Patient experiencing acute depressive symptoms within the past 30 days, according to the Investigator's opinion, that required treatment with an antidepressant
5. Has a current or recent (within 12 months) DSM-V diagnosis of moderate or severe substance use disorder (except for tobacco use disorder) or has a positive urine drug screen for prohibited substances at screening.
6. Have impaired hepatic (ALT/AST >1.5 times higher than the upper limit of normal) or renal function (eGFR<50 mL/min)
7. Previously defined hypersensitivity to Risperidone
8. History of neuroleptic malignant syndrome (NMS)
9. Electroconvulsive therapy within 6 months of admission
10. Requires current use of agents that are strong inhibitors and inducers of cytochrome P450;
11. Known hypersensitivity or allergy to lidocaine or any local anesthetic agent of the amide type (local anesthetic used during implant and explant procedures);
12. Presence of clinically significant skin disorders (such as, but not limited to, skin cancer, psoriasis, eczema, or atopic dermatitis), evidence of recent sunburn, scar tissue, tattoo, open sore, body piercing or branding at the intended implantation site that would interfere with the implantation procedure or interfere with implant site assessments as determined by the investigator;
13. History of clinically significant hypersensitivity or allergic reactions;

14. Known allergy or hypersensitivity to PABA;
15. Known allergy or hypersensitivity to parabens, local anesthetics of the ester type, and sulfa drugs including antibiotics and thiazide diuretics;
16. Known hypersensitivity to titanium, implant materials or procedure;
17. Administration of an investigational drug or device within 1 month prior to first dosing;
18. Positive result for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibody, or HIV antibody;
19. Pregnant or lactating patients. Positive pregnancy test;
20. Positive drug test for Methamphetamines, Opiates, Cocaine, Phencyclidine, Benzodiazepines, Barbiturates, Methadone, Antidepressants and Amphetamines or positive alcohol test at screening or prior to first dose;
21. Poor CYP2D6 metabolizer;
22. History of skin picking or delusional parasitosis;
23. Known history of abnormal scar formation or family history of keloid formation

10.4 Patient Withdrawal Criteria

Patients will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the investigator, or medically trained nominee, may discontinue a patient from the study, according to the following criteria, to protect the patient's health:

1. The need to take medication which may interfere with study measurements;
2. Intolerable/unacceptable adverse experiences;
3. Major deviation of study protocol procedures;
4. Non-compliance of patient with protocol;
5. Patient unwilling to proceed and/or consent is withdrawn; or
6. Withdrawal from the study if, in the investigator’s judgement, it is in the patient’s best interest.
7. Signs of impending relapse

The reasons for discontinuation will be recorded in the Case Report Form (CRF) and included in the final clinical study report, along with any adverse events and necessary medical treatment.

Any patient who prematurely discontinued the study should undergo all Early Termination assessments/procedures (**Appendix 1**. Overall Schedule of Assessments).

In the event that a patient is discontinued from the study due to an SAE, the investigator, or medically trained nominee, will evaluate the urgency of the event. If the situation warrants, the investigator, or medically trained nominee, will take appropriate diagnostic and therapeutic measures and make attempt to notify the sponsor medical representative. If the situation is not an immediate emergency, the investigator, or medically trained nominee, at the clinical study facility will attempt to contact the sponsor representative for consultation. No medical help, diagnosis, or advice will be withheld from the patient due to an inability to contact the sponsor. The patient will be encouraged to remain available for follow-up medical monitoring. The sponsor will be notified as soon as possible of any patient withdrawals.

10.5 Patient Replacement

Final confirmation of eligibility will be checked on dosing day. Patients who withdraw consent from the study prior to completion of the supervised oral risperidone treatment period may be replaced at the discretion of the investigator and following consultation with the sponsor.

Patients who withdraw consent from the study prior to completion of the first week of the implant treatment period for reasons other than occurrence of an SAE will be replaced.

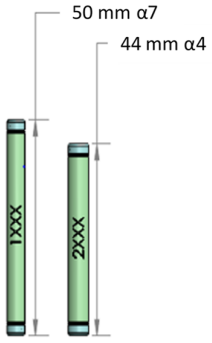


Figure 2C: Relative Length of α4 and α7 devices

11 INVESTIGATIONAL PRODUCT

11.1 Identification and Description

Two versions of the DLP-114 device will be tested, the α4 device which is designed to operate for 6 months and the α7 device which is intended to operate for 1 year. Both DLP-114 device versions are drug-device combination products consisting of a cylindrical titanium reservoir (5 mm in diameter and either 44 mm in length for the α4, or 50 mm in length for the α7) filled with a dry compressed mixture of risperidone aminobenzoate plus an excess of PABA. Standard Polyvinylidene difluoride (PVDF) membranes are positioned at each end of the reservoir (**Figures 2A, 2B, and 2C**). The device is sealed in a vial under vacuum and activated by the end-user by introduction of sterile saline into the vial (similarly to the reconstitution of a lyophilized product).

11.2 Investigational Substance

Risperidone base powder will be received from the supplier (INKE, part of NEURAXPHARM GROUP, DMF 15682) by Hantel Technologies, an ISO 13485-compliant contract manufacturing organization. Identity testing will be conducted.

The drug substance is risperidone, a psychotropic agent belonging to the chemical class of benzisoxazole derivatives.

Table 3. DLP-114 drug substance components, component amounts per device and projected daily exposure after implantation. Alpha-4 / Alpha-7

Component	Total Loaded Equivalents (mg)[1]	Projected Daily Exposure (mg)[2]
Risperidone Base	360/435	1/1
PABA	240/290	<1/<1
PVP 40	32/40	<0.3/<0.3
Stearic Acid	12/16	<0.1/<0.1

[1]Mass loaded into individual units assuming a fill weight of 650 mg (alpha-4) and 780 mg (alpha-7)

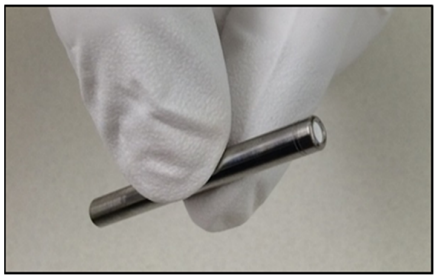


Figure 2A: Image of DLP-114 Titanium Implant

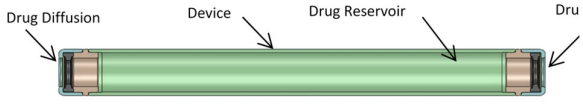


Figure 2B: Section View of the DLP-114 Device

[2]Normalized to dose elution rate of 1.0 mg/day projected for active

The DLP-114 reservoir (**Figure 2B**) is filled with tablets made from a powder intermediate consisting of risperidone plus a 2x stochiometric excess of PABA. To aid in tableting the formulation, PVP40 and stearic acid are added. The formulation components and projected daily exposure are shown in **Table 3.** The fill weight is 650 mg (alpha-4) and 780 mg (alpha-7)

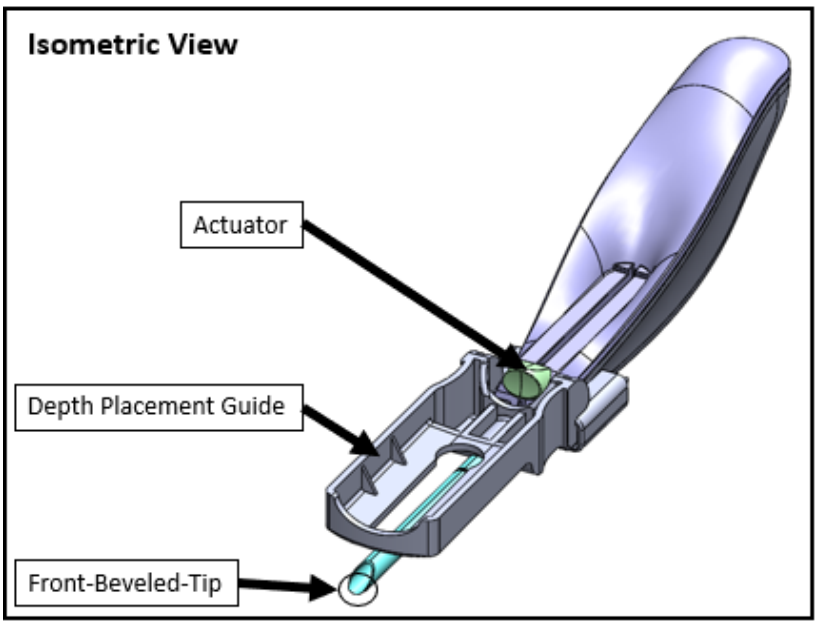


Figure 3: Image of the DLP-114 Implanter Tool.

11.3 Identification and Description of Reference Product

Risperdal® (risperidone) will be used for the oral treatment period of the study.

Risperdal® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange).

Risperdal® is manufactured by Janssen Pharmaceutica Products, LP. Additional information for Risperdal® is provided in the Risperdal® (risperidone) Product Information (**Appendix 4 –** Risperidal® (risperidone) Product Information).

11.4 Description of the Investigational Device

The clinical implant devices are designed under the Food and Drug Administration Design Controls (FDA 21 CFR 820.30) for human use. The device, shown as a section in **Figure 2B**, is a symmetrical cylinder 5 mm in diameter and either 44 mm in length for the DLP-114-α4 or 50 mm in length for the DLP-114-α7, with an internal drug compartment and diffusion ports at either end.

The cylindrical titanium reservoir is filled with a dry compressed mixture of risperidone plus a 2-fold molar excess of para-aminobenzoic acid (PABA) (**Figure 2B**).

The mechanism of release from DLP-114 is passive diffusion, no mechanical parts or osmotic engines are needed; the entire reservoir volume is available for loading of the drug formulation.

The only components directly exposed to tissues are the titanium reservoir and PVDF membranes, all have been shown to be biocompatible.

11.5 Implanter Tool

The DLP-114 will be implanted using the Implanter Tool (**Figure 3**). This is a medical device used by medical professionals to implant the DLP-114 subcutaneously, where risperidone can be slowly released into the surrounding tissue. Both the DLP-114 device and the Implanter Tool are modeled after existing approved devices with respect to materials, size and shape.

The Implanter Tool is manufactured by using well-characterized materials suitable for medical devices. Detailed instructions on the correct handling and application of the Implanter Tool for implanting of DLP-114 are described in the IFU (see **Appendix 5**).

11.6 Preparation, Labelling and Supply

The investigational device and reference product to be administered will be labeled according to Good Manufacturing Practice for Medicinal Products. The detail on the labels will include, but not be limited to:

- The notation- '*Caution: New Drug--Limited by Federal (or United States) law to investigational use*';
- Protocol number;
- Investigator/site identification;
- Trial patient number;
- Name of sponsor;
- Route of administration;
- Batch number;
- Retest date/expiry date;
- Storage conditions.

A sample of the label is attached under **Appendix 6**. Study drug supplies will be stored securely at the Pharmacy.

Investigational products (DLP-114) will be supplied to the Pharmacy by the sponsor (or delegate). The Risperdal® will be procured by the site.

Detailed instructions for the preparation, labeling and supply of the investigational products are described in the study pharmacy manual.

11.7 Storage, Handling and Accountability of Investigational and Reference Products

11.7.1 *DLP-114 Storage and Handling*

Devices are stored and distributed to clinical sites sealed in lyophilization vials under vacuum, and should be stored at 2°-8°C.

11.7.2 *Risperdal® Storage and Handling*

Risperdal® tablets should be stored at controlled room temperature 15°-25°C and protected from light and moisture.

Additional information for Risperdal® is provided in the Risperdal® (risperidone) Product Information (**Appendix 4 -** Risperdal ® (risperidone) Product Information).

11.7.3 *Accountability*

Standard Operating Procedures will be followed for the receipt, handling and accountability of the investigational products.

Investigational product must be stored in a locked area and protected from temperature extremes. Refer to the study pharmacy manual for additional storage requirements.

The Pharmacy must ensure that deliveries of investigational products from the sponsor are correctly received by a responsible person, that all receipts of drug shipments are recorded on the appropriate Drug Accountability forms prepared by Pharmacy and that the products are stored in a secure area under recommended storage conditions. It is the responsibility of the investigator to ensure that the integrity of packaged investigational products not be jeopardized prior to dispensing.

All materials supplied are for use only in this clinical study and should not be used for any other purpose.

The Investigator, the site Pharmacist, or other personnel with authorized access to the investigational products will be responsible for ensuring that the study drug supplies used in the study are securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements.

All study drugs will be dispensed in accordance with the investigator's prescription and it is the investigator's responsibility to ensure that an accurate record of "Investigational Product issued and returned" is maintained.

The Pharmacy will dispense the investigational products to the clinical facility. Dispensing and supply will be verified by a second staff member. Dispensation will be recorded in the drug accountability records. The study pharmacy manual defines the procedures for dispensing. The clinical facility staff will administer the study medication only to patients included in this study following the procedures set out in this study protocol.

Each patient will be given only the investigational product preparation carrying his/her study number. Study drug administration will be documented in the CRF and other study drug record(s). The investigator (or designated trained site staff) is responsible for assuring the retrieval of all left-over study supplies following administration to each patient.

Any quality issue noticed with the receipt or use of an investigational product (packaging, appearance, pertaining documentation, labelling, expiry date, etc.) should be promptly notified to the sponsor, who will initiate recall procedures.

Under no circumstances will the investigator supply any of the investigational products used in this study to a third party, allow the investigational product to be used other than as directed by this Clinical Trial Protocol, or dispose of investigational product in any other manner.

12 ADMINISTRATION OF INVESTIGATIONAL PRODUCTS

12.1.1 *Oral Risperidone Administration*

Risperidone tablets must be taken approximately 1 hour prior to any food consumption at approximately the same time each morning.

On Day -7, or as early as Day -10 at the PI's discretion, through Day -5, patients who are currently on oral risperidone therapy (2-3 mg/day) will self-administer 3 mg/day oral risperidone.

During the conversion phase, subjects who are stable on an antipsychotic other than oral

risperidone (2-3 mg/day) will be tapered off their current antipsychotic and titrated, at the PI's discretion, to oral Risperidone 3 mg/day. Subjects will be dispensed a sufficient quantity of oral risperidone to last until the next scheduled study visit (+/- 3 days). Oral risperidone 1 mg to 3 mg/day will be self-administered at the investigator's discretion in the conversion phase, either unsupervised or under the supervision of the investigator or other trained designee. Compliance with oral study medication will be monitored by tablet counts. Subjects who are noncompliant with oral study medication, in the Investigator's judgment, are to be counselled on the importance of adhering to the daily administration schedule

Figure 4A: Appearance of bubble in DLP-114 vial following proper hydration

On Days -4 to -1, patient will self-administer 3 mg/day oral risperidone in the clinical facility under the supervision of the investigator or other trained designee.

Each oral dose of risperidone will be administered with a full cup (approximately 240 mL) of non-carbonated room temperature water.

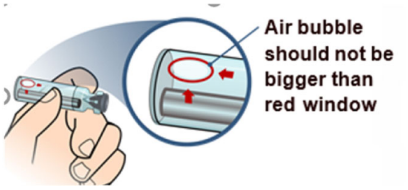


Figure 4B: The IFU provides guidance on how to check the hydration bubble size

Tablets must be swallowed whole and not chewed, divided, dissolved or crushed.

Oral risperidone will be taken daily for 6 days as follows:

- Day -4 to Day 2 (6 days) – 3 mg/day

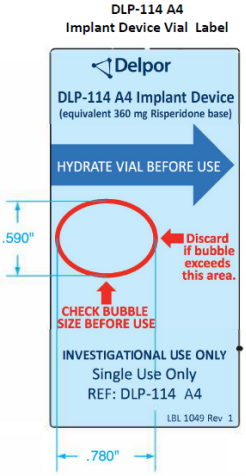


Figure 4C: Vial label with bubble indicator

The penultimate dose of oral risperidone will be administered immediately prior to the DLP-114 implantation, and the final dose of oral risperidone, will be administered 24 hours after the DLP-114 implantation. The exact dates and times and dose of each study drug administration will be recorded in the CRF.

12.1.2 *DLP-114 Implantation*

Each DLP-114 device is activated by the end-user on site. A detailed description of the hydration protocol is given in the DLP-114 Instruction for Use. One precaution to ensure proper hydration is to inspect the vials following introduction of saline. A bubble is expected to form in the vial as shown in **Figure 4A**. Any larger bubble would indicate inadequate hydration and the device should not be used. A bubble size indicator is included on the vial label which allows the user to check if the bubble size is acceptable (**Figure 4B and 4C**)

Subcutaneous implantation of two DLP-114 devices (either α4 or α7) will be performed by a qualified medical professional with experience conducting minor surgical procedures.

The DLP-114 devices will be implanted in a quadrant of the abdomen 5 cm from midline and 5 cm from the ribs using a sterile disposable implanter tool and local anesthesia in a minimally invasive procedure similar to that of other approved drug device products. Refer to the **"Device Instructions for Use"** for a guide on proper handling and application of the Implanter Tool for

implanting of DLP-114. While the IFU contains detailed instructions, the implanting physician may deviate based on their clinical knowledge. If the physician does choose to deviate, they should record this on the implant-explant physician report.

The device will remain implanted for either 183 (± 7) days (Group 1, α4) or 364 (± 7) days (Group 2, α7).

Upon completion of the implant treatment period, the device will be removed by a qualified medical professional.

13 CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

Compliance to these restrictions will be assessed throughout the duration of the study.

13.1 Concomitant Medications

Prior and Concomitant Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 45 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the patient's/subject's eligibility to participate or continue to participate in the study. Any medication the patient takes between Screening and the end of the study, other than the study drug, is considered to be a concomitant medication. All concomitant medications must be recorded.

Permitted, Prohibited, and Restricted Concomitant Medications

Medications Prohibited During the Trial

- Potent Cytochrome P450 2D6 inhibitors (fluoxetine, paroxetine, bupropion, quinidine, cinacalcet, ritonavir) are prohibited during any Phase of the study. (NOTE: Any fluoxetine containing compound must be washed out for 42 days)
- The use of investigational drugs will be restricted for at least 30 days (or 5-times the half-life of the drug, if known and longer) prior to first study drug administration and throughout the study.
- Mood stabilizers will be tapered and discontinued in the Screening Period at least 7 days prior to the Oral Treatment Period. Mood stabilizers are not permitted during any the Phases of the study.
- Nutritional supplements and nonprescription herbal preparations with central nervous system effects (e.g., St. John's Wort, omega-3 fatty acids, kava extracts, gamma-aminobutyric should be tapered and discontinued at least 14 days prior to the end of the Screening Period and are not permitted in any of the Phases of the study.

Medications Restricted During the Trial

- Benzodiazepines are allowed during all Phases of the study up to a maximum of 6 mg/day of lorazepam or equivalent.
- Anticholinergics ≤ 4 mg/day benztropine or equivalent for EPS are permitted.
- Propranolol (for akathisia or tremor) up to a maximum of 60 mg/day is permitted.
- Subjects should discontinue any non-steroidal anti-inflammatory (NSAID) or aspirin-containing medications one week prior to the Oral Treatment Period and one week prior to explantation.
- Antipsychotics are allowed during the Screening period but are tapered off and converted to oral risperidone during the Conversion Phase. No antipsychotics, other than the Risperidone Implants are permitted following the conversion phase, except in certain cases. The certain cases include, where antipsychotics may be used during the study upon consultation with the medical monitor for maximum of 7 days throughout the study.

NOTE: In the instance that the investigator believes that the subject is not experiencing a true exacerbation of schizophrenia, a supplemental antipsychotic may be used for a maximum of 14 days upon consultation with the medical monitor.

Medications Permitted During the Trial

- Non-benzodiazepine sleep aids are permitted
- Non-sedating antihistamines (e.g., loratadine, cetirizine) are the treatment of choice for allergies.

On a case-by-case basis, the Investigator is permitted to allow the use of some concomitant medications, for example, to treat an AE, as long as the Investigator determines that the medication will not affect the patient's/subject's safety or study integrity (e.g., topical medications). Whenever possible, the Investigator should obtain approval from the sponsor's medical monitor prior to administering the medication.

13.2 Contraception

Female patients must use appropriate contraceptive methods from screening until the EOS visit. Male patient must use appropriate contraceptive methods and must not donate sperm following dosing with study drug until the EOS visit.

Appropriate contraception is defined as using hormonal contraceptives or an intrauterine device combined with at least 1 of the following forms of contraception: a diaphragm or cervical cap, or a condom. Also, total abstinence, in accordance with the lifestyle of the patient, is acceptable.

13.3 Exercise

Patients will be instructed to refrain from strenuous exercise and from participation in any contact sport activities for a period of 7 days following the implantation of DLP-114.

13.4 Caffeine, and Alcohol

The consumption of caffeine or alcohol are prohibited during periods of confinement to the clinical facility.

14 STUDY PROCEDURES AND ASSESSMENTS

14.1 Informed Consent

The Patient Information and Consent Form (PICF) will be provided to the study volunteers at screening, prior to any study procedures being performed.

14.2 Medical History

Medical history and demographic data, including name, gender, age, race, Body Mass Index (BMI) will be recorded at screening.

14.3 Safety Assessments

This study will assess the safety and tolerability of DLP-114. Safety will be determined by evaluating physical examinations, vital signs, ECGs, clinical laboratory parameters, clinical ratings (e.g. C-SSRS), and adverse events. Local tolerance at the implantation site will be examined and scored for severity of visible signs of irritation/inflammation. If deemed necessary, additional safety measurements will be performed at the discretion of the investigator (or delegate). For details on the time points and frequency of all safety assessments, please see **Appendix 1** (Overall Schedule of Assessments).

14.3.1 *Physical Examination*

Complete physical examination performed at screening will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

Physical examination may be performed at various unscheduled time points if deemed necessary by the investigator. All physical examinations will be conducted by a licensed physician.

14.3.2 *Implantation Site Inspection and Wound Care*

Subjects will receive written instructions that explain how to care for the surgical site after implant insertion and removal. Subjects should be informed about care of the implant site and implant site safety, educated about situations where they should seek medical attention, and queried about implant-related AEs.

If an expulsion of an implant(s) occurs, and the subject appears to be compliant and wants to continue with the study, the current implant site will have the remaining implant removed and new implants (same dosage strength as original) will be implanted into another quadrant. If an expulsion occurs, the site is to contact the medical monitor to discuss if oral risperidone should be given to the patient prior to the following implantation.

Implantation site inspection will be by visual and physical examination at each assessment visit. The physician will palpate the device and measure from the proximal end of the device to the incision to determine whether it has migrated by noting a change in distance from the incision site to the proximal end of the device. Healing of the incision will be monitored. Dermal reactions will be scored on a Skin Irritation Scoring System (**Appendix 3,** [1].) recommended for transdermal dosage forms that describes the amount of erythema, edema, and other features indicative of irritation. Any changes from baseline will be noted and captured as an AE.

The DLP-114 implant should be implanted in a quadrant of the abdomen 5 cm from midline and 5 cm below the ribs. Any migration of the implant from this area, spontaneous expulsion on an implant(s), or other device-related event that does not qualify as an adverse event will be captured in the CRF on the Implant/Device Event form.

14.3.3 *Electrocardiogram*

Single 12-lead ECG will be performed at selected time points (**Appendix 1**. Overall Schedule of Assessments). The patient should be in the semi-supine position for at least 10 minutes before the measurement is started and the following variables will be provided automatically: RR, PR, QRS, QT and QTcF intervals and pulse rate. In case of evident bad quality (muscle tremor) of the tracing, the ECG will be repeated. A description of the overall assessment (i.e. normal or abnormal plus reason) including clinical significance will be made and a copy of the trace placed with the source data. All ECGs should be obtained prior to vital signs and blood sampling when applicable.

14.3.4 *Vital Signs*

Assessments will include systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate. Patient should be resting in a semi-supine position for at least 5 minutes prior to

and while vital signs measurements are obtained. Orthostatic blood pressure and pulse (after standing for 1, 3, and 5 minutes) will be performed at selected time-points (**Appendix 1**. Overall Schedule of Assessments).

14.3.5 *Safety Laboratory Tests*

All safety laboratory analysis will be performed by the clinical site's certified laboratory, using the laboratory's normal ranges. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The following clinical laboratory safety tests will be performed (**Appendix 1**. Overall Schedule of Assessments):

Hematology

Leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes; (partial automated differentiation): lymphocytes, monocytes, eosinophils, basophils, neutrophils.

Serum Chemistry

Sodium, potassium, calcium, phosphate, blood urea nitrogen (BUN), serum creatinine, glucose, lactic acid dehydrogenase (LDH), alanine transferase (ALT), aspartate transferase (AST), total bilirubin, alkaline phosphatase, gamma glutamyl transferase (GGT), total proteins, albumin and urates.

Lipid profile analysis: total cholesterol, LDL, HDL, non-HDL and triglycerides.

Patients will be required to fast for at least 4 hours prior to the initial Serum Chemistry time-point sample collection.

Coagulation

Prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT).

Urinalysis

Urine samples for urinalysis will be collected at specified time points. The following urinalysis parameters will be assessed: hemoglobin, urobilinogen, ketones, bilirubin, glucose, protein, nitrite, leukocytes, pH, specific gravity.

14.3.6 *Viral Serology*

Blood will be collected for screening for hepatitis B surface antigen, hepatitis C antibody and HIV at the screening visit only.

14.3.7 *Pregnancy Test*

Female patients will be screened for pregnancy: serum human chorionic gonadotropin (hCG) at the screening visit and urine hCG test at selected subsequent visits. If the urine hCG test is positive, pregnancy will be confirmed by a serum hCG test. In instances of a positive pregnancy result prior to dosing, the patient will be replaced.

14.3.8 *Alcohol and Drugs of Abuse Screen*

Alcohol breath test will be conducted at screening and prior to first dose. Urine drug test will include screen for: Methamphetamines, Opiates, Cocaine, Phencyclidine, Benzodiazepines, Barbiturates, Methadone, Tricyclic Antidepressants and Amphetamines.

14.3.9 *Ultrasound*

On visit Day 14 an ultrasound will be taken of the implant site to determine depth of device placement. The ultrasound will be repeated at the visit prior to implant removal to determine if the depth has changed.

14.3.10 *C-SSRS, CGI-1 and PANSS,*

C-SSRS will be administered at screening and each patient visit (at least biweekly). CGI-I will be administered at least monthly and PANSS approximately every 3 months. PANSS will be administered more frequently if the CGI-I worsens.

14.3.10.1 *Columbia-Suicide Severity Rating Scale (C-SSRS)*

The Columbia Suicide Severity Rating Scale (C-SSRS) [7] is a suicidal ideation rating scale. The scale identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. The C-SSRS Baseline/Screening version will be conducted at Screening and the Since Last Visit version will be used for all subsequent visits per the Schedule of Events.

14.3.10.2 *Positive and Negative Syndrome Scale (PANSS)*

The Positive and Negative Syndrome Scale (PANSS) measures positive and negative syndromes associated with schizophrenia. The scale consists of 33 items, 30 of which contribute to the PANSS Total Score (i.e., the sum of the seven P, or positive, items with the seven N, or negative, items with the 16 G, or general pathology, items). The PANSS Total Score ranges from 30 – 210, with higher scores indicating greater pathology.

Individual PANSS items are scored from 1 – 7, as follows:

1 = Absent

2 = Minimal

3 = Mild

4 = Moderate

5 = Moderate/ Severe

6 = Severe

7 = Extreme

The PANSS is administered at screening, baseline, and at additional timepoints noted in the Schedule of Assessments. Of note, for study eligibility, the PANSS Total Score at

screening must be ⩽ 80 and the following five individual items must be ⩽ 4: Conceptual Disorganization; Suspiciousness; Hallucinatory Behavior; Unusual Thought Content; and Hostility. Additionally, there must not be a ⩾ 20% change in the PANSS Total Score from screening to baseline. Finally, should the PANSS Total Score worsen by ≥30% compared to baseline at subsequent study visits (confirmed at an additional visit 1 – 7 days later), the subject may be exhibiting signs of relapse and may meet stopping criteria.

14.3.10.3 *CGI-S and CGI-I*

Clinical Global Impression of Severity (CGI-S) will be rated based upon the severity of schizophrenia symptoms at screening and Day -1 during the oral treatment period, immediately prior to the implant + oral period.

Severity of illness will be assessed based on following ratings:

0 = Not assessed

1 = Normal, not at all symptomatic

2 = Minimally symptomatic

3 = Mildly symptomatic

4 = Moderately symptomatic

5 = Markedly symptomatic

6 = Severely symptomatic

7 = Among the most extremely symptomatic subjects

Drug response on symptoms of schizophrenia will be evaluated by the Clinical Global Impressions – Improvement (CGI-I). The CGI-I will be performed according to the timepoints in the Schedule of Assessments. The CGI-I scores range from 1 to 7:

0 = not assessed (missing),

1 = very much improved,

2 = much improved,

3 = minimally improved,

4 = no change,

5 = minimally worse,

6 = much worse,

7 = very much worse

14.3.11 *EPS*

EPS symptoms will be monitored by the Barnes akathisia rating scale (BARS), Simpson–Angus scale (SAS) and abnormal involuntary movement scale (AIMS) at the beginning and at the end of the study, and may be performed more frequently based on symptoms at the PI's discretion.

14.3.11.1 *Barnes Akasthisia Rating Scale (BARS)*

The Barnes Akasthisia Rating Scale (BARS) is a rating scale administered by physicians to assess the severity of drug-induced akathisia. This scale includes objective and subjective items such as the level of restlessness and global clinical assessment of akathisia. The BARS assessment will be performed at the time points indicated in the Schedule of Assessments.

14.3.11.2 *Abnormal Involuntary Movements Scale (AIMS)*

The Abnormal Involuntary Movement Scale (AIMS) is a clinician-administered scale used to detect tardive dyskinesia (TD) and to follow the severity of a person’s TD over time. This 12-item anchored scale is clinician administered and scored.

Items 1 through 10 are rated on a 5-point anchored scale:

0=None

1=Minimal, may be extreme normal

2=Mild

3=Moderate

4-Severe

Items 1 through 4 assess orofacial movements.

Items 5 through 7 assess extremity and truncal dyskinesia.

Items 8 through 10 assess global severity as judged by the examiner and the person’s awareness of the movements and the distress associated with them.

Items 11 and 12 are yes-no questions concerning problems with teeth and/or dentures, because such problems can lead to a mistaken diagnosis of dyskinesia.

A positive AIMS examination is a score of 2 in multiple movements or a score of 3 or 4 in a single movement. The AIMS assessment will be performed at the time points indicated in the Schedule of Assessments.

14.3.11.3 *Simpson-Angus Scale (SAS)*

The Simpson-Angus Scale (SAS) is a clinician-administered 10-item rating scale assessing the presence of drug-related extrapyramidal signs. The 10 performance tasks are rated on a scale of 0 – 4 (normal to severe, as relevant to the task assessed). The

SAS will be performed at the timepoints indicated in the Schedule of Assessments.

14.3.12 *Signs of impending relapse*

Any of the following signs would call for withdrawing the patient from the study:

- Hospitalization due to worsening of schizophrenia;
- Increase (worsening) of the PANSS of ≥30% from baseline. $PANSS_T$ score confirmed at a second visit conducted within 1-7 days;
- Clinically significant emergent or worsening suicidal, homicidal, or aggressive behavior;
- A CGI-I Improvement (CGI-I) score of 6 (much worse) or 7 (very much worse) after start of study;
- A need for additional antipsychotic treatment, with the exception of protocol permitted short-term add-on therapy.

14.3.13 *Video Recording*

Four of the first subjects enrolled in the DLP-114-03 trial will have their implant and explant procedure video recorded and uploaded to a central repository. Approved video-recording equipment and standardized instructions for videotaping will be provided to the site. Each video recording will be identified by subject number, date, and time (including no personal identifying information). The camera will be positioned in such a way that the subjects' face will not be included in the recording to protect the identity of the subject. Subjects who do not wish to be video recorded will be allowed to participate in the study.

The purpose of video-recording a small number of implant and explant procedures is to:

- Assess the performed procedure to ensure that it is aligned with the instructions provided in the training.
- Identify and assess any observed misuses. Assessments will help drive product design changes and/or label changes to alleviate the risk's severity or occurrence of the misuse.

14.4 Pharmacokinetics

Blood will be collected for the determination of plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) at the end of oral risperidone treatment, throughout the duration of the DLP-114 implant treatment and following removal of the DLP-114 implant.

Clinic staff are required to take the blood samples for PK analysis at the scheduled time points within the time windows indicated (**Appendix 2.** Pharmacokinetic Sample Collection Schedule). Actual sampling dates and times are to be recorded in the CRF.

If a patient discontinues prior to completion of the study, all of the PK data collected prior to discontinuation will be included in the PK analysis as appropriate.

Three (3) mL of blood will be obtained for each PK sampling time point.

The clinical site PK manual provides detailed instructions on sample processing, storage and shipping.

14.5 Total Blood Sample Volumes

Blood samples for clinical labs and PK analysis will be collected from each patient throughout the study. An approximate total of no more than 250 mL of blood will be collected in Group 1 patients and 500 mL in Group 2 patients.

15 STUDY CONDUCT SCHEDULES AND GUIDELINES

15.1 Screening, Selection and Consent

Screening will be conducted within a period of 28 days prior to the start of the conversion phase or unsupervised oral dosing risperidone 3 mg/day. Informed consent will be obtained following provision of the PICF at screening and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study.

All screening laboratory test values (including viral) used for study eligibility assessment may be derived from patient medical history/record if obtained within a 28-day window prior to commencement of dosing for this study.

Documentation of each patient's fulfillment of the eligibility criteria (for all patients considered for the study and subsequently included or excluded) is to be completed by the investigator, or medically qualified delegate, including documentation that the patient has been stable on oral risperidone (2-3 mg/day) for at least 2 weeks, as well as if they have completed the conversion phase. Documentation of screening failure details may be recorded using eligibility screening forms or a patient screen failure log. Eligible patients will be assigned to either Group 1 or 2.

The following assessments/procedures will be performed at the screening visit:

- Informed consent;
- Review of eligibility criteria;
- Demographics;
- Medical history;
- Height;
- Body weight;
- Calculation of BMI;
- Review of prior medications;
- Physical examination (complete);
- Viral serology;
- Alcohol breath test;
- Urine drug screen (drugs of abuse);
- Serum hCG pregnancy test (females only);
- Safety laboratory tests (blood);
- Safety laboratory tests (urine);
- 12-lead ECG;
- Vital signs (includes orthostatic blood pressure and pulse).
- CYP2D6 Genotype (if subject provides documentation of a previous CYP2D6 result that shows the subject is not a poor metabolizer, it does not need to be repeated)
- CGI-S
- PANSS
- C-SSRS
- BARS
- SAS

- AIMS
- AE monitoring

15.2 Clinical Conduct (Day -7 to Day -5): Groups 1 and 2

Eligible patients who are currently on oral risperidone therapy (2-3 mg/day) will begin unsupervised dosing with oral risperidone 3 mg/day, starting on Day -7, or as early as Day -10 at PI's discretion, through Day -5. Subjects will notify the site if the experience any AEs during the unsupervised oral dosing period.

15.3 Clinical Conduct (Weekly Visits for a minimum of 2 weeks through Day -14): Groups 1 and 2

Eligible patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) will be required to begin the conversion phase starting a minimum of 2 weeks prior to implant at the PI's discretion. During weekly visits in the conversion phase, subjects will cross-titrate, at the PI's discretion, from other antipsychotic(s) to oral risperidone therapy. The objective of the oral conversion phase is for all subjects to achieve an oral risperidone dose of 3 mg by Day -14.

The following assessments will be performed at each weekly visit during the conversion phase:

- Review of prior medications;
- Vital signs and pulse (pre-dose);
- C-SSRS;
- AE monitoring;
- Update/review of concomitant medications

In addition, the Investigator will document details of the cross-titration that may occur during the conversion phase to bring about a stable transition from previous antipsychotic treatment(s) to oral risperidone 3 mg. The Investigator will also document the subject's compliance with medications taken during the conversion phase.

15.4 Clinical Conduct (Days -4 to 4): Groups 1 and 2

15.4.1 *DAY -4 (outpatient visit)*

Eligible patients will present at the clinical facility on the morning of Day -4 (start of supervised dosing with oral risperidone 3 mg/day). On arrival at the clinical facility on Day -4, the investigator, or delegate, will meet with patients to explain all study procedures and encourage patients to ask any questions. All patients shall undergo a check-in procedure during which questions will be asked regarding protocol compliance and safety monitoring.

The following assessments will be performed on each patient:

- Review of eligibility criteria;
- Body weight/height (includes calculation of BMI in the CRF);
- Review of prior medications;
- Vital signs and pulse (pre-dose);
- **Self- administration of investigational product under supervision at the clinical facility (3 mg oral risperidone);**
- C-SSRS
- Urine hCG pregnancy test (females only)
- AE monitoring;
- Update/review of concomitant medications

15.4.2 *DAY -3 and DAY -2 (outpatient visits)*

The following assessments/procedures will be performed:

- Update/review of concomitant medications;
- **Self- administration of investigational product under supervision at the clinical facility (3 mg oral risperidone);**
- AE monitoring;
- Vital signs;

15.4.3 *DAY -1 (confinement to the clinical facility)*

Patients will be admitted to the clinical facility on Day -1.

Patients will be confined to the clinical facility overnight (Day -1 to Day 4). If patients experience any clinically significant adverse events during this study period, they may be required to remain in the clinical facility for further observation at the discretion of the investigator.

The following assessments/procedures will be performed on Day -1:

- Update/review of concomitant medications;
- Vital signs (pre-dose);
- Blood sampling for PK (within 10 min prior to dose administration);
- **Self- administration of investigational product under supervision at the clinical facility (3 mg oral risperidone) – fourth dose of oral risperidone; oral dose should be given at least 25 hours prior to implantation to allow for the Day 1 pre-implant PK sample to be collected at least 30 minutes after the Day -1 24 hours post-dose PK sample**
- Blood sampling for PK at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose (**Appendix 2**. Pharmacokinetic sample collection schedule);
- AE monitoring.
- Urine drug screen
- Alcohol breath test
- Urine hCG pregnancy test (females only)
- Safety laboratory tests (blood);
- Safety laboratory tests (urine);
- 12-lead ECG;
- CGI-S
- PANSS
- C-SSRS
- BARS
- SAS
- AIMS

15.4.4 *DAY 1 (DLP-114 implantation day, confinement to the clinical facility)*

The following assessments/procedures will be performed:

- Update/review of concomitant medications;
- Vital signs - includes orthostatic blood pressure and pulse measurement (pre-implantation);

- **Self- administration of investigational product under supervision at the clinical facility (3 mg oral risperidone) (1 hour (± 30 min) prior to DLP-114 implantation)– fifth dose of oral risperidone;**
- Blood sampling for PK (1 hour (± 30 min) prior to DLP-114 implantation) (**Appendix 2**. Pharmacokinetic sample collection schedule);
- **DLP-114 implantation (two implant devices per patient, Group 1 α4, Group 2 α7);**
- Provide wound care instructions;
- AE monitoring;
- Implantation site is inspected;
- Vital signs (every hour for the first 8 hours post-implantation) - includes orthostatic blood pressure and pulse measurement at 4 hours post-dose;
- 12-lead ECG (4 hours post-implantation);
- Blood sampling for PK at 1, 2, 3, 4, 6, 8 and 12 hours post-implantation (**Appendix 2**. Pharmacokinetic sample collection schedule).
- C-SSRS

15.4.5 *DAY 2 (confinement to the clinical facility)*

The following assessments/procedures will be performed:

- Update/review of concomitant medications;
- Approximately 24 hours post-implantation:
    - Vital signs;
    - Implantation site is inspected;
    - 12-lead ECG;
    - **Self- administration of investigational product under supervision at the clinical facility (3 mg oral risperidone) – sixth (final) dose of oral risperidone;**
- Blood sampling for PK, 4 samples are collected at 24, 28, 32 and 36 hours following implantation of DLP-114 (**Appendix 2**. Pharmacokinetic sample collection schedule);
- AE monitoring.

15.4.6 *DAY 3 (confinement to the clinical facility)*

The following assessments/procedures will be performed:

- Update/review of concomitant medications;
- Vital signs - includes orthostatic blood pressure and pulse measurement (approximately 48 hours post-implantation);
- AE monitoring;
- Implantation site is inspected;
- Blood sampling for PK - 2 samples are collected at 48 and 52 hours following implantation of DLP-114 (**Appendix 2**. Pharmacokinetic sample collection schedule);

15.4.7 *DAY 4-6 (confinement to the clinical facility)*

The following assessments/procedures will be performed:

- Vital signs;
- AE monitoring;
- Update/review of concomitant medications;
- Implantation site is inspected;

- One blood sample for PK (**Appendix 2**. Pharmacokinetic sample collection schedule). If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping;

Participants may be discharged as early as Day 4 upon consultation with the study's medical monitor. If patients are discharged prior to Day 7, the assessments listed in 15.4.8 shall be performed on the day of discharge, and the assessments listed in 15.5.1 shall be performed on Day 7. Additionally, if patients are discharged prior to Day 7, the Day 4-6 assessments/procedures are unnecessary.

15.4.8 *DAY 7 (discharge)*

The following assessments/procedures will be performed:

- Body weight;
- Update/review of concomitant medications;
- Vital signs;
- CGI-I;
- C-SSRS;
- Safety laboratory tests (blood) (excludes coagulation, and lipid profile);
- Safety laboratory tests (urine);
- AE monitoring;
- Implantation site is inspected;
- 12-lead ECG;
- One blood sample for PK (**Appendix 2**. Pharmacokinetic sample collection schedule);

Patients will be given a study card and/or safety alert bracelet upon discharge from the clinic.

15.5 Clinical Conduct (Days 14 to End of Study) – Group 1

15.5.1 *DAYS 14, 21, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, and 168 (outpatient visits)*

After study Day 7, all outpatient visits during the implant treatment period may be performed within a window of ± 1 day.

The following assessments/procedures will be performed at every outpatient visit:

- Body weight
- Vital signs;
- C-SSRS
- AE monitoring;
- Implantation site is inspected;
- One blood sample for PK (**Appendix 2**. Pharmacokinetic sample collection schedule). If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping;
- Update/review of concomitant medications.

The following assessments/procedures will be performed on selected outpatient visits (see **Appendix 1**, Overall Schedule of Assessments; assessments may be performed more frequently based on symptoms at the PIs discretion):

- Urine Drug Screen;
- Urine hCG pregnancy test (females only);

- Safety Lab Test (Blood);
- Safety Lab Test (urine);
- 12-lead ECG;
- CGI-I;
- PANSS;
- BARS;
- SAS;
- AIMS;
- Ultrasound.

15.5.2 *DAY 183 (± 7 days) (confinement to the clinical facility)*

The following assessments/procedures will be performed:

- Body weight
- Update/review of concomitant medications.
- Urine Drug Screen
- Urine hCG pregnancy test (females only)
- 12-lead ECG
- Vital Signs
- CGI-I
- PANSS
- C-SSRS
- AE monitoring;
- Implantation site monitored
- Ultrasound (to measure if the implant has migrated vertically; implant should be located through palpation before removal)
- **DLP-114 implants are removed;**
- Blood sampling for PK at 1, 2, 3
- , 4, 6, 8- and 12-hours following removal of the DLP-114 implant (**Appendix 2**. Pharmacokinetic sample collection schedule).
- Safety laboratory tests (blood) (excludes coagulation, includes lipid profile) (4 hours following removal of the DLP-114 implant);
- Safety laboratory tests (urine) (4 hours following removal of the DLP-114 implant);
- Vital signs (every hour for the first 4 hours following removal of the DLP-114 implant);
- 12-lead ECG (4 hours following removal of the DLP-114 implant);

15.5.3 *DAY 184 (confinement to the clinical facility)*

On Day 184 (or 1-day post implant removal) the following assessments/procedures will be performed:

- Update/review of concomitant medications.
- Approximately 24 hours following removal of the DLP-114 implant:
  - Vital signs;
  - Implantation site is inspected;
- AE monitoring;
- One blood sample for PK (collected at 24 hours following removal of the implant) (**Appendix 2**. Pharmacokinetic sample collection schedule).

15.5.4 *DAY 185 (confinement to the clinical facility ends)*

On Day 185 (or 2-days post implant removal) the following assessments/procedures will be performed:

- Update/review of concomitant medications.
- Approximately 48 hours following removal of the DLP-114 implant:
  - Vital signs;
  - Implantation site is inspected;
- C-SSRS
- AE monitoring;
- One blood sample for PK (collected at 48 hours following removal of the implant) (**Appendix 2**. Pharmacokinetic sample collection schedule).
- Resume oral administration of patient's original dose (2-3 mg)
- Physical examination (complete);
- Confinement ends

15.5.5 *DAY 186 (outpatient visit)*

On Day 186 (or 3 days post implant removal) the following assessments/procedures will be performed:

- Vital signs;
- C-SSRS
- AE monitoring;
- Implantation site is inspected;
- One blood sample for PK (**Appendix 2**. Pharmacokinetic sample collection schedule). If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping;
- Update/review of concomitant medications.

15.5.6 *DAY 190 (End of Study, outpatient visit)*

On Day 190 (or 7 days post implant removal) the following assessments/procedures will be performed as the End of Study Visit:

- Body weight
- AE monitoring/review;
- Implantation site is inspected;
- Urine hCG pregnancy test (females only);
- C-SSRS
- Vital signs;
- Update/review of concomitant medications.

15.6 Clinical Conduct (Days 14 to End of Study) – Group 2

15.6.1 *DAYS 14, 21, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, 182, 196, 210, 224, 238, 252, 266, 280, 294, 308, 322, 336, and 350 (outpatient visits)*

After study Day 7, all outpatient visits during the implant treatment period may be performed within a window of ± 1 day.

The following assessments/procedures will be performed at every outpatient visit:

- Body weight
- Vital signs;
- C-SSRS
- AE monitoring;
- Implantation site is inspected;
- One blood sample for PK (**Appendix 2**. Pharmacokinetic sample collection schedule). If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping;
- Update/review of concomitant medications.

The following assessments/procedures will be performed on selected outpatient visits (see **Appendix 1**, Overall Schedule of Assessments; assessments may be performed more frequently based on symptoms at the PIs discretion):

- Urine Drug Screen;
- Urine hCG pregnancy test (females only);
- Safety Lab Test (Blood);
- Safety Lab Test (urine);
- 12-lead ECG;
- CGI-I;
- PANSS;
- BARS;
- SAS;
- AIMS;
- Ultrasound.

15.6.2 *DAY 364 (± 7 days) (confinement to the clinical facility)*

The following assessments/procedures will be performed:

- Body weight
- Update/review of concomitant medications.
- Urine Drug Screen
- Urine hCG pregnancy test (females only)
- 12-lead ECG
- Vital Signs
- CGI-I
- PANSS
- C-SSRS
- AE monitoring;
- Implantation site monitored
- Ultrasound (to measure if the implant has migrated vertically; implant should be located through palpation before removal)
- **DLP-114 implants are removed;**
- Blood sampling for PK at 1, 2, 3, 4, 6, 8- and 12-hours following removal of the DLP-114 implant (**Appendix 2**. Pharmacokinetic sample collection schedule).

- Safety laboratory tests (blood) (excludes coagulation, includes lipid profile) (4 hours following removal of the DLP-114 implant);
- Safety laboratory tests (urine) (4 hours following removal of the DLP-114 implant);
- Vital signs (every hour for the first 4 hours following removal of the DLP-114 implant);
- 12-lead ECG (4 hours following removal of the DLP-114 implant);

15.6.3 *DAY 365 (confinement to the clinical facility)*

On Day 365 (or 1-day post implant removal) the following assessments/procedures will be performed:

- Update/review of concomitant medications.
- Approximately 24 hours following removal of the DLP-114 implant:
  - Vital signs;
  - Implantation site is inspected;
- AE monitoring;
- One blood sample for PK (collected at 24 hours following removal of the implant) (**Appendix 2**. Pharmacokinetic sample collection schedule).

15.6.4 *DAY 366 (confinement to the clinical facility ends)*

On Day 366 (or 2-days post implant removal) the following assessments/procedures will be performed:

- Update/review of concomitant medications.
- C-SSRS
- Approximately 48 hours following removal of the DLP-114 implant:
  - Vital signs;
  - Implantation site is inspected;
- AE monitoring;
- One blood sample for PK (collected at 48 hours following removal of the implant) (**Appendix 2**. Pharmacokinetic sample collection schedule).
- Resume oral administration of patient's original dose (2-3 mg)
- Physical examination (complete);
- Confinement ends

15.6.5 *DAY 367 (outpatient visit)*

On Day 367 (or 3 days post implant removal) the following assessments/procedures will be performed:

- Vital signs;
- C-SSRS
- AE monitoring;
- Implantation site is inspected;
- One blood sample for PK (**Appendix 2**. Pharmacokinetic sample collection schedule). If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping;

- Update/review of concomitant medications.

15.6.6 *DAY 371 (End of Study, outpatient visit)*

On Day 371 (or 7 days post implant removal) the following assessments/procedures will be performed as the End of Study Visit:

- Body weight
- AE monitoring/review;
- Implantation site is inspected;
- Urine hCG pregnancy test (females only);
- C-SSRS
- Vital signs;
- Update/review of concomitant medications.

15.7 Early Termination Procedures

The following assessments/procedures will be performed on a patient at an early termination visit to the clinical facility:

If early termination occurs during the DLP-114 implant treatment period:

- One blood sample for PK prior to removal.
- Implantation site is inspected, and **the DLP-114 implant is removed**;
- Update/review of concomitant medications;
- Physical examination;
- Urine hCG pregnancy test (females only);
- Safety laboratory tests (blood) (excludes coagulation, includes lipid profile) (4 hours following removal of the DLP-114 implant);
- Safety laboratory tests (urine) (4 hours following removal of the DLP-114 implant);
- Vital signs (every hour for the first 4 hours following removal of the DLP-114 implant);
- 12-lead ECG (4 hours following removal of the DLP-114 implant);
- AE review;
- CGI-I
- PANSS
- C-SSRS
- Implantation site monitored
- BARS
- SAS
- AIMS

Patients will be requested to return to the clinic for a follow up visit 6 (±3) days following the removal of the implant, for implant site inspection and AE assessment.

If early termination occurs during the oral risperidone treatment period:

- Update/review of concomitant medications;
- Urine hCG pregnancy test (females only);
- Safety laboratory tests (blood) (excludes coagulation and lipid profile);
- Safety laboratory tests (urine);
- 12-lead ECG;

- Vital signs;
- AE review.

15.8 Timing of Treatments and Procedures

Clinical staff are required to perform assessments at the nominated time-points within the time windows indicated in this protocol. Actual times of procedures for each patient may vary depending on scheduling and will be recorded in the CRF. In the event of multiple procedures scheduled at the same time, the order will be:

1. 12-lead ECG;
2. Vital signs;
3. Blood sampling for PK;
4. Blood sampling for safety laboratory tests;
5. Assessment of implantation site.

16 ASSESSMENT AND MANAGEMENT OF ADVERSE EVENTS

16.1 Adverse Event Definitions

An **Adverse Event (AE)** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening (the term 'life-threatening' in the definition of 'serious' refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death, if it were more severe);
- Requires inpatient hospitalization or prolongation of an existing hospitalization (only hospitalizations that are longer than expected based on Investigator judgment, will be considered prolonged hospitalizations);
- Results in persistent or significant disability/incapacity (an AE that results in a substantial disruption of a person's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect (a congenital anomaly/birth defect that occurs in the offspring of a patient exposed to the investigational product);
- Is a medically important event or reaction (an AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above).

Medical and scientific judgment should be exercised in deciding whether other situations, should be considered serious such as important medical events that may not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug

abuse.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)**: is an AE that is believed to be related to the investigational product and is both unexpected and serious. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Abnormal laboratory findings (e.g. clinical chemistry, hematology, coagulation and urinalysis) or other abnormal assessments (e.g., ECG tracings for safety assessment, vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definitions stated in above. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

An **Implant/Device Event (IDE)** is defined as an expulsion, migration, or other device-related event that does not qualify as an adverse event. The evaluating physician will make the determination as to the root cause of the event and classify it accordingly. See section 14.3.2 for instructions on expulsion procedure.

16.2 Evaluating AE and SAE

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgment. The intensity of each AE and SAE will be graded using the most current version of the Common Terminology Criteria for Adverse Events (CTCAE) 5-point scale:

- **Mild (Grade I)**: Asymptomatic or mild symptoms: clinical or diagnostic observations only; intervention not indicated;
- **Moderate (Grade II)**: Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL);
- **Severe (Grade III)**: Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL;
- **Life-threatening (Grade IV)**: Life-threatening consequences; urgent intervention indicated;
- **Death (Grade V)**: Death related to the event.

If an AE has multiple aspects, the aspect with the highest severity will be graded.

The term severe is a measure of severity. Thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

16.2.1 *Assessment of Causality*

The investigator will make an assessment as to the relationship between investigational product effect and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine whether or not the AE/SAE is causally related to the investigational drug product. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator's Brochure in the determination of his/her assessment.

The causal relationship of the investigational product to an AE will be rated according to the following 5-point scale:

- **Unrelated:** Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable;
- **Unlikely:** Does not follow a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered;
- **Possibly:** Follows a reasonable temporal sequence from administration; may have been produced by the patient's clinical state or by environmental factors or other therapies administered;
- **Probably:** Clear temporal association with improvement on cessation of investigational product or reduction in dose. Reappears upon re-challenge or follows a known pattern of response to the investigational product;
- **Definitely:** An AE that cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE form to the sponsor. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE form and the CRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

16.2.2 *Action Taken and Outcome*

For all AEs reported, the actions taken and outcomes will be specified.

Actions taken may include any of the following:

- No action;
- Medication required;
- Tests required;
- Hospitalization required (or prolonged);
- Investigational product administration interrupted/withdrawn;
- Other (specify).

The following terms and definitions are used in assessing the final outcome of an AE:

- **Recovered** - The patient has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent.
- **Recovering** - The condition is improving and the patient is expected to recover from the

event.

- **Recovered with sequelae** - The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered** - The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known at the time of reporting.
- **Fatal** - This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as “recovered”, “recovering”, “recovered with sequelae” or “not recovered”. An AE with fatal outcome must be reported as an SAE.
- **Unknown** - This term is only applicable if the patient is lost to follow-up.

16.3 Procedures and Time Period for Detecting Adverse Events

The investigator or designee is responsible for detection, recording and reporting of events that meet the criteria and definition of AE.

As a consistent method of soliciting AE, the patient shall be asked a non-leading question such as: "How do you feel?”.

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical/Surgical History. In addition, any change in health status, which is reported after informed consent is obtained but prior to starting study treatment will be documented as Medical/Surgical History.

Any medical occurrence reported or observed after the informed consent form is signed until completion of the last study related procedure (includes follow-up for safety assessments) will be recorded as an AE.

Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent assessments as necessary. If these have resolved, this should be documented.

A post-study AE is defined as any event that occurs outside of the nominal AE study detection period. Investigators are not obligated to actively seek AE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has completed the study and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the sponsor.

Patients must be provided with a “study card” indicating the name of the investigational product, the study number, the investigator’s name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications. Patients will also be offered a safety alert bracelet bearing the same information, if desired, instead of or in addition to the study card. The study card and/or bracelet will be provided upon discharge from the clinic following the implant device administration.

16.4 Recording of AEs and SAEs

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the CRF and/or other sources. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be

recorded in the CRF and reported according to sponsor instructions.

16.5 Reporting of SAEs and SUSARs

In accordance with ICH guidelines for GCP, a copy of the written report of any SAEs should promptly be sent to the study sponsor. The investigator must notify the study sponsor (and the designated study safety officer) within 24 hours of becoming aware of the occurrence of an SAE.

Table 4. Contact details for transmission of SAE reporting forms to the sponsor and sponsor designated safety officer.

Sponsor Contact	**Designated Safety Officer**
Dr. Frank Martin Chief Science Officer Delpor, Inc 150 Hill Drive, Suite 25 Brisbane, CA 94005	Lawrence Frederick Blob, MD Chief Medical Officer CRC 200 Central Avenue, Suite 1230 Saint Petersburg, FL 33701
Email: frank.martin@delpor.com	lblob@cogres.com
Fax: (415) 480 6871	Fax: (727) 897-9009
Phone: (415) 480 6872	Office: (727) 897-9000
Mobile: (650) 759 0155	Mobile: (410) 262-1908

Information regarding SAEs will be transmitted to the sponsor using a SAE Form (or Medical Device Incident Report form) as described in the study Safety Reporting Plan. The SAE Form must be completed and signed by a member of the investigational staff, and transmitted to the sponsor (and designated study safety officer) within 24 hours (**Table 4**). The initial and follow-up reports of an SAE should be made by facsimile (fax) or e-mail.

The investigator must report SAEs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR. The investigator's opinion regarding the assessment of expectedness (if provided) and causality will be taken into account in the sponsor's determination of the SAE as a SUSAR. The causality assessment given by the investigator cannot be downgraded by the sponsor.

SAEs (and SUSARs) will be reported to competent authorities in accordance with national requirements. The sponsor assumes responsibility for appropriate reporting of SAEs (and SUSARs) to the regulatory authorities.

16.6 Follow-up of AE and SAE

After the initial AE/SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves;
- The event stabilizes;
- The event returns to Baseline, if a Baseline value is available;
- The event can be attributed to agents other than the investigational product or to factors unrelated to study conduct;

- It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

The investigator will ensure that SAE follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the event. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the SAE. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on a new SAE form and the CRF. The updated SAE form should be sent to the sponsor.

16.7 Exposure *In Utero* Management and Reporting

In instances of pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age) while the patient is on investigational product:

- Female patient - dosing of the investigational product must be discontinued immediately. The pregnant patient should be advised to call her healthcare provider.
- Partner of male patient - dosing of the investigational product to the male patient may continue at the discretion of the investigator. The pregnant partner of the male patient should be advised to call her healthcare provider.

The investigator will notify the sponsor and designated study safety officer of this event and document the pregnancy on the Exposure in Utero Form as described in the study Safety Reporting Plan.

The investigator shall obtain Informed Consent from the pregnant patient (or the pregnant partner of the male patient) in order to allow him/her (or delegate) to conduct follow-up throughout the gestational period and on the infant following delivery. The investigator shall follow-up newborn infants that have been exposed to investigational product *in utero* for a minimum of 6 months. Upon discovery of any congenital anomalies (or neonatal deaths) the investigator shall submit a follow-up report to the sponsor (and study safety officer) using an SAE Form (as per study Safety Reporting Plan) including information regarding the status of the newborn. A miscarriage or abortion shall also be reported by the investigator to the study Safety Officer (and the sponsor) using an SAE Form.

17 PATIENTS LOST TO FOLLOW-UP AFTER IMPLANTATION

When a subject is “lost to follow-up” (i.e., fails to return for study visits), a reasonable effort will be made to contact him/her to determine a reason for the failure to return and encourage the subject to return for removal of the implant. The detailed plan that the research center will follow in attempts to contact a subject that fails to return for a visit is listed below.

In the event a subject misses a scheduled outpatient visit during the study, the following procedures will be conducted to locate the patient:

- The study coordinator will attempt to contact the subject (e.g., phone, email, or text) for

four consecutive weeks in an effort to locate the subject and coordinate his/her return to the research site.

- If unsuccessful in contacting the subject the coordinator will contact the subject's caregiver/emergency contact.
- Once contact is established, the Investigator will assess the subject's ability to continue in the study.
- If the patient does not contact the site, the Sponsor will request for a third party to locate the patient to have the implant removed.

All attempts to contact the subject must be documented in the source data. The subject will be considered lost to follow up if the subject is not successfully located using the plan outlined above and should be identified as "lost to follow-up" in the CRF. However, the research site will request that all listed contacts continue to monitor for the subject and request that they call the emergency numbers if contact is made with the subject. The research site will also continue to monitor their psychiatric network in efforts to locate the subject.

18 STATISTICS AND DATA ANALYSIS

This section describes the general framework to be used for the analysis and presentation of data in this study. The information described in this section may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data that could affect planned analyses. All available data will be included in data listings and tabulations. No imputation of values for missing data will be performed. A formal Statistical Analysis Plan will be issued prior to database lock.

18.1 Sample Size Considerations

The maximum sample size is 30. The primary objective of this study is to determine safety and tolerability of DLP-114 and as such the sample size for this study was based upon qualitative considerations. No formal sample size calculations were performed.

18.2 Demographic Data

For all patients who received at least 1 dose of study treatment, descriptive statistics (mean, standard deviation, median, minimum, maximum) will be performed for age, gender, body mass index, weight, and height.

18.3 Safety/Tolerability Data

All patients who receive at least 1 dose of study treatment will be included in the safety and tolerability analysis. Baseline for all vital signs, 12-lead ECG measurements, and clinical laboratory assessments will be defined as the last evaluation done before the start of study treatment administration on Day -4.

Safety evaluations will be based on the incidence, intensity and type of AE and clinically significant changes in the patient's physical examination findings, vital signs, 12-lead ECGs, and clinical laboratory results. Safety variables will be tabulated and presented for all patients who receive study treatment, i.e., the safety population.

Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by study treatment showing patient counts and percentages.

The original terms used in the CRF by investigators to identify AEs will be coded using the current version of the Medical Dictionary of Regulatory Activities (MedDRA). The percentage of patients with treatment-emergent AEs will be summarized for each treatment.

Special attention will be given to those patients who have discontinued treatment due to an AE or who experienced a severe or a SAE.

Laboratory data will be summarized by the type of laboratory test. Normal reference ranges and markedly abnormal results will be used in the summary of laboratory data. Raw data and change from baseline in clinical laboratory parameters will be summarized using descriptive statistics. A listing of patients with any laboratory results outside the reference ranges that are deemed clinically significant will be provided.

18.4 Pharmacokinetic Data

Plasma concentrations of plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) determined at specified time points will be used to calculate PK parameters. Data will be listed for all patients with available plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone). All concentrations below the limit of quantification (LOQ) or missing data will be labeled as such in the concentration data listings. Concentrations designated as LOQ will be treated as 0 in the summary statistics and for the calculation of PK parameters.

Reasons for exclusion of a patient or a sample from the analysis include, but are not limited, to the following:

- Vomiting within 6 hours after investigational product administration (oral risperidone only);
- Too few data (greater than 10% missing values for a patient);
- Noncompliance with study procedures affecting pharmacokinetics (e.g., concomitant medication).

All patients and samples excluded from the analysis will be clearly documented in the PK study report. Pharmacokinetic parameters for risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) will be calculated using non-compartmental analysis. Only plasma concentrations greater than the LOQ for the assay will be used in the PK analysis. Actual sampling times will be used in all PK analyses. Per protocol times will be used to calculate mean plasma concentrations for graphical displays.

Listing of individual patient plasma concentrations, actual blood sampling times, and PK parameters and graphs of concentration vs. time will be prepared by study treatment. Plasma concentrations and PK parameters will be summarized by and compared between study treatments using descriptive statistics.

Statistical analysis will be performed on the pharmacokinetic parameters using validated statistical software.

19 DATA HANDLING AND RECORDKEEPING

19.1 Patient Identification and Enrolment Log and Patient Screening Log

The investigator agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The patient enrollment log will be treated as confidential and will be filed by the investigator in the Investigator Site File (ISF). All reports and communications relating to the study will identify patients by initials and assigned number only.

The investigator must also complete a patient screening log, which reports on all patients who were seen to determine eligibility for inclusion in the study.

19.2 Source Documentation

Source documentation must be available to substantiate patient identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety parameters; adequate reporting and follow-up of adverse events; administration of concomitant medication; drug receipt/dispensing/return records; investigational product administration information; and date of patient completion, discontinuation from treatment, or withdrawal from the study, and the reason if appropriate. Specific items required as source documents will be reviewed with the investigator before the study.

At a minimum the following data must be maintained in source documentation: patient identification, patient eligibility, exposure to investigational product, adverse events, and concomitant medication. It is recommended that the author of an entry in the source documents be identifiable. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the patients' source documentation.

Following the ICH-GCP guidelines, direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data.

19.3 Case Report Form

A CRF must be completed for each patient who has received at least 1 supervised dose of 3 mg/day risperidone.

For reasons of confidentiality, the name of the patient should not appear in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

CRFs will be completed according to the sponsor's (or designee) instructions and reviewed by the sponsor (or designee) to determine their accuracy and acceptability. If necessary, CRF queries will be raised by the sponsor (or designee) relating to CRF data entries. The investigator or authorized study site staff must address all CRF queries raised.

20 ETHICS AND REGULATORY COMPLIANCE

20.1 Investigator Responsibilities

The investigator agrees to conduct the clinical study in accordance with the protocol, current International Council on Harmonization (ICH) guidelines for Good Clinical Practice (GCP), and applicable regulatory and legal requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

20.2 Independent Ethics Committee or Institutional Review Board (IEC/IRB)

This study protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, as required. The sponsor (or designee) is responsible for regulatory submissions. This clinical study may not be initiated until all local regulatory requirements are met.

Before the start of the study, a written favorable opinion or approval must be received from the IEC/IRB. To achieve this, the investigator or the sponsor will submit to the IEC/IRB, as required by local regulations, current and complete copies of relevant documents.

The written favorable opinion or approval must be dated and must clearly identify the documents reviewed, which should include the final protocol and any amendments, the informed consent form, applicable recruiting materials, and any patient compensation program.

During the study, the investigator or sponsor, as required, will submit the following for IEC/IRB review or opinion/approval:

1. Revisions or updates of documents previously submitted to the IEC/IRB
2. Relevant new information or documents, as required:
    a. Summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC/IRB);
    b. Reports of adverse events that are serious, unlisted, and associated with the investigational drug;
    c. Deviations from or changes to the study protocol to eliminate immediate hazards to the patients.

When and where required by local regulations, before implementation of any change, study protocol amendments and revised documents must receive IEC/IRB favorable opinion or approval.

The IEC/IRB will be given official notification of the study completion.

20.3 Required Pre-study Documentation

The study protocol and any amendment(s) signed and dated by the investigator, the completed investigator financial disclosure form from the investigator, and signed and dated statement of investigator (e.g., Form FDA 1572), if applicable, and any other documents specified by ICH-GCP guidelines must be provided to the sponsor before the study is started at an investigational site.

20.4 Clinical Laboratory Certification and Reference Ranges

Before the initiation of this study, the investigator (or nominee) will obtain a copy of the certification form, with certification number and expiration date for all clinical laboratories used in the study. Reference ranges for each clinical laboratory test used in this study will be obtained from the appropriate laboratory, which will perform the test for the study.

20.5 Informed Consent

Each patient must give written consent according to local requirements after receiving a full explanation of the nature of the study. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent process and form should be in accordance with principles that originated in the Declaration of Helsinki, current ICH-GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before a patient's entry into the study, the investigator or an authorized member of the clinical staff must explain to the potential patient the aims, methods, and potential hazards of the study, and any discomfort it may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care a patient will receive.

Finally, patients will be informed that the investigator will maintain a patient enrolment log for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the patient is authorizing such access, and agrees to be re-contacted after study completion, by health authorities and authorized sponsor staff, for the purpose of obtaining consent for additional safety evaluations if needed.

Patients will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's personally dated signature. After the consent is obtained, a copy of the informed consent form must be given to the patient.

20.6 Privacy of Personal Data

In order to maintain patient privacy, all CRF, investigational product accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Delpor (or designee) and regulatory authorities access to the patient’s original medical records for verification of data gathered on the CRF and to audit the data collection process. The patient’s confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

20.7 Study Completion/Site Closure

The study is considered completed at the last visit of the last patient undergoing the study. The final data from the investigational site will be sent to the sponsor (or designee) in the time frame specified in the Clinical Trial Agreement. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

21 QUALITY CONTROL AND ASSURANCE

21.1 Study Monitoring

The sponsor will assign monitors who will perform on-site monitoring visits as frequently as necessary and in compliance with the ICH-GCP Section 5.18.4.

Monitoring visits will include checking the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. Findings from the review of CRF and source documents will be discussed with the clinical staff.

The sponsor expects that, during monitoring visits, the relevant clinical staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

21.2 Audits, Inspections Study Quality Management

To ensure compliance with ICH GCP and all applicable regulatory requirements, Delpor (or a designated third party), may conduct a quality assurance audit of the study site. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to notify the sponsor as soon as possible following awareness of an impending regulatory inspection. The investigator and Institution agree to allow the

auditor/inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The sponsor (or its designee) will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the investigator (and delegate(s)) generating the data.

Prior to the study initiation, the sponsor (or its designee) will explain the protocol, Investigator's Brochure, and CRF to the investigator and clinical facility staff involved in this study. In addition, the assigned study monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

21.3 Data Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor (or designee). Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples. CRF completion training will be conducted with study personnel before the start of the study. The sponsor's monitor will review electronic data for accuracy and completeness during onsite monitoring visits and after his/her return to the sponsor's office; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

21.4 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all source documents that support the data collected from each patient, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained as per the applicable regulatory requirements for the country where the site is located or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to all study documentation.

22 STUDY PROTOCOL GUIDELINES

22.1 Protocol Amendments, Deviations and Violations

Neither the investigator nor the sponsor will modify this protocol without a formal amendment.

All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. When the amendment(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) needs only to be notified.

A protocol deviation is an accidental or unintentional change to, or non-compliance with this study protocol that does not increase risk or decrease benefit or; does not have a significant effect on the patient's rights, safety or welfare; and/or on the integrity of the data. No deviations to this protocol are permitted, except in instances when an emergency occurs that requires a departure from the protocol to protect the safety of an individual.

A protocol violation is an accidental or unintentional change to, or non-compliance with the IEC/IRB approved protocol (without prior sponsor and IEC/IRB approval), which increases the risk or decreases the benefit, affects the patient's rights, safety, or welfare, or the integrity of the data. Reporting of protocol violations to IEC/IRB and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

In situations requiring a departure from the protocol, the investigator (or other physician) in attendance will contact the appropriate sponsor representative by fax or telephone or e-mail (see Contact Information pages provided separately). If possible, this contact will be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action.

The data recorded in the CRF and source document will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

23 USE OF INFORMATION AND PUBLICATION POLICY

All information, including but not limited to information regarding DLP-114 or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remains the sole property of the sponsor. The investigator agrees to maintain this information in confidence and to use this information only to conduct this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of DLP-114, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study. The results of the study will be reported in a Clinical Study Report generated by the sponsor (or designee) under the supervision of the sponsor and will contain all data from all investigational sites. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work. The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the

sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. The investigator will recognize the integrity of a multi-center study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multi-center study publication. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

24 LIABILITY AND INSURANCE

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The sponsor will provide insurance coverage for the clinical study as required by national regulations. Delpor will be subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the study protocol as well as with applicable law and professional standards prior to the dosing of the first patient.

25 REFERENCES

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26 APPENDICES

26.1 APPENDIX 1. Overall Schedule of Assessments

Group 1

Treatment Period	Screening	Conversion Phase[1]	Oral Treatment Period (Unsupervised)			Oral Treatment Period (Supervised)				Implant + Oral Period		Implant Treatment Period																				Recovery Period		Follow Up	EOS		ET[24]	ET Oral
Study Day	Varies (28 day window)	Varies to -5	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	14	21	28	42	56	70	84	98	112	126	140	154	168	183	184	185	186	190			
Confinement									X	X	X	X	X	X	X															X	X						
Outpatient Visit	X	X				X	X	X								X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
ASSESSMENT																																						
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]		X																																			
Informed Consent	X																																				
Review of Eligibility Criteria	X																																				
Demographics	X																																				
Medical History	X																																				
Height	X					X																															
Body Weight	X					X										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X			
Calculation of BMI	X					X																															
Review of Prior Medications	X					X																															
Physical Examination (Complete)	X																															X				X	
Viral Serology	X																																				
Alcohol Breath Test[4]	X								X																												
Urine Drug Screen[4]	X								X														X						X								
Serum hCG Pregnancy Test[2]	X																																				
Urine hCG Pregnancy Test[2,4]						X			X										X		X		X		X		X			X				X	X	X	X
Safety Laboratory Tests (blood)[4]	X								X							X			X				X				X			X^{11}					X^{11}	X^{11}
Safety Laboratory Tests (urine)[4]	X								X							X			X				X				X			X^{11}					X^{11}	X
12-lead ECG[3,4]	X								X	X^{7}	X^{9}					X			X				X				X			X^{11}					X^{11}	X
Vital Signs[25]	X	X				X^{5}	X	X	X^{5}	$X^{6,8}$	X^{9}	X^{10}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X^{12}	X^{13}	X^{14}	X	X	X^{12}	X
CYP2D6 Genotype	X																																				
CGI-S	X								X																												
CGI-I[4]																X	X		X		X		X		X		X		X	X					X	
PANSS[4]	X								X														X							X					X	
C-SSRS	X	X				X			X	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
BARS[4]	X								X																				X						X		
SAS[4]	X								X																				X						X		
AIMS[3]	X								X																				X						X		
Self Administration of Investigational Product Under Supervision (Oral)						X	X	X	X	X^{19}	X^{9}																											
Self Administration of Investigational Product Not Under Supervision (Oral)			X	X	X																																
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Update/Review of Concomitant Medications		X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK[16]									$X^{17,18}$	$X^{19,20}$	X^{21}	X^{22}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X^{23}	X^{13}	X^{14}	X		X^{15}	
Implant Device Administration										X																												
Issuing of study card and/or safety alert bracelet																X																						
Implant Site Inspection										X	X^{9}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X^{13}	X^{14}	X	X	X	
Ultrasound[4]																	X													X							
Implant removal																														X					X		

Group 2

Treatment Period	Screening	Conversion Phase[1]	Oral Treatment Period (Unsupervised)			Oral Treatment Period (Supervised)				Implant + Oral Period		Implant Treatment Period							
Study Day	Varies (28 day window)	Varies to -5	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	14	21	28
Confinement									X	X	X	X	X	X	X				
Outpatient Visit	X	X				X	X	X								X	X	X	X
ASSESSMENT																			
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]		X																	
Informed Consent	X																		
Review of Eligibility Criteria	X					X													
Demographics	X																		
Medical History	X																		
Height	X					X													
Body Weight	X					X										X	X	X	X
Calculation of BMI	X					X													
Review of Prior Medications	X					X													
Physical Examination (Complete)	X																		
Viral Serology	X																		
Alcohol Breath Test[4]	X								X										
Urine Drug Screen[4]	X								X										
Serum hCG Pregnancy Test[2]	X																		
Urine hCG Pregnancy Test[2,4]						X			X										X
Safety Laboratory Tests (blood)[4]	X								X							X			X
Safety Laboratory Tests (urine)[3]	X								X							X			X
12-lead ECG[3,4]	X								X	X[7]	X[9]					X			X
Vital Signs[25]	X	X				X[5]	X	X	X[5]	X[57]	X[8]	X[10]	X	X	X	X	X	X	X
CYP2D6 Genotype	X																		
CGI-S	X								X										
CGI-I[4]																X	X		X
PANSS[4]	X								X										
C-SSRS	X	X				X			X	X						X	X	X	X
BARS[4]	X								X										
SAS[4]	X								X										
AIMS[4]	X								X										
Self Administration of Investigational Product Under Supervision (Oral)						X	X	X	X	X[19]	X[9]								
Self Administration of Investigational Product Not Under Supervision (Oral)			X	X	X														
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Update/Review of Concomitant Medications		X				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK[16]									X[17,18]	X[19,20]	X[21]	X[22]	X	X	X	X	X	X	X
Implant Device Administration										X									
Issuing of study card and/or safety alert bracelet																X			
Implant Site Inspection										X	X[9]	X	X	X	X	X	X	X	X
Ultrasound[4]																	X		
Implant removal																			

Treatment Period	Implant Treatment Period																								Recovery Period		Follow Up	EOS	ET[24]	ET Oral
Study Day	42	56	70	84	98	112	126	140	154	168	182	196	210	224	238	252	266	280	294	308	322	336	350	364	365	366	367	371		
Confinement																								X	X					
Outpatient Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
ASSESSMENT																														
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]																														
Informed Consent																														
Review of Eligibility Criteria																														
Demographics																														
Medical History																														
Height																														
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X		
Calculation of BMI																														
Review of Prior Medications																														
Physical Examination (Complete)																										X			X	
Viral Serology																														
Alcohol Breath Test[4]																														
Urine Drug Screen[4]				X							X													X						
Serum hCG Pregnancy Test[2]																														
Urine hCG Pregnancy Test[2,4]		X		X		X		X			X		X		X		X	X		X		X		X				X	X	X
Safety Laboratory Tests (blood)[4]				X				X			X				X			X			X			X[11]					X[11]	X[11]
Safety Laboratory Tests (urine)[3]				X				X			X				X			X			X			X[10]					X[11]	X
12-lead ECG[3,4]				X				X			X				X			X			X			X[11]					X[10]	X
Vital Signs[25]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]	X[13]	X[14]	X	X	X[12]	X
CYP2D6 Genotype																														
CGI-S																														
CGI-I[4]		X		X		X		X		X	X		X		X		X	X		X		X	X	X					X	
PANSS[4]				X							X							X						X					X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
BARS[4]													X		X		X					X	X						X	
SAS[4]													X		X		X					X	X						X	
AIMS[4]													X		X		X					X	X						X	
Self Administration of Investigational Product Under Supervision (Oral)																														
Self Administration of Investigational Product Not Under Supervision (Oral)																														
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Update/Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	X[13]	X[14]	X		X[15]	
Implant Device Administration																														
Issuing of study card and/or safety alert bracelet																														
Implant Site Inspection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	X[14]	X	X	X	
Ultrasound[4]																								X						
Implant removal																								X					X	

Footnotes: Overall Schedule of Assessments (6-month arm and 12-month arm)

[1] Patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) will have weekly visits during the conversion phase, during which they will cross-titrate, at the PI's discretion, from the other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks. The objective of the oral conversion phase is for all subjects to achieve an oral risperidone dose of 3 mg by Day -14

[2] Females only

[3] All ECGs should be obtained prior to vital signs and blood sampling when applicable.

[4] May be performed more frequently based on symptoms at the PI's discretion

[5] Pre-dose

[6] Pre-implantation

[7] 4 hours post-implantation

[8] Every hour for the first 8 hours post-implantation

[9] Approximately 24 hours post-implantation

[10] Approximately 48 hours post-implantation

[11] 4 hours following removal of the DLP-114 implant

[12] Every hour for the first 4 hours following removal of the DLP-114 implant

[13] 24 hours following removal of the DLP-114 implant

[14] 48 hours following removal of the DLP-114 implant

[15] Prior to removal

[16] See Appendix 2. Pharmacokinetic sample collection schedule

[17] Within 10 min prior to dose administration

[18] 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose

[19] 1 hour (± 30 min) prior to DLP-114 implantation

[20] 1, 2, 3, 4, 6, 8 and 12 hours post-implantation

[21] 24, 28, 32 and 36 hours following implantation of DLP-114

[22] 48 and 52 hours following implantation of DLP-114

[23] 1, 2, 3, 4, 6, 8- and 12-hours following removal of the DLP-114 implant

[24] Patients will be requested to return to the clinic for a follow up visit 6 (±3) days following the removal of the implant, for implant site inspection and AE assessment.

[25] Vital signs will include systolic and diastolic blood pressure, pulse, body temperature, and respiratory rate. In addition, orthostatic blood pressure and pulse will be collected after 1, 3, and 5 minutes standing at Screening, on Day 1 prior to the implant and 4 hours post-implantation, and on Day 3 approximately 48 hours post-implantation

26.2 APPENDIX 2. Pharmacokinetic Sample Collection Schedule

Group 1

Treatment	Day	Study Event	Hours	Time Window	Sample No.
Oral Risperidone (3 mg/day)	-1		-0.17	*Within 10 min prior to dosing*	1
		Dose (Oral Risperidone 3 mg)	0		
			0.5	±2 min	2
			1	±5 min	3
			2	±15 min	4
			3	±15 min	5
			4	±15 min	6
			6	±15 min	7
			8	±15 min	8
			12	±15 min	9
	0		24	±15 min	10
Co-administration of Oral Risperidone (3 mg/day) and 2X DLP-114 Implants	**1**	Dose (Oral Risperidone 3 mg)	-1	±30 min	11
		2 x DLP-114 Device Implantation	0		
			1	±5 min	12
			2	±15 min	13
			3	±15 min	14
			4	±15 min	15
			6	±15 min	16
			8	±15 min	17
			12	±15 min	18
	2	Dose (Oral Risperidone 3 mg)	24	±15 min	19
			28	±15 min	20
			32	±15 min	21
			36	±15 min	22
2X DLP-114 Implants	**3**		48	±15 min	23
			52	±15 min	24
	4		*AM**	±1 day	25
	5		*AM**	±1 day	26
	6		*AM**	±1 day	27
	7		*AM**	±1 day	28
	14		*AM**	±1 day	29
	21		*AM**	±1 day	30
	28		*AM**	±1 day	31
	42		*AM**	±1 day	32
	56		*AM**	±1 day	33
	70		*AM**	±1 day	34
	84		*AM**	±1 day	35
	98		*AM**	±1 day	36
	112		*AM**	±1 day	37
	126		*AM**	±1 day	38
	140		*AM**	±1 day	39
	154		*AM**	±1 day	40
	168		*AM**	±1 day	41
Recovery	**183 ± 7 days**		-1	±15 min	42
		DLP-114 Removal	0		
			1	±5 min	43
			2	±15 min	44
			3	±15 min	45
			4	±15 min	46
			6	±15 min	47
			8	±15 min	48
			12	±15 min	49
	184		24	±60 min	50
	185		48	±60 min	51
Follow-Up	**186**		72	±60 min	52
Early Termination	**ET**		-1	±45 min	
		DLP-114 Removal	0		

Treatment	Day	Study Event	Hours	Time Window	Sample No.

** 8 AM-12 Noon on the morning of the designated Study Day.*

Group 2

Treatment	Day	Study Event	Hours	Time Window	Sample No.
Oral Risperidone (3 mg/day)	-1		-0.17	*Within 10 min prior to dosing*	1
		Dose (Oral Risperidone 3 mg)	0		
			0.5	±2 min	2
			1	±5 min	3
			2	±15 min	4
			3	±15 min	5
			4	±15 min	6
			6	±15 min	7
			8	±15 min	8
			12	±15 min	9
	0		24	±15 min	10
Co-administration of Oral Risperidone (3 mg/day) and 2X DLP-114 Implants	1	Dose (Oral Risperidone 3 mg)	-1	±30 min	11
		2 x DLP-114 Device Implantation	0		
			1	±5 min	12
			2	±15 min	13
			3	±15 min	14
			4	±15 min	15
			6	±15 min	16
			8	±15 min	17
			12	±15 min	18
	2	Dose (Oral Risperidone 3 mg)	24	±15 min	19
			28	±15 min	20
			32	±15 min	21
			36	±15 min	22
2X DLP-114 Implants	3		48	±15 min	23
			52	±15 min	24
	4		*AM**	±1 day	25
	5		*AM**	±1 day	26
	6		*AM**	±1 day	27
	7		*AM**	±1 day	28
	14		*AM**	±1 day	29
	21		*AM**	±1 day	30
	28		*AM**	±1 day	31
	42		*AM**	±1 day	32
	56		*AM**	±1 day	33
	70		*AM**	±1 day	34
	84		*AM**	±1 day	35
	98		*AM**	±1 day	36
	112		*AM**	±1 day	37
	126		*AM**	±1 day	38
	140		*AM**	±1 day	39
	154		*AM**	±1 day	40
	168		*AM**	±1 day	41
	182		*AM**	±1 day	42
	196		*AM**	±1 day	43
	210		*AM**	±1 day	44
	224		*AM**	±1 day	45
	238		*AM**	±1 day	46
	252		*AM**	±1 day	47
	266		*AM**	±1 day	48
	280		*AM**	±1 day	49
	294		*AM**	±1 day	50
	308		*AM**	±1 day	51
	322		*AM**	±1 day	52
	336		*AM**	±1 day	53

Treatment	Day	Study Event	Hours	Time Window	Sample No.
	350		*AM**	±1 day	54
	364 ± 7 days		-1	±45 min	55
Recovery		DLP-114 Removal	0		
			1	±5 min	56
			2	±15 min	57
			3	±15 min	58
			4	±15 min	59
			6	±15 min	60
			8	±15 min	61
			12	±15 min	62
	365		24	±60 min	63
	366		48	±60 min	64
Follow-Up	**367**		72	±60 min	65
Early Termination	**ET**		-1	±45 min	
		DLP-114 Removal	0		

** 8 AM-12 Noon on the morning of the designated Study Day.*

26.3 APPENDIX 3. Skin Irritation Scoring System

(Kim, Choi et al, Drug Design and Therapy 2015, 8, 1419)[1]

Dermal Response:

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal popular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema, and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site

Other Effects:

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
F = glazing with fissures
G = film of dried serous exudate covering all or part of the patch* site
H = small petechial erosions and/or scabs

**For this study this refers to the implantation site and surrounding area.*

26.4 APPENDIX 4. Risperdal® (risperidone) Product Information

RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

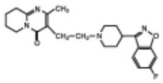
RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

7503231
5/06
01RS1795

Increased Mortality in Elderly Patients with Dementia–Related Psychosis
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

DESCRIPTION

RISPERDAL® (risperidone) is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is a white to slightly beige powder. It is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL® tablets are available in 0.25 mg (dark yellow), 0.5 mg (red-brown), 1 mg (white), 2 mg (orange), 3 mg (yellow), and 4 mg (green) strengths. Inactive ingredients are colloidal silicon dioxide, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25 mg tablets contain yellow iron oxide; the 0.5 mg tablets contain red iron oxide; the 2 mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3 mg and 4 mg tablets contain D&C Yellow No. 10; the 4 mg tablets contain FD&C Blue No. 2 Aluminum Lake.

RISPERDAL® is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

RISPERDAL® M-TAB® Orally Disintegrating Tablets are available in 0.5 mg (light coral), 1 mg (light coral), 2 mg (light coral), 3 mg (coral), and 4 mg (coral) strengths.

RISPERDAL® M-TAB® Orally Disintegrating Tablets contain the following inactive ingredients: Amberlite® resin, gelatin, mannitol, glycine, simethicone, carbomer, sodium hydroxide, aspartame, red ferric oxide, and peppermint oil. In addition, the 3 mg and 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablets contain xanthan gum.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of RISPERDAL® (risperidone), as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of RISPERDAL®.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α_1 and α_2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10^{-5} M) for cholinergic muscarinic or β_1 and β_2 adrenergic receptors.

Pharmacokinetics

Absorption

Risperidone is well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Pharmacokinetic studies showed that RISPERDAL® M-TAB® Orally Disintegrating Tablets and RISPERDAL® Oral Solution are bioequivalent to RISPERDAL® Tablets.

Plasma concentrations of risperidone, its major metabolite, 9–hydroxyrisperidone, and risperidone plus 9–hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg BID). Following oral administration of solution or tablet, mean peak plasma concentrations of risperidone occurred at about 1 hour. Peak concentrations of 9–hydroxyrisperidone occurred at about 3 hours in extensive metabolizers, and 17 hours in poor metabolizers. Steady-state concentrations of risperidone are reached in 1 day in extensive metabolizers and would be expected to reach steady-state in about 5 days in poor metabolizers. Steady-state concentrations of 9–hydroxyrisperidone are reached in 5-6 days (measured in extensive metabolizers).

Food Effect

Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9–hydroxyrisperidone, is 77%. Neither risperidone nor 9–hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and 9–hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9–hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway i *N*-dealkylation. The main metabolite, 9–hydroxyrisperidone, has similar pharmacological risperidone. Consequently, the clinical effect of the drug (e.g., the active moiety) results from the concentrations of risperidone plus 9–hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolisn neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject t polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrat quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9–hydroxyrisperidone poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers h risperidone and higher 9–hydroxyrisperidone concentrations than poor metabolizers, the pharma of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizer

Risperidone could be subject to two kinds of drug-drug interactions (see PRECAUTION Interactions). First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9–hydroxyri This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile poor metabolizers. The therapeutic benefits and adverse effects of risperidone in patients receivin have not been evaluated, but observations in a modest number (n≅70) of poor metaboli risperidone do not suggest important differences between poor and extensive metabolizers co-administration of known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with r may cause a decrease in the combined plasma concentrations of risperidone and 9–hydroxyris would also be possible for risperidone to interfere with metabolism of other drugs metabolized by Relatively weak binding of risperidone to the enzyme suggests this is unlikely.

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weel co-administration, the plasma concentrations of risperidone and its pharmacologically active r 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepi appear to be affected. Co-administration of other known enzyme inducers (e.g., phenytoin, rifa phenobarbital) with risperidone may cause similar decreases in the combined plasma concen risperidone and 9–hydroxyrisperidone, which could lead to decreased efficacy of risperidone treat PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Admini RISPERDAL® with Certain Other Medications).

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma cor of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma conce 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about PRECAUTIONS – Drug Interactions and DOSAGE AND ADMINISTRATION – Co-Admini RISPERDAL® with Certain Other Medications).

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or pea concentrations (C_{max}) of lithium (n=13) (see PRECAUTIONS – Drug Interactions).

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma conc and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placel However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after co administration of risperidone (see PRECAUTIONS – Drug Interactions).

There were no significant interactions between risperidone (1 mg QD) and erythromycin (500 mg PRECAUTIONS – Drug Interactions).

Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, re However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the active moiety by 20%.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety.

In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of don galantamine, which are metabolized by CYP 2D6.

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of d

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C-risperidone administered as three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% i and 14% in the feces.

The apparent half-life of risperidone was 3 hours (CV=30%) in extensive metabolizers and (CV=40%) in poor metabolizers. The apparent half-life of 9–hydroxyrisperidone was about (CV=20%) in extensive metabolizers and 30 hours (CV=25%) in poor metabolizers. The pharmacc the active moiety, after single and multiple doses, were similar in extensive and poor metabolize overall mean elimination half-life of about 20 hours.

Special Populations

Renal Impairment

In patients with moderate to severe renal disease, clearance of the sum of risperidone and metabolite decreased by 60% compared to young healthy subjects. RISPERDAL® doses should b in patients with renal disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Hepatic Impairment

While the pharmacokinetics of risperidone in subjects with liver disease were comparable to thos healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% b the diminished concentration of both albumin and α_1-acid glycoprotein. RISPERDAL® doses reduced in patients with liver disease (see PRECAUTIONS and DOSAGE AND ADMINISTRATIO

Elderly

In healthy elderly subjects, renal clearance of both risperidone and 9–hydroxyrisperidone was c and elimination half-lives were prolonged compared to young healthy subjects. Dosing should b accordingly in the elderly patients (see DOSAGE AND ADMINISTRATION).

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a pharmacokinetic analysis did not identify important differences in the disposition of risperidc gender (whether corrected for body weight or not) or race.

CLINICAL TRIALS

Schizophrenia

Short-Term Efficacy

The efficacy of RISPERDAL® in the treatment of schizophrenia was established in four s (4- to 8-week) controlled trials of psychotic inpatients who met DSM-III-R criteria for schizophreni

Several instruments were used for assessing psychiatric signs and symptoms in these studies, an the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology t used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (c disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is cor

1

particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Positive and Negative Syndrome Scale (PANSS) and the Scale for Assessing Negative Symptoms (SANS) were employed.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=160) involving titration of RISPERDAL® in doses up to 10 mg/day (BID schedule), RISPERDAL® was generally superior to placebo on the BPRS total score, on the BPRS psychosis cluster, and marginally superior to placebo on the SANS.

(2) In an 8-week, placebo-controlled trial (n=513) involving 4 fixed doses of RISPERDAL® (2, 6, 10, and 16 mg/day, on a BID schedule), all 4 RISPERDAL® groups were generally superior to placebo on the BPRS total score, BPRS psychosis cluster, and CGI severity score; the 3 highest RISPERDAL® dose groups were generally superior to placebo on the PANSS negative subscale. The most consistently positive responses on all measures were seen for the 6 mg dose group, and there was no suggestion of increased benefit from larger doses.

(3) In an 8-week, dose comparison trial (n=1356) involving 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day, on a BID schedule), the four highest RISPERDAL® dose groups were generally superior to the 1 mg RISPERDAL® dose group on BPRS total score, BPRS psychosis cluster, and CGI severity score. None of the dose groups were superior to the 1 mg group on the PANSS negative subscale. The most consistently positive responses were seen for the 4 mg dose group.

(4) In a 4-week, placebo-controlled dose comparison trial (n=246) involving 2 fixed doses of RISPERDAL® (4 and 8 mg/day on a QD schedule), both RISPERDAL® dose groups were generally superior to placebo on several PANSS measures, including a response measure (> 20% reduction in PANSS total score), PANSS total score, and the BPRS psychosis cluster (derived from PANSS). The results were generally stronger for the 8 mg than for the 4 mg dose group.

Long-Term Efficacy

In a longer-term trial, 365 adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medication were randomized to RISPERDAL® (2-8 mg/day) or to an active comparator, for 1 to 2 years of observation for relapse. Patients receiving RISPERDAL® experienced a significantly longer time to relapse over this time period compared to those receiving the active comparator.

Bipolar Mania

Monotherapy

The efficacy of RISPERDAL® in the treatment of acute manic or mixed episodes was established in 2 short-term (3-week) placebo-controlled trials in patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes. These trials included patients with or without psychotic features.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=246), limited to patients with manic episodes, which involved a dose range of RISPERDAL® 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 4.1 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

(2) In another 3-week placebo-controlled trial (n=286), which involved a dose range of 1-6 mg/day, once daily, starting at 3 mg/day (mean modal dose was 5.6 mg/day), RISPERDAL® was superior to placebo in the reduction of Y-MRS total score.

Combination Therapy

The efficacy of risperidone with concomitant lithium or valproate in the treatment of acute manic or mixed episodes was established in one controlled trial in patients who met the DSM-IV criteria for Bipolar I Disorder. This trial included patients with or without psychotic features and with or without a rapid-cycling course.

(1) In this 3-week placebo-controlled combination trial, 148 in- or outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL®, placebo, or an active comparator, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.8 mg/day), combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.4 mEq/L or 50 mcg/mL to 120 mcg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 3-week placebo-controlled combination trial, 142 in- or outpatients on lithium, valproate, or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive RISPERDAL® or placebo, in combination with their original therapy. RISPERDAL®, in a dose range of 1-6 mg/day, once daily, starting at 2 mg/day (mean modal dose of 3.7 mg/day), combined with lithium, valproate, or carbamazepine (in therapeutic ranges of 0.6 mEq/L to 1.4 mEq/L for lithium, 50 mcg/mL to 125 mcg/mL for valproate, or 4-12 mcg/mL for carbamazepine, respectively) was not superior to lithium, valproate, or carbamazepine alone in the reduction of Y-MRS total score. A possible explanation for the failure of this trial was induction of risperidone and 9–hydroxyrisperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9–hydroxyrisperidone.

INDICATIONS AND USAGE

Schizophrenia

RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia.

The efficacy of RISPERDAL® in schizophrenia was established in short-term (6- to 8-weeks) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY).

The efficacy of RISPERDAL® in delaying relapse was demonstrated in schizophrenic patients who had been clinically stable for at least 4 weeks before initiation of treatment with RISPERDAL® or an active comparator and who were then observed for relapse during a period of 1 to 2 years (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, the physician who elects to use RISPERDAL® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Bipolar Mania

Monotherapy

RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® was established in two placebo-controlled trials (3-week) with patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACOLOGY).

Combination Therapy

The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatme manic or mixed episodes associated with Bipolar I Disorder.

The efficacy of RISPERDAL® in combination with lithium or valproate was established in one controlled (3-week) trial with patients meeting DSM-IV criteria for Bipolar I Disorder who currently an acute manic or mixed episode with or without psychotic features (see CLINICAL PHARMACO

The effectiveness of RISPERDAL® for longer-term use, that is, for more than 3 weeks of treatment episode, and for prophylactic use in mania, has not been systematically evaluated in controlled cli Therefore, physicians who elect to use RISPERDAL® for extended periods should periodically re-e long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTR

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the proc

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approve treatment of dementia-related psychosis (see Boxed Warning).

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyp muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diag important to identify cases in which the clinical presentation includes both serious medical ill pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal symptoms (EPS). Other important considerations in the differential diagnosis include central anti toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monit (3) treatment of any concomitant serious medical problems for which specific treatments are avail is no general agreement about specific pharmacological treatment regimens for uncomplicated N

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintro drug therapy should be carefully considered. The patient should be carefully monitored, since recu NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patie with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the in antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsyc products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are l increase as the duration of treatment and the total cumulative dose of antipsychotic drugs admi the patient increase. However, the syndrome can develop, although much less commonly, afte brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, hov suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may pos the underlying process. The effect that symptomatic suppression has upon the long-term cou syndrome is unknown.

Given these considerations, RISPERDAL® (risperidone) should be prescribed in a manner that is to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should ge reserved for patients who suffer from a chronic illness that: (1) is known to respond to antipsych and (2) for whom alternative, equally effective, but potentially less harmful treatments are not a appropriate. In patients who do require chronic treatment, the smallest dose and the shortest treatment producing a satisfactory clinical response should be sought. The need for continued should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL®, dr tinuation should be considered. However, some patients may require treatment with RISPERDA the presence of the syndrome.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementi Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with demer psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascul events in patients treated with risperidone compared to patients treated with placebo. RISPERD approved for the treatment of patients with dementia-related psychosis. (See also **Boxed W WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessr relationship between atypical antipsychotic use and glucose abnormalities is complicated by the p an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing of diabetes mellitus in the general population. Given these confounders, the relationship betwe antipsychotic use and hyperglycemia-related adverse events is not completely understood. epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-relate events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycer adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsycho be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes me obesity, family history of diabetes) who are starting treatment with atypical antipsychotics shoul fasting blood glucose testing at the beginning of treatment and periodically during treatment. A treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglyce treatment with atypical antipsychotics should undergo fasting blood glucose testing. In so hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, som required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures

During premarketing testing, seizures occurred in 0.3% (9/2607) of RISPERDAL®-treated patients, two in association with hyponatremia. RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**)

Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. As is common with compounds which increase prolactin release, an increase in pituitary gland, mammary gland, and pancreatic islet cell hyperplasia and/or neoplasia was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). However, neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related, and in a study utilizing a checklist to detect adverse events, 41% of the high-dose patients (RISPERDAL® 16 mg/day) reported somnolence compared to 16% of placebo patients. Direct questioning is more sensitive for detecting adverse events than spontaneous reporting, by which 8% of RISPERDAL® 16 mg/day patients and 1% of placebo patients reported somnolence as an adverse event. Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism

Rare cases of priapism have been reported. While the relationship of the events to RISPERDAL® use has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that RISPERDAL® may share this capacity. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® use. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for RISPERDAL® should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

Use in Patients With Concomitant Illness

Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9–hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²), and an increase in the free fraction of risperidone is seen in patients with severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®:

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

Interference With Cognitive and Motor Performance

Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients cautioned about operating hazardous machinery, including automobiles, until they are reasonal that RISPERDAL® therapy does not affect them adversely.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to becom during therapy.

Nursing

Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any pres over-the-counter drugs, since there is a potential for interactions.

Alcohol

Patients should be advised to avoid alcohol while taking RISPERDAL®.

Phenylketonurics

Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegra contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Table 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contain phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contain phenylalanine.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in co with other centrally acting drugs and alcohol.

Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive other therapeutic agents with this potential.

RISPERDAL® may antagonize the effects of levodopa and dopamine agonists.

Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety. Cime ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the A active moiety by 20%.

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Carbamazepine and Other Enzyme Inducers

In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weel co-administration, the plasma concentrations of risperidone and its pharmacologically active r 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepi appear to be affected. The dose of risperidone may need to be titrated accordingly for patients carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-adm of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone r similar decreases in the combined plasma concentrations of risperidone and 9–hydroxyrisperid could lead to decreased efficacy of risperidone treatment.

Fluoxetine and Paroxetine

Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma cor of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma conce 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 1(either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-ev dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine t the pharmacokinetics of risperidone and 9–hydroxyrisperidone have not been studied.

Lithium

Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or pea concentrations (C_{max}) of lithium (n=13).

Valproate

Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or averag concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) cor placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (concomitant administration of risperidone.

Digoxin

RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of

Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9–hydroxyrisperidone by CYP 2D6, an enzyme that is polymor population and that can be inhibited by a variety of psychotropic and other drugs (see (PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9–hydroxyr would increase the plasma concentrations of risperidone and lower the concentr 9–hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolize does not suggest that poor and extensive metabolizers have different rates of adverse e comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2 and 3A4, are only weak inhibitors of risperidone metabolism.

There were no significant interactions between risperidone and erythromycin (see (PHARMACOLOGY).

Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RIS is not expected to substantially inhibit the clearance of drugs that are metabolized by this pathway. In drug interaction studies, risperidone did not significantly affect the pharmacol donepezil and galantamine, which are metabolized by CYP 2D6.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperi administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended hu (MRHD) (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, a

the MRHD (rats) on a mg/m² basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The following table summarizes the multiples of the human dose on a mg/m² (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m² (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	female	0.2 (2.4)	none
	rat	female	0.4 (2.4)	none
	rat	male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies. An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia).

Mutagenesis

No evidence of mutagenic potential for risperidone was found in the Ames reverse mutation test, mouse lymphoma assay, *in vitro* rat hepatocyte DNA-repair assay, *in vivo* micronucleus test in mice, the sex-linked recessive lethal test in *Drosophila*, or the chromosomal aberration test in human lymphocytes or Chinese hamster cells.

Impairment of Fertility

Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two Segment I and a multigenerational study) at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect appeared to be in females, since impaired mating behavior was not noted in the Segment I study in which males only were treated. In a subchronic study in Beagle dogs in which risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

Pregnancy

Pregnancy Category C

The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m² basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m² basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m² basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m² basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m² basis.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decrea function, care should be taken in dose selection, and it may be useful to monitor renal fun DOSAGE AND ADMINISTRATION).

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis incidence of mortality was observed in patients treated with furosemide plus risperidone when to patients treated with risperidone alone or with placebo plus furosemide. No pathological mech been identified to explain this finding, and no consistent pattern for cause of death was obs increase of mortality in elderly patients with dementia-related psychosis was seen with t RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approv treatment of patients with dementia-related psychosis. (See **Boxed WARNING, WARNINGS: I Mortality in Elderly Patients with Dementia-Related Psychosis.**)

ADVERSE REACTIONS

The following findings are based on the short-term, placebo-controlled, North American, pre trials for schizophrenia and acute bipolar mania. In patients with Bipolar I Disorder, treatment adverse events are presented separately for risperidone as monotherapy and as adjunctive mood stabilizers.

Certain portions of the discussion below relating to objective or numeric safety parameters, nar dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG ch derived from studies in patients with schizophrenia. However, this information is also generally ap bipolar mania.

Associated With Discontinuation of Treatment

Schizophrenia

Approximately 9% (244/2607) of RISPERDAL® (risperidone)-treated patients in Phase 2 and discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% control drugs. The more common events (≥0.3%) associated with discontinuation and consid possibly or probably drug-related included:

Adverse Event	RISPERDAL®	Placebo
Extrapyramidal symptoms	2.1%	0%
Dizziness	0.7%	0%
Hyperkinesia	0.6%	0%
Somnolence	0.5%	0%
Nausea	0.3%	0%

Suicide attempt was associated with discontinuation in 1.2% of RISPERDAL®-treated patients co 0.6% of placebo patients, but, given the almost 40-fold greater exposure time in RISPERDAL® co placebo patients, it is unlikely that suicide attempt is a RISPERDAL®-related adverse e PRECAUTIONS). Discontinuation for extrapyramidal symptoms was 0% in placebo patients, b active-control patients in the Phase 2 and 3 trials.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (1 RISPERDAL®-treated patients discontinued treatment due to an adverse event, comp approximately 6% (7/125) of placebo-treated patients. The adverse events associated with disc and considered to be possibly, probably, or very likely drug-related included paroniria, sor dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events o one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%).

In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® placebo).

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials

Schizophrenia

In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adve with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least tw placebo were anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial c RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detectir events, a method that is more sensitive than spontaneous reporting. By this method, the following common and drug-related adverse events occurred at an incidence of at least 5% and twice placebo: increased dream activity, increased duration of sleep, accommodation disturbances salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desi dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

Bipolar Mania

In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observe events associated with the use of RISPERDAL® (incidence of 5% or greater and at least tw placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnc saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therap stabilizers, the most commonly observed adverse events associated with the use of RISPERI somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, an incontinence.

Adverse Events Occurring at an Incidence of 1% or More Among RISPERDAL®-Treated Schizophrenia

The table that follows enumerates adverse events that occurred at an incidence of 1% or more, more frequent among RISPERDAL®-treated patients treated at doses of ≤10 mg/day than amon treated patients in the pooled results of two 6- to 8-week controlled trials. Patients received RIS doses of 2, 6, 10, or 16 mg/day in the dose comparison trial, or up to a maximum dose of 10 mg titration study. This table shows the percentage of patients in each dose group (≤ 10 mg/day or 1 who spontaneously reported at least one episode of an event at some time during their treatmer given doses of 2, 6, or 10 mg did not differ materially in these rates. Reported adverse events were using the World Health Organization preferred terms.

The prescriber should be aware that these figures cannot be used to predict the incidence of side the course of usual medical practice where patient characteristics and other factors differ from th prevailed in this clinical trial. Similarly, the cited frequencies cannot be compared with figures obt other clinical investigations involving different treatments, uses, and investigators. The cited figures do provide the prescribing physician with some basis for estimating the relative contribution of dru drug factors to the side effect incidence rate in the population studied.

Table 1. Incidence of Treatment-Emergent Adverse Events in 6- to 8-Week Controlled Clinical Trials[1]

Body System/ Preferred Term	RISPERDAL® ≤10 mg/day (N=324)	RISPERDAL® 16 mg/day (N=77)	Placebo (N=142)
Psychiatric			
Insomnia	26%	23%	19%
Agitation	22%	26%	20%
Anxiety	12%	20%	9%
Somnolence	3%	8%	1%
Aggressive reaction	1%	3%	1%
Central & peripheral nervous system			
Extrapyramidal symptoms[2]	17%	34%	16%
Headache	14%	12%	12%
Dizziness	4%	7%	1%
Gastrointestinal			
Constipation	7%	13%	3%
Nausea	6%	4%	3%
Dyspepsia	5%	10%	4%
Vomiting	5%	7%	4%
Abdominal pain	4%	1%	0%
Saliva increased	2%	0%	1%
Toothache	2%	0%	0%
Respiratory system			
Rhinitis	10%	8%	4%
Coughing	3%	3%	1%
Sinusitis	2%	1%	1%
Pharyngitis	2%	3%	0%
Dyspnea	1%	0%	0%
Body as a whole - general			
Back pain	2%	0%	1%
Chest pain	2%	3%	1%
Fever	2%	3%	0%
Dermatological			
Rash	2%	5%	1%
Dry skin	2%	4%	0%
Seborrhea	1%	0%	0%
Infections			
Upper respiratory	3%	3%	1%
Visual			
Abnormal vision	2%	1%	1%
Musculo-Skeletal			
Arthralgia	2%	3%	0%
Cardiovascular			
Tachycardia	3%	5%	0%

[1] Events reported by at least 1% of patients treated with RISPERDAL® ≤ 10 mg/day are included, and are rounded to the nearest %. Comparative rates for RISPERDAL® 16 mg/day and placebo are provided as well. Events for which the RISPERDAL® incidence (in both dose groups) was equal to or less than placebo are not listed in the table, but included the following: nervousness, injury, and fungal infection.

[2] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders. Although the incidence of 'extrapyramidal symptoms' does not appear to differ for the '10 mg/day' group and placebo, the data for individual dose groups in fixed dose trials do suggest a dose/response relationship (see ADVERSE REACTIONS – Dose Dependency of Adverse Events).

Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania

Tables 2 and 3 display adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms.

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® (N=134)	Placebo (N=125)
Central & peripheral nervous system		
Dystonia	18%	6%
Akathisia	16%	6%
Dizziness	11%	9%
Parkinsonism	6%	3%
Hypoaesthesia	2%	1%
Psychiatric		
Somnolence	28%	7%
Agitation	8%	6%
Manic reaction	8%	6%
Anxiety	4%	2%
Concentration impaired	2%	1%
Gastrointestinal system		
Dyspepsia	11%	6%
Nausea	11%	2%
Saliva increased	5%	1%
Mouth dry	3%	2%
Body as a whole - general		
Pain	5%	3%
Fatigue	4%	2%
Injury	2%	0%

Table 2. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Monotherapy in Bipolar Mania[1] (conti

Body System/ Preferred Term	RISPERDAL® (N=134)	Placeb (N=125
Respiratory system		
Sinusitis	4%	1%
Rhinitis	3%	2%
Coughing	2%	2%
Skin and appendages		
Acne	2%	0%
Pruritus	2%	1%
Musculo-Skeletal		
Myalgia	5%	2%
Skeletal pain	2%	1%
Metabolic and nutritional		
Weight increase	2%	0%
Vision disorders		
Vision abnormal	6%	2%
Cardiovascular, general		
Hypertension	3%	1%
Hypotension	2%	0%
Heart rate and rhythm		
Tachycardia	3%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are rou the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that we than the incidence reported by patients treated with placebo are not listed in the table, but inclu following: headache, tremor, insomnia, constipation, back pain, upper respiratory tract inf pharyngitis, and arthralgia.

Table 3. Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial - Adjunctive Therapy in Bipolar Mania[1]

Body System/ Preferred Term	RISPERDAL® + Mood Stabilizer (N=52)	Placeb + Mood Stal (N=51)
Gastrointestinal system		
Saliva increased	10%	0%
Diarrhea	8%	4%
Abdominal pain	6%	0%
Constipation	6%	4%
Mouth dry	6%	4%
Tooth ache	4%	0%
Tooth disorder	4%	0%
Central & peripheral nervous system		
Dizziness	14%	2%
Parkinsonism	14%	4%
Akathisia	8%	0%
Dystonia	6%	4%
Psychiatric		
Somnolence	25%	12%
Anxiety	6%	4%
Confusion	4%	0%
Respiratory system		
Rhinitis	8%	4%
Pharyngitis	6%	4%
Coughing	4%	0%
Body as a whole - general		
Asthenia	4%	2%
Urinary system		
Urinary incontinence	6%	2%
Heart rate and rhythm		
Tachycardia	4%	2%
Metabolic and nutritional		
Weight increase	4%	2%
Skin and appendages		
Rash	4%	2%

[1] Events reported by at least 2% of patients treated with RISPERDAL® are included and are r to the nearest %. Events reported by at least 2% of patients treated with RISPERDAL® that we than the incidence reported by patients treated with placebo are not listed in the table, but in the following: dyspepsia, nausea, vomiting, headache, tremor, insomnia, chest pain, fatigue skeletal pain, hypertension, and vision abnormal.

Dose Dependency of Adverse Events

Extrapyramidal Symptoms

Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal s associated with risperidone treatment.

Two methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial compar doses of risperidone (2, 6, 10, and 16 mg/day), including (1) a parkinsonism score (mean ch baseline) from the Extrapyramidal Symptom Rating Scale, and (2) incidence of spontaneous c of EPS:

Dose Groups	Placebo	Ris 2	Ris 6	Ris 10	Ris 16
Parkinsonism	1.2	0.9	1.8	2.4	2.6
EPS Incidence	13%	13%	16%	20%	31%

Similar methods were used to measure extrapyramidal symptoms (EPS) in an 8-week trial comparing 5 fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day):

Dose Groups	Ris 1	Ris 4	Ris 8	Ris 12	Ris 16
Parkinsonism	0.6	1.7	2.4	2.9	4.1
EPS Incidence	7%	12%	18%	18%	21%

Other Adverse Events

Adverse event data elicited by a checklist for side effects from a large study comparing 5 fixed doses of RISPERDAL® (1, 4, 8, 12, and 16 mg/day) were explored for dose-relatedness of adverse events. A Cochran-Armitage Test for trend in these data revealed a positive trend ($p<0.05$) for the following adverse events: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation.

Vital Sign Changes

RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS).

Weight Changes

The proportions of RISPERDAL® and placebo-treated patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes

A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS).

ECG Changes

Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute).

Other Events Observed During the Premarketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 patients in Phase 2 and 3 studies. The conditions and duration of exposure to RISPERDAL® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term or longer-term exposure. In most studies, untoward events associated with this exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In two large studies, adverse events were also elicited utilizing the UKU (direct questioning) side effect rating scale, and these events were not further categorized using standard terminology. (Note: These events are marked with an asterisk in the listings that follow.)

In the listings that follow, spontaneously reported adverse events were classified using World Health Organization (WHO) preferred terms. The frequencies presented, therefore, represent the proportion of the 2607 patients exposed to multiple doses of RISPERDAL® who experienced an event of the type cited on at least one occasion while receiving RISPERDAL®. All reported events are included, except those already listed in Table 1, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Psychiatric Disorders

Frequent: increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders

Frequent: increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastrointestinal Disorders

Frequent: anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders

Frequent: fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders

Infrequent: hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders

Frequent: increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders

Infrequent: palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders

Infrequent: abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders

Infrequent: hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypopr hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders

Frequent: polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary cystitis, renal insufficiency.

Musculo-Skeletal System Disorders

Infrequent: myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female

Frequent: menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, an female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual vaginal hemorrhage.

Liver and Biliary System Disorders

Infrequent: increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, ch cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding, and Clotting Disorders

Infrequent: epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombo

Hearing and Vestibular Disorders

Rare: tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders

Infrequent: anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male

Frequent: erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders

Rare: leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders

Rare: gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses

Rare: bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports

Adverse events reported since market introduction which were temporally (but not necessarily related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, ap fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal ob jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. relationship with RISPERDAL® has not been established. It is important to note that su unexpected death may occur in psychotic patients whether they remain untreated or whethe treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

RISPERDAL® (risperidone) is not a controlled substance.

Physical and Psychological Dependence

RISPERDAL® has not been systematically studied in animals or humans for its potential tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any dr behavior, these observations were not systematic and it is not possible to predict on the basis of experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once Consequently, patients should be evaluated carefully for a history of drug abuse, and such patie be observed closely for signs of RISPERDAL® misuse or abuse (e.g., development of tolerance, in dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Premarketing experience included eight reports of acute RISPERDAL® (risperidone) overdc estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symp those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drows sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and wide Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience includes reports of acute RISPERDAL® overdosage, with estimated d to 360 mg. In general, the most frequently reported signs and symptoms are those resultin exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tac hypotension, and extrapyramidal symptoms. Other adverse events reported since market introduc were temporally (but not necessarily causally) related to RISPERDAL® overdose, include t pointes, prolonged QT interval, convulsions, cardiopulmonary arrest, and rare fatality assoc multiple drug overdose.

Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxyger ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of charcoal together with a laxative should be considered. Because of the rapid disintegration of RIS M-TAB® Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained w

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following ove create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence in and should include continuous electrocardiographic monitoring to detect possible arrhy antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a t hazard of QT-prolonging effects that might be additive to those of risperidone. Similarly, it is rea expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, problematic hypotension.

There is no specific antidote to RISPERDAL®. Therefore, appropriate supportive measures instituted. The possibility of multiple drug involvement should be considered. Hypotension and collapse should be treated with appropriate measures, such as intravenous fluids and/or sympat agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypo

the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Schizophrenia

Usual Initial Dose

RISPERDAL® (risperidone) can be administered on either a BID or a QD schedule. In early clinical trials, RISPERDAL® was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that total daily risperidone doses of up to 8 mg on a QD regimen are also safe and effective. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 4 to 16 mg/day in the clinical trials supporting effectiveness of RISPERDAL®; however, maximal effect was generally seen in a range of 4 to 8 mg/day. Doses above 6 mg/day for BID dosing were not demonstrated to be more efficacious than lower doses, were associated with more extrapyramidal symptoms and other adverse effects, and are not generally recommended. In a single study supporting QD dosing, the efficacy results were generally stronger for 8 mg than for 4 mg. The safety of doses above 16 mg/day has not been evaluated in clinical trials.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long the schizophrenic patient treated with RISPERDAL® should remain on it, the effectiveness of RISPERDAL® 2 mg/day to 8 mg/day at delaying relapse was demonstrated in a controlled trial in patients who had been clinically stable for at least 4 weeks and were then followed for a period of 1 to 2 years. In this trial, RISPERDAL® was administered on a QD schedule, at 1 mg QD initially, with increases to 2 mg QD on the second day, and to a target dose of 4 mg QD on the third day (see CLINICAL PHARMACOLOGY – Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment with an appropriate dose.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval off RISPERDAL®, the initial titration schedule should be followed.

Switching From Other Antipsychotics

There are no systematically collected data to specifically address switching schizophrenic patients from other antipsychotics to RISPERDAL®, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some schizophrenic patients, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching schizophrenic patients from depot antipsychotics, if medically appropriate, initiate RISPERDAL® therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

Bipolar Mania

Usual Dose

Risperidone should be administered on a once daily schedule, starting with 2 mg to 3 mg per day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments/decrements of 1 mg per day, as studied in the short-term, placebo-controlled trials. In these trials, short-term (3 week) anti-manic efficacy was demonstrated in a flexible dosage range of 1-6 mg per day (see CLINICAL PHARMACOLOGY – Clinical Trials). RISPERDAL® doses higher than 6 mg per day were not studied.

Maintenance Therapy

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with risperidone. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone in such longer-term treatment (i.e., beyond 3 weeks).

Pediatric Use

Safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or acute mania associated with Bipolar I Disorder have not been established.

Dosage in Special Populations

The recommended initial dose is 0.5 mg BID in patients who are elderly or debilitated, patients with severe renal or hepatic impairment, and patients either predisposed to hypotension or for whom hypotension would pose a risk. Dosage increases in these patients should be in increments of no more than 0.5 mg BID. Increases to dosages above 1.5 mg BID should generally occur at intervals of at least 1 week. In some patients, slower titration may be medically appropriate.

Elderly or debilitated patients, and patients with renal impairment, may have less ability to eliminate RISPERDAL® than normal adults. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect (see CLINICAL PHARMACOLOGY). Patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk likewise need to be titrated cautiously and carefully monitored (see PRECAUTIONS). If a once-a-day dosing regimen in the elderly or debilitated patient is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2-3 days at the target dose. Subsequent switches to a once-a-day dosing regimen can be done thereafter.

Co-Administration of RISPERDAL® with Certain Other Medications

Co-administration of carbamazepine and other enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of active moiety (the sum of risperidone and 9–hydroxyrisperidone), which could lead to decreased efficacy of risperidone treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Fluoxetine and paroxetine have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 10%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

Directions for Use of RISPERDAL® M-TAB® Orally Disintegrating Tablets

Tablet Accessing

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 1 mg, and 2 mg are supplied in blist 4 tablets each.

Do not open the blister until ready to administer. For single tablet removal, separate one of the units by tearing apart at the perforations. Bend the corner where indicated. Peel back foil to e tablet. DO NOT push the tablet through the foil because this could damage the tablet.

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg

RISPERDAL® M-TAB® Orally Disintegrating Tablets 3 mg and 4 mg are supplied in a child-resist containing a blister with 1 tablet each.

The child-resistant pouch should be torn open at the notch to access the blister. Do not open until ready to administer. Peel back foil from the side to expose the tablet. DO NOT push the tabl the foil, because this could damage the tablet.

Tablet Administration

Using dry hands, remove the tablet from the blister unit and immediately place t RISPERDAL® M-TAB® Orally Disintegrating Tablet on the tongue. The RISPERDAL® M-TA Disintegrating Tablet should be consumed immediately, as the tablet cannot be stored once rem the blister unit. RISPERDAL® M-TAB® Orally Disintegrating Tablets disintegrate in the mouth withi and can be swallowed subsequently with or without liquid. Patients should not attempt to split the tablet.

HOW SUPPLIED

RISPERDAL® (risperidone) tablets are imprinted "JANSSEN", and either "Ris" and the strength "0 or "R" and the strength "1", "2", "3", or "4".

0.25 mg dark yellow tablet: bottles of 60 NDC 50458-301-04, bottles of 500 NDC 50458-301-5 unit dose packs of 100 NDC 50458-301-01.

0.5 mg red-brown tablet: bottles of 60 NDC 50458-302-06, bottles of 500 NDC 50458-302-50, h dose packs of 100 NDC 50458-302-01.

1 mg white tablet: bottles of 60 NDC 50458-300-06, blister pack of 100 NDC 50458-300-01, bot NDC 50458-300-50.

2 mg orange tablet: bottles of 60 NDC 50458-320-06, blister pack of 100 NDC 50458-320-01, bot NDC 50458-320-50.

3 mg yellow tablet: bottles of 60 NDC 50458-330-06, blister pack of 100 NDC 50458-330-01, bot NDC 50458-330-50.

4 mg green tablet: bottles of 60 NDC 50458-350-06, blister pack of 100 NDC 50458-350-01.

RISPERDAL® (risperidone) 1 mg/mL oral solution (NDC 50458-305-03) is supplied in 30 mL bot calibrated (in milligrams and milliliters) pipette. The minimum calibrated volume is 0.25 mL, maximum calibrated volume is 3 mL.

Tests indicate that RISPERDAL® (risperidone) oral solution is compatible in the following bevera coffee, orange juice, and low-fat milk; it is NOT compatible with either cola or tea, however.

RISPERDAL® M-TAB® (risperidone) Orally Disintegrating Tablets are etched on one side with "R "R2", "R3", and "R4", respectively. RISPERDAL® M-TAB® Orally Disintegrating Tablets 0.5 mg, 2 mg are packaged in blister packs of 4 (2 X 2) tablets. RISPERDAL® M-TAB® Orally Disi Tablets 3 mg and 4 mg are packaged in a child-resistant pouch containing a blister with 1 tablet.

0.5 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-395-28, long packaging of 30 tablets NDC 50458-395-30.

1 mg light coral, square, biconvex tablets: 7 blister packages per box, NDC 50458-315-28, long packaging of 30 tablets NDC 50458-315-30.

2 mg light coral, round, biconvex tablets: 7 blister packages per box, NDC 50458-325-28.

3 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-335-28.

4 mg coral, round, biconvex tablets: 28 blisters per box, NDC 50458-355-28.

Storage and Handling

RISPERDAL® tablets should be stored at controlled room temperature 15°-25°C (59°-77°F). Pr light and moisture.

Keep out of reach of children.

RISPERDAL® 1 mg/mL oral solution should be stored at controlled room temperature 15°-25°C (Protect from light and freezing.

Keep out of reach of children.

RISPERDAL® M-TAB® Orally Disintegrating Tablets should be stored at controlled room te 15°-25°C (59°-77°F).

Keep out of reach of children.

Rx Only

7503231 Revised March 2006 © Jans

RISPERDAL® tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico or Janssen-Cilag, SpA, Latina, Italy

RISPERDAL® oral solution is manufactured by:
Janssen Pharmaceutica N.V., Beerse, Belgium

RISPERDAL® M-TAB® Orally Disintegrating Tablets are manufactured by:
JOLLC, Gurabo, Puerto Rico

RISPERDAL® tablets, RISPERDAL® M-TAB® Orally Disintegrating Tablets, and oral solution are distributed by:
Janssen, L.P., Titusville, NJ 08560

Janssen L.P.

01RS1795

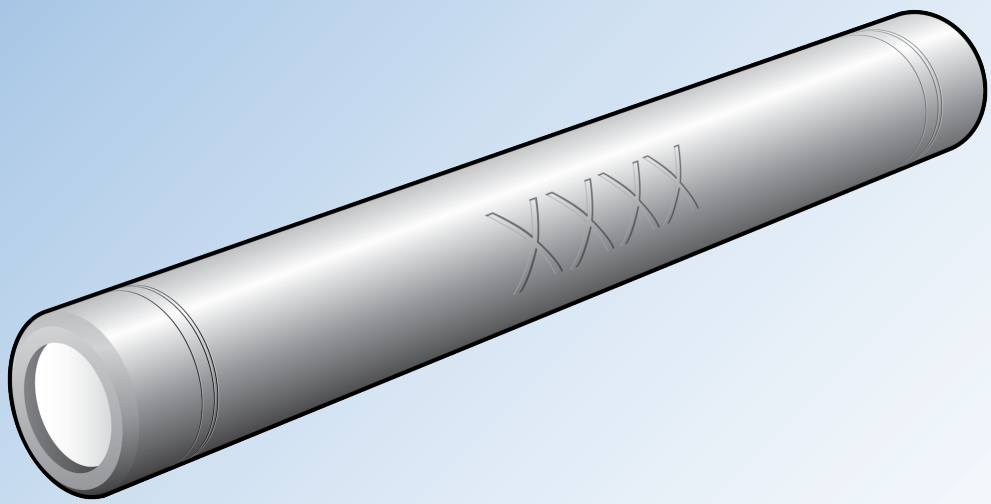
7

26.5 APPENDIX 5. Instructions for Use (IFU)

INSTRUCTIONS FOR USE

DLP-114

Risperidone Implant



For Investigational Use Only
Instructions for Use
Risperidone Implant, DLP-114

Delpor™

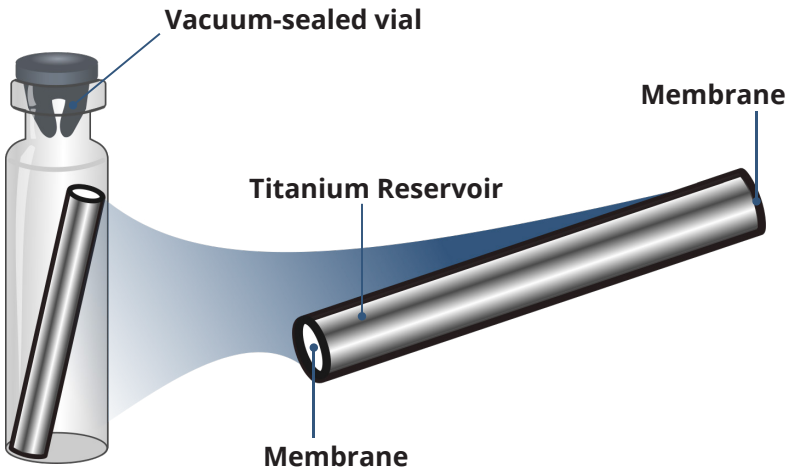
Contents

About DLP-114

DLP-114 is used for maintenance treatment of schizophrenia in adult patients.

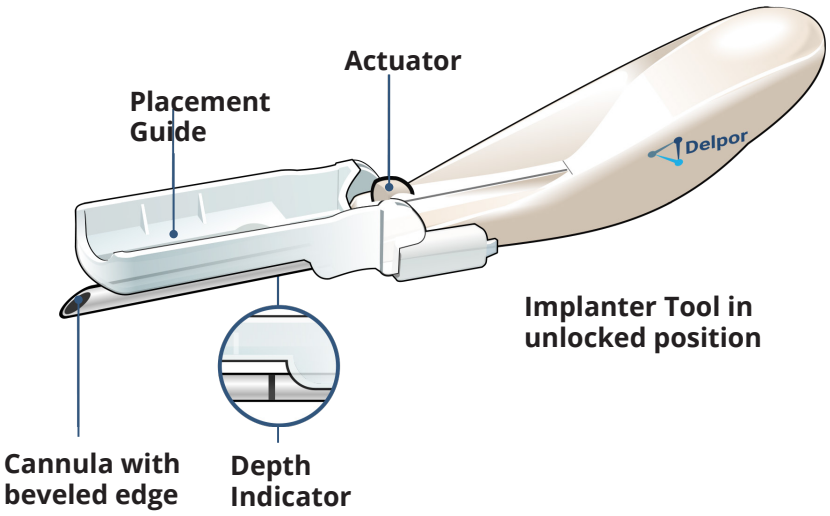
DLP-114 Implant Device

DLP-114 Implant Device is a drug-device combination product intended to deliver risperidone for 6 months following subcutaneous implantation in the abdomen. The device comes in a vacuum-sealed vial and requires hydration prior to implantation.



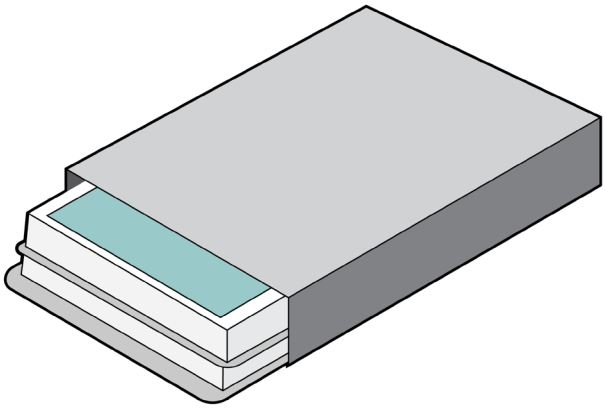
DLP-114 Implanter Tool

DLP-114 Implanter Tool is used to insert DLP-114 Implant Device subcutaneously into the abdomen.



DLP-114 Surgical Kit

DLP-114 Surgical Kit contains all the supplies necessary to perform the implantation and/or explantation procedure.



Important Safety Information

For Investigational Use Only

INDICATIONS FOR USE

DLP-114 is maintenance treatment of schizophrenia in adults

DOSAGE INFORMATION

Implant Version	Total Risperidone	Targeted Dose
Alpha 4	360 mg	1.0 mg/day
Alpha 7	435 mg	1.0 mg/day

CONTRAINDICATIONS

Known hypersensitivity to the product

ADVERSE REACTIONS

Common adverse reactions include somnolence, appetite increased, fatigue, rhinitis, upper respiratory tract infection, vomiting, coughing, urinary incontinence, saliva increased, constipation, fever, Parkinsonism, dystonia, abdominal pain, anxiety, nausea, dizziness, dry mouth, tremor, rash, akathisia, and dyspepsia.

To report SUSPECTED ADVERSE REACTIONS, contact Delpor, Inc. at 1-800-718-8120, or the FDA at 1-800-FDA-1088, or www.fda.gov/medwatch

DRUG INTERACTIONS

- Due to CNS effects, use caution when administering with other centrally-acting drugs. Avoid alcohol.
- Due to hypotensive effects, hypotensive effects of other drugs with this potential may be enhanced.
- Effects of levodopa and dopamine agonists may be antagonized.
- Cimetidine and ranitidine increase the bioavailability of risperidone.
- Clozapine may decrease clearance of risperidone.
- Fluoxetine and paroxetine increase plasma concentrations of risperidone.
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone.

USE IN SPECIFIC POPULATIONS

- Nursing mothers should not breast feed.

⚠ WARNINGS AND PRECAUTIONS

DO NOT administer DLP-114 in patients with the following conditions:

- A body mass index (BMI) **outside of** the ≥18.5≤ 40 kg/m2 inclusive range.
- Known hypersensitivity to titanium
- Known hypersensitivity or allergy to lidocaine or any local anesthetic agent of the amid type (local anesthetic used during implant and explant procedures)
- History of abnormal scar formation or family history of keloid formation
- Previously defined hypersensitivity to risperidone
- Tested positive for hepatitis B, hepatitis C or HIV infection
- History of clinically significant hypersensitivity or allergic reactions
- Used an investigational drug or device within 3 months prior to first dosing
- Pregnant or nursing

Take additional precautions for patients with the following condictions:

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. Risperidone is not approved for use in patients with dementia-related psychosis.
- Neuroleptic Malignant Syndrome
- Tardive dyskinesis
- Hyperglycemia and diabetes mellitus
- Hyperprolactinemia
- Orthostatic hypotension
- Leukopenia, Neutropenia, and Agranulocytosis: has been reported with antipsychotic. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.
- Potential for cognitive and motor impairment
- Seizures
- Dysphagia
- Priapism
- Disruption of body temperature regulation
- Antiemetic Effect
- Suicide
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies
- Diseases or conditions that could affect metabolism or hemodynamic responses

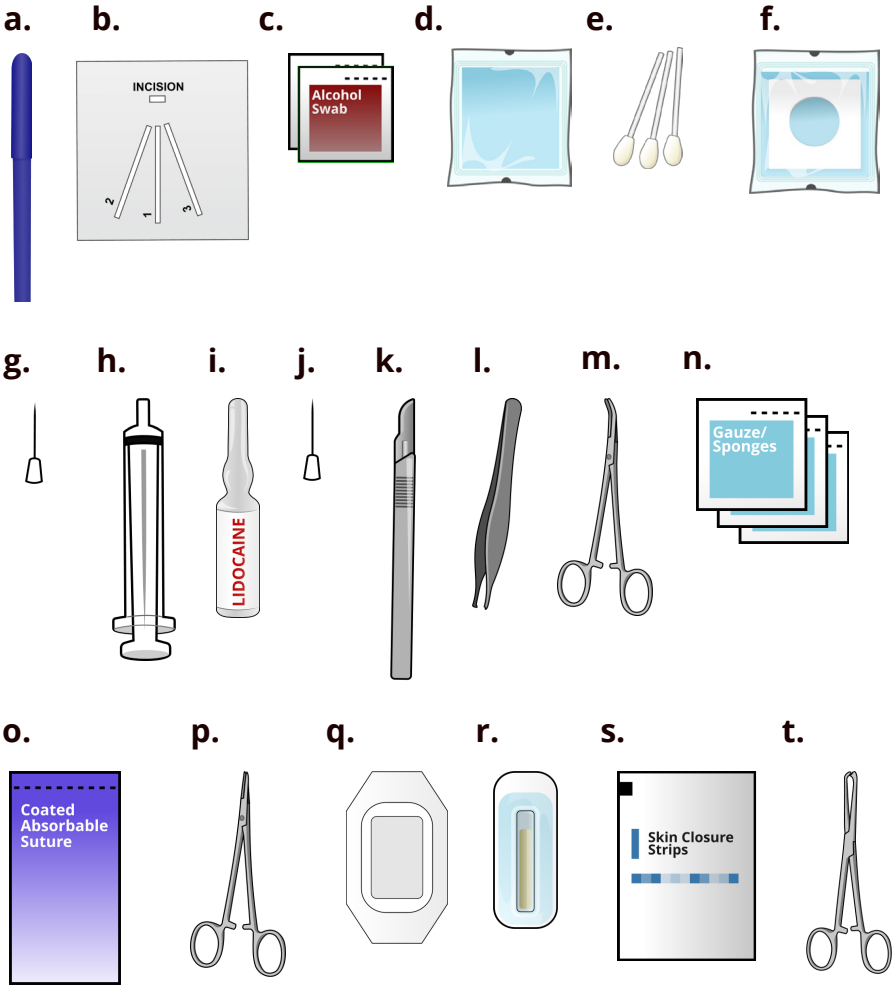
Symbols Glossary

Symbol	Standard Reference	Symbol Title	Explanatory Text
	ISO 15223-1, Clause 5.1.6	Catalog Number	Indicates the manufacturer's catalog number so that the medical device can be identified.
	ISO 15223-1 Clause 5.1.5	Batch Code	Indicates the manufacturer's batch code so that the batch or lot can be identified.
	ISO 15223-1 Clause 5.1.7	Serial Number	Indicates the manufacturer's serial number so that a specific medical device can be identified.
	ISO 15223-1 Clause 5.1.4	Use By	Indicates the date after which the medical device is not to be used.
	ISO 15223-1	Quantity	Indicates the number of units in the associated packaging.
	ISO 15223-1 Clause 5.2.4	Sterilized using irradiation	Indicates a medical device that has been sterilized using radiation.
	21 CFR 801.15 (c)(1)(i)(F)	Prescription only	Requires a prescription to use in the United States.
	ISO 15223-1 Clause 5.4.3	Consult instructions for use	Indicates the need for the user to consult the instructions for use.
	ISO 15223-1 Clause 5.6.3	Non pyrogenic	Indicates a medical device that is non-pyrogenic
	ISO 15223-1	Contains titanium	Indicates the product contains titanium
	ISO 15223-1 Clause 5.4.2	Do not reuse	Indicates a medical device that is intended for one use, or for use on a single patient during a single procedure
	ISO 15223-1 Clause 5.3.7	Storage temperature range	Indicates the temperature to which the medical device can be safely exposed
	ISO 15223-1 Clause 5.2.8	Do not use if package is damaged	Indicates a medical device that should not be used if package has been damaged or opened
	ISO 15223-1 Clause 5.3.4	Keep dry	Indicates a medical device that needs to be protected from moisture
	ISO 15223-1 Clause 5.4.4	Attention: read all pre-cautions and warnings in instructions for use	Indicates the need for the user to consult the instructions for use for important cautionary information such as warnings and precautions
	ISO 15223-1 Clause 5.1.1	Manufacturer	Indicates the medical device manufacturer

Supplies

Box 1

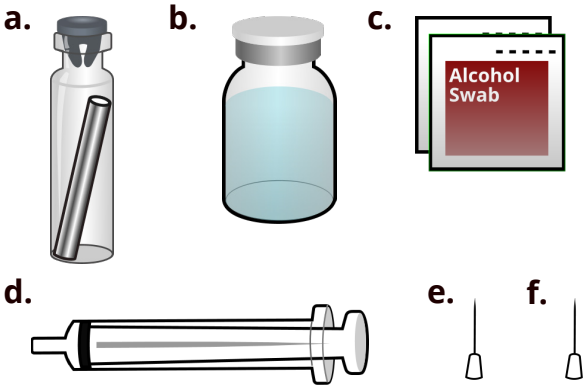
a. Marking pen
b. Marking stencil
c. Alcohol prep swabs
d. Non-fenestrated drape
e. ChloraPrep Triple Swabstick
f. Fenestrated drape
g. 20 Ga x 0.5” needle
h. Syringe, 30mL
i. Lidocaine hydrochloride USP 2%
j. 25 Ga x 1.5” needle
k. Scalpel (size 15)
l. Adson tissue forceps
m. Hemostat forceps
n. Gauze sponges
o. Suture with needle
p. Needle driver
q. Transparent field dressing
r. Liquid adhesive
s. Wound Closure Strips
t. Allis grasping forceps



Box 2

One box needed for each implant inserted

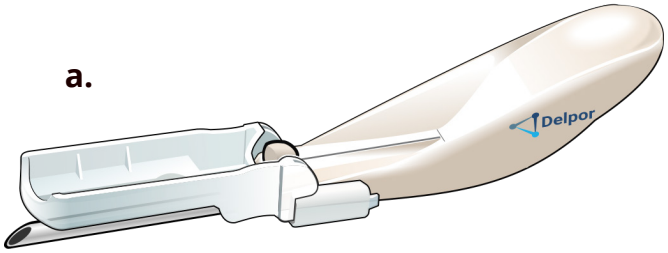
a. Implant Device in vacuum-sealed vial
b. 50 mL saline vial
c. Alcohol swabs
d. 60 mL syringe
e. 20G x 0.5” needle
f. Venting needle



Box 3

Implanter Tool

a. Implanter tool



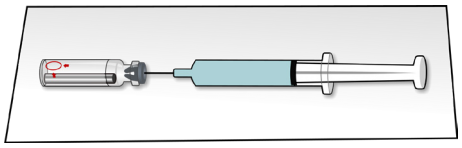
Implantation Procedure Overview

Below is a high level overview of the steps you will take when implanting the device. Please follow the Implantation Procedure detailed instructions starting on page 9.

1. Hydrate Implant Device(s)

Supplies: Box 2

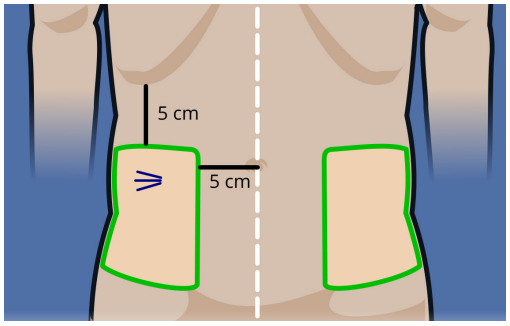
Implant Device needs to be hydrated with sterile saline at least 10 minutes and up to 4 hours before implantation. This step activates the release of the drug.



2. Prepare Implantation Site

Supplies: Box 1

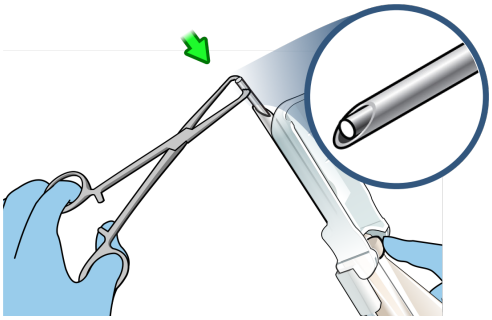
Implant Device is implanted under the skin in the abdomen greater than 5 cm away from the midline and greater than 5 cm below the ribcage (either on the right of left side of the patient).



3. Load Implanter Tool with Implant

Supplies: Box 3 and Hydrated Implant from Step 1

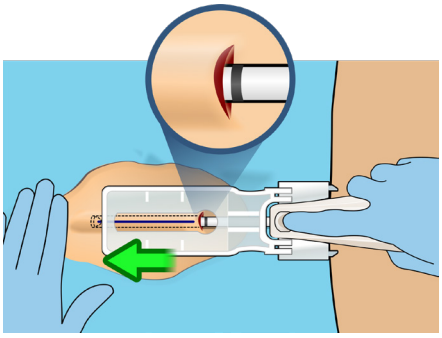
The hydrated Implant Device is removed from the vial and placed in the cannula of the implanter tool.



4. Insert Implant(s)

Supplies: Loaded Implanter Tool from Step 3

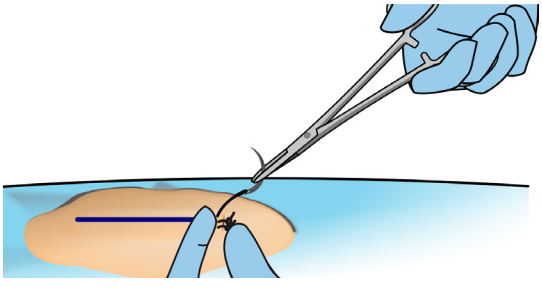
The loaded Impanter Tool is used to insert the implant device subcutaneously in the abdomen. Multiple implants must be inserted in a fan shape through a single incision.



5. Complete Procedure

Supplies: Box 2

Sutures are used to close the incision after the implant(s) have been inserted.



Delpor

IMPLANTATION PROCEDURE

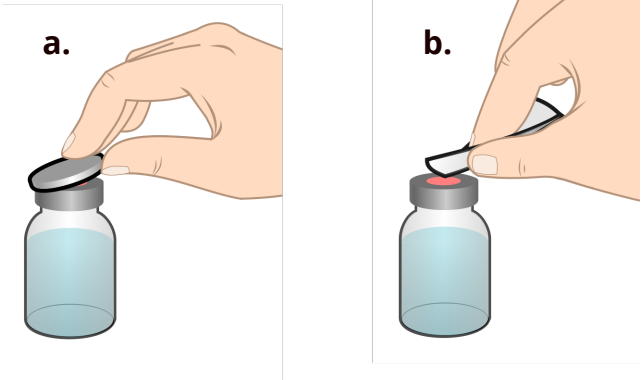
1 Hydrate Implant

ⓘ SUPPLIES NEEDED FOR THIS STEP (BOX 2):

- 50 mL saline vial
- Alcohol swabs
- 60 mL syringe
- Venting needle
- Implant Device in vacuum-sealed vial
- 20G x 0.5needle

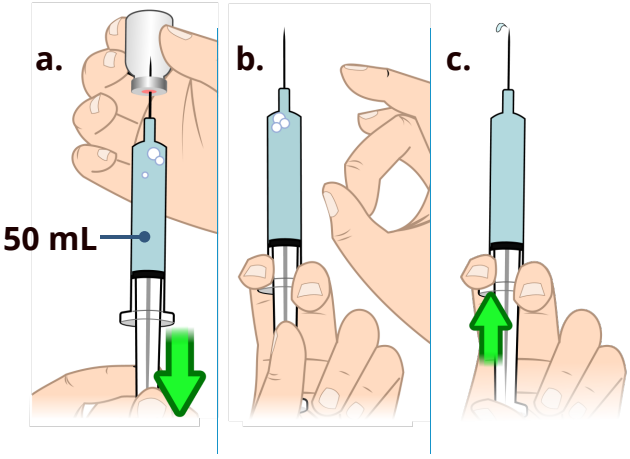
1.1 Prepare saline vial

a. Carefully open the Implant Device kit (Box 2) and remove all contents from the box.
b. Remove flip cover on saline vial to expose vial septum.
c. Swab septum with alcohol prep swab.



1.2 Fill hydration syringe

a. Insert venting needle into saline vial.
b. Use included needle and syringe to draw 50 mL of saline from the swabbed vial.
c. Ensure no air bubbles in syringe by tapping syringe with needle pointed up to loosen bubbles, and depress syringe plunger until fluid comes out.



1.3 Inject saline into implant vial

⚠ **CAUTION:** The implant device has white membranes at either end, which should remain undamaged for proper drug delivery. Hydrate the implant vial in a horizontal position to ensure that the needle cannot reach the membrane

a. Lay the DLP-114 implant vial on a flat surface so that the device inside is horizontal.

b. Penetrate the vial's septum with the saline filled syringe, taking care not to strike the device with the needle. Allow the saline to be drawn into the vial.

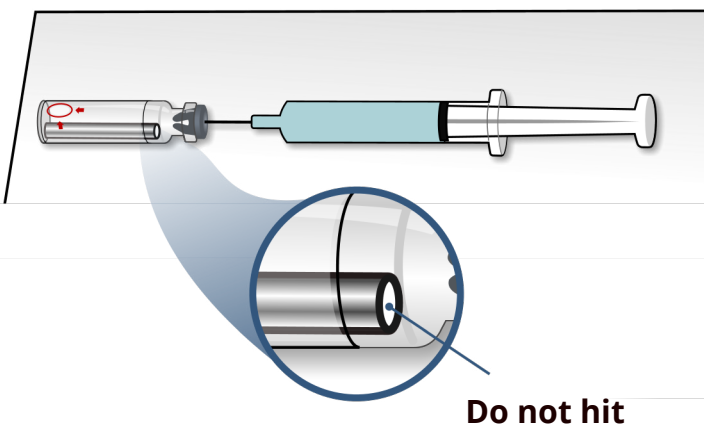
c. Once no more saline is being drawn into the vial, pull needle out of implant vial.

d. Check implant is properly submerged. Make sure air bubble is no bigger than the red window on vial label.

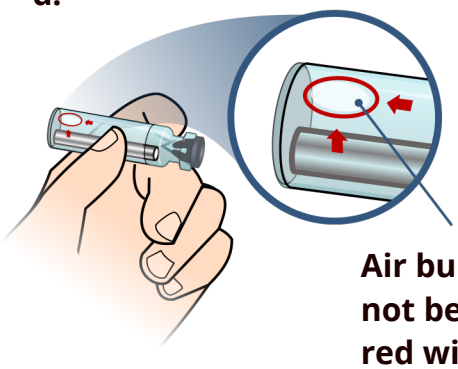
⚠ **CAUTION:** To ensure proper vacuum and seal integrity, **DO NOT** use vial if there is a bubble that exceeds the red outline on the vial label OR if implant is not fully submerged in saline.

e. Stand vial upright for at least 10 minutes, but no more than 4 hours.

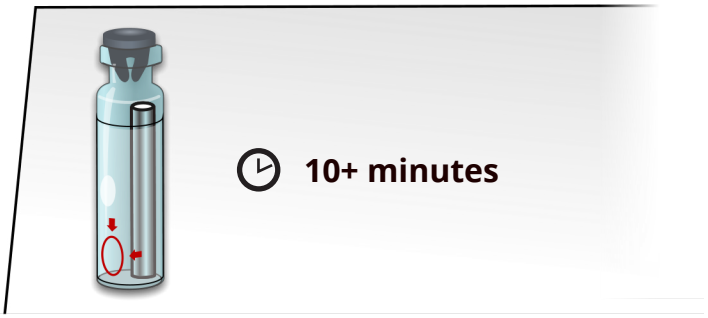
b.



d.

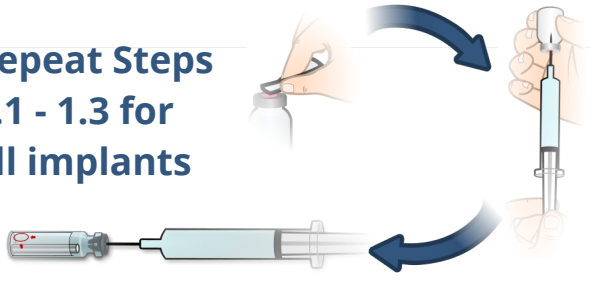


e.



1.4 Repeat for all implants

a. Confirm patient's dosage and repeat implant hydration steps (1.1- 1.3) for the total number of implants the patient requires.



2 Prepare Implantation Site

SUPPLIES NEEDED FOR THIS STEP (BOX 1):

- Marking pen
- Fenestrated drape
- 25G x 1.5” needle
- Non-fenestrated drape
- ChloraPrep swabstick
- Marking Stencil
- 20G x 0.5” needle
- Hemostat forceps
- Lidocaine HCl 2% with epinephrine
- Alcohol swabs
- 30 mL syringe
- Adson tissue forceps
- Scalpel

2.1 Position the patient

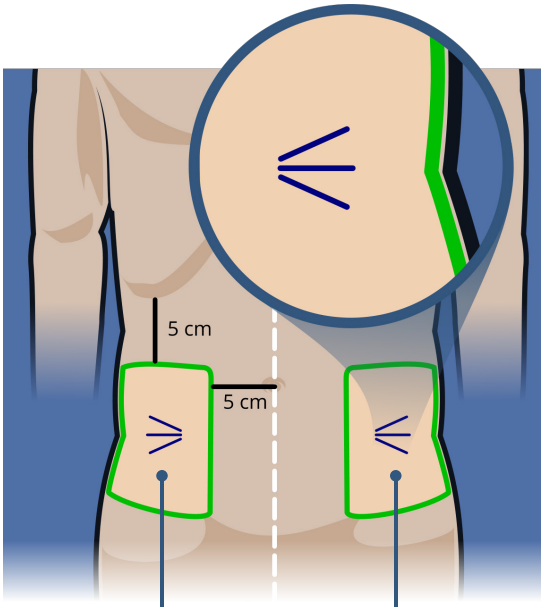
a. Have patient lie on back.

2.2 Mark implantation site

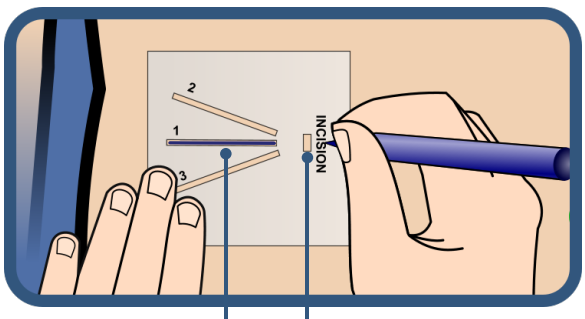
a. Use marking pen and stencil to draw lines to indicate the implantation site(s) and incision. Stencil should be placed greater than 5 cm away from the ribs and greater than 5 cm from the midline.

> ⚠ **CAUTION:** Take care to implant greater than 5 cm away from the midline to avoid damaging superficial epigastric arteries. Consider patient lifestyle habits (such as belt line) for additional implant location guidance.

b. Up to 3 implants, each represented by a solid line, can be implanted through a single incision in a fan-shaped layout as described by the stencil.



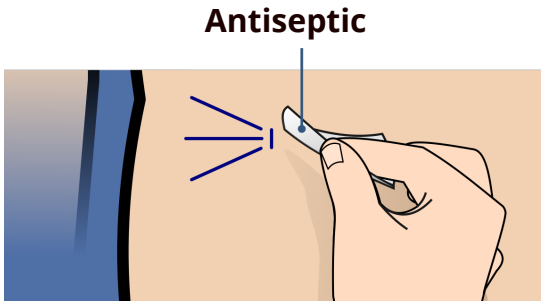
Possible Implantation Areas - Implant either to the left or right of midline



Implantation Site **Incision**

2.3 Clean site

a. Use alcohol swab or other antiseptic to perform first cleaning of implantation site.

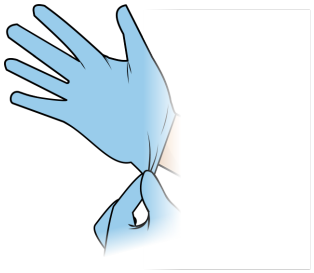


2.4 Wash hands

a. Perform proper surgical hand scrub.

2.5 Put on latex-free sterile gloves

a. Perform appropriate hand hygiene technique and put sterile gloves on both hands.



2.6 Lay out surgical instruments

ⓘ **NOTE:** Assistance is required to remove packaging as needed throughout the procedure. Have the assistant open any packaging, and use sterile technique to retrieve the contents.

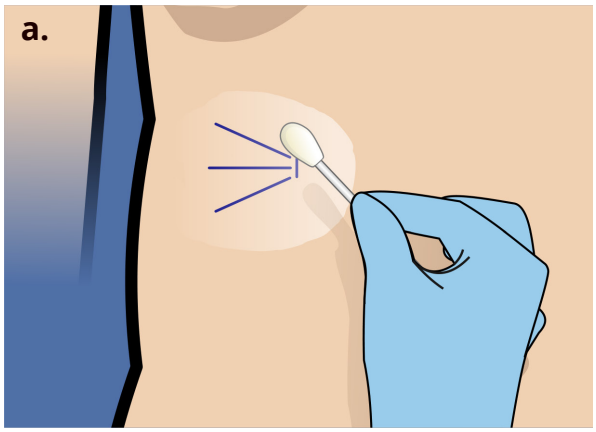
a. Using proper aseptic technique, remove remaining items from surgical kit (Box 1) and arrange on sterile field drape.

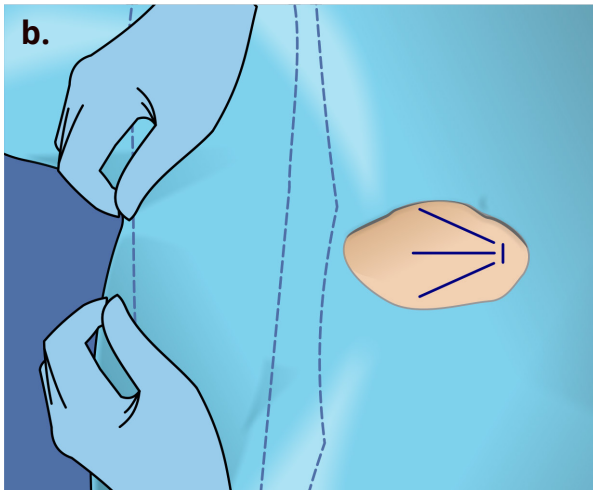
⚠ **CAUTION:** Surgical kit box and all packaging are **NOT** sterile and **SHOULD NOT** be placed onto sterile field drape.

2.7 Clean implantation site

a. Using repeated back-and-forth strokes, swab the implantation site with a Chloraprep swabstick for 30 seconds before letting the site air dry for 30 seconds. If the implantation site is moist, increase swab time to 2 minutes and air dry for 1 minute.

b. Drape patient's abdomen with fenestrated drape.





2.8 Apply anesthetic

ⓘ **RECOMMENDATION:** It is recommended that local anesthesia is applied following the procedure described below, but the method of application is at the discretion of the health care provider.

⚠ **CAUTION:** Check for any known allergies to lidocaine before injecting anesthetic.

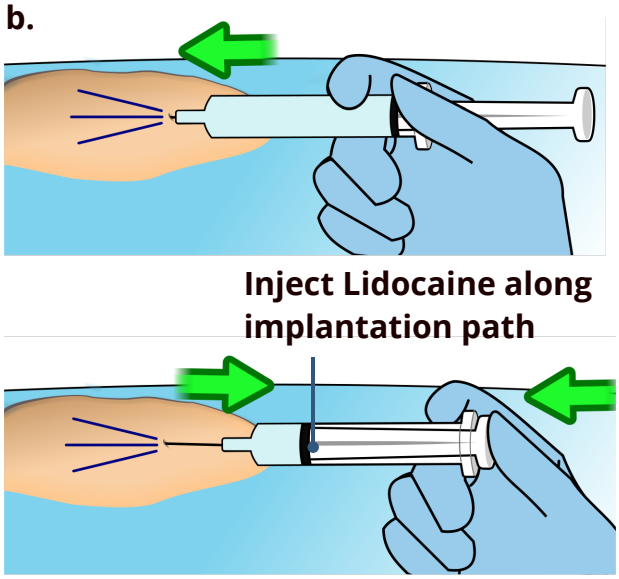
a. Starting at one end of the marked line, insert entire length of needle along the marked line.

b. Slowly pull the needle out while depressing syringe to inject lidocaine. Anesthetization of the implantation site(s) and incision site may be performed with two or three needle reentries.

c. Determine that anesthesia is adequate. 10mL of lidocaine is recommended for complete anesthetization of each marked track.

d. Repeat steps for each implant

b.

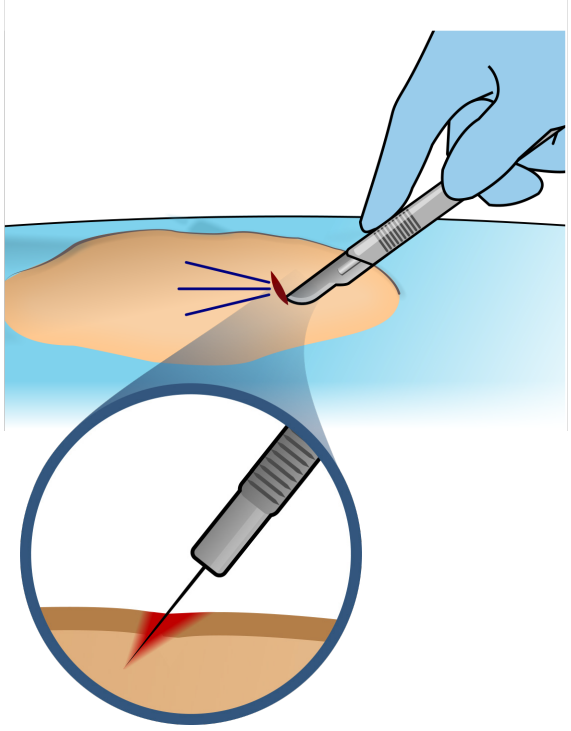


Inject Lidocaine along implantation path

2.9 Make incision at an angle

a. At the end of the marked line(s) closer to the patient's midline, use scalpel to make a single 5mm incision. Take care to cut only through the dermis.

ⓘ **NOTE:** Up to 3 implants can be inserted through a single incision, following the fan-shaped pattern described by the provided stencil.



Make incision at an angle

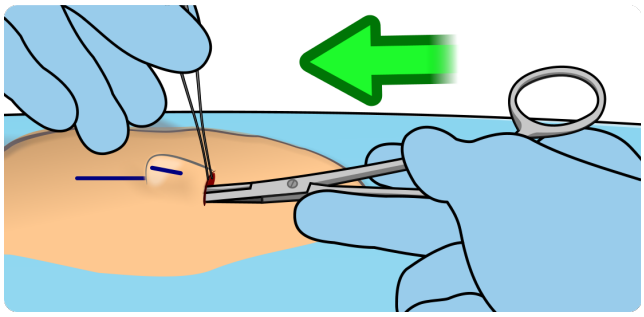
cross-sectional view

2.10 Use hemostat tip as dilator to deepen the pocket.

ⓘ **NOTE:** Use a technique called tenting to visibly raise the skin when performing pocket-making or insertion procedures to ensure correct subcutaneous placement of the implant, “just under the skin”.

a. Lift the edge of the incision with Adson tissue forceps. Use blunt end of closed hemostat forceps (curved end up) to create pocket (about 1 to 3 mm) using blunt dissection - keeping curved end of forceps up. Slide hemostat forceps back and out of the pocket.

b. Repeat 2.10 as needed to create additional pockets for each additional implant.



Repeat step 2 for all implants

3 Load Implant Device

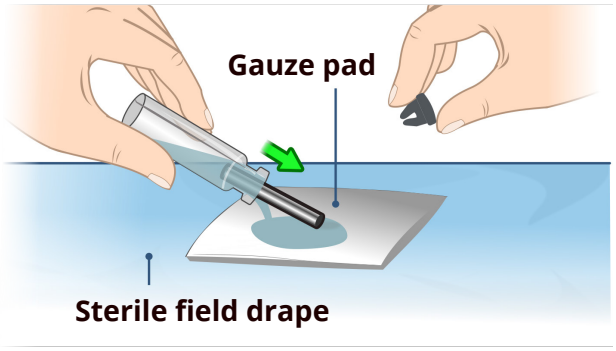
SUPPLIES NEEDED FOR THIS STEP (BOX 1, BOX 3):

- Hydrated Implant Device from Step 1
- Gauze pads
- Implanter Tool (Box 3)

3.1 Pour contents of implant vial onto sterile area and retrieve implant

a. After implant has been hydrating in vial for 10 minutes, remove vial's rubber stopper.

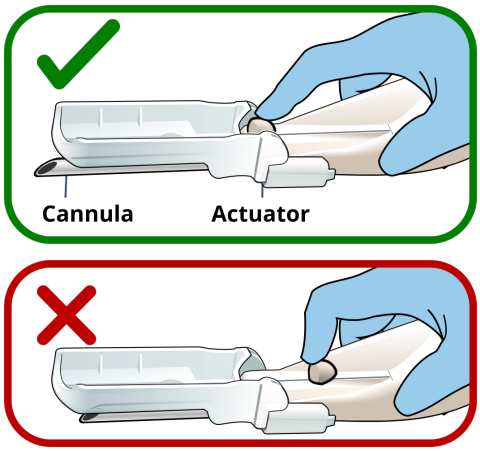
b. Pour implant onto gauze pad within sterile field. The implant can then be handled with sterile gloves or forceps.



3.2 Check implanter tool position

a. Remove implanter tool from packaging (Box 3) and place on sterile field drape.

b. Confirm that cannula of implanter tool is fully extended, and that actuator is in its most forward position.

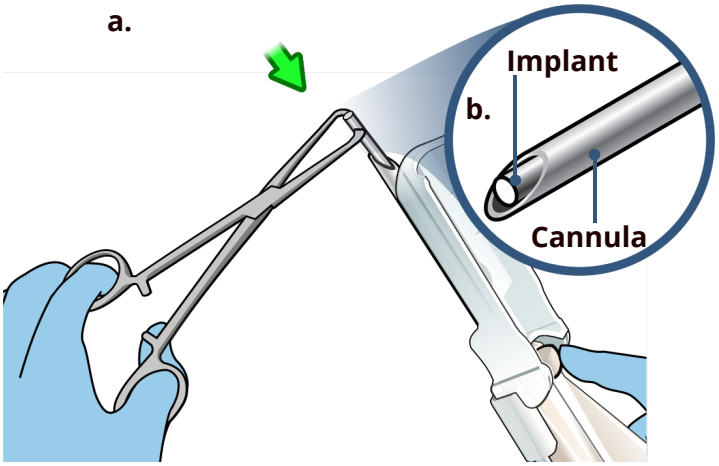


3.3 Load implant in cannula using aseptic techniques

a. Use forceps to insert and slide implant into end of cannula.

b. Push implant until it stops. The beveled end of the cannula will prevent the membrane from being punctured.

c. Set aside within sterile field while preparing insertion site.



4 Implant Insertion into Site

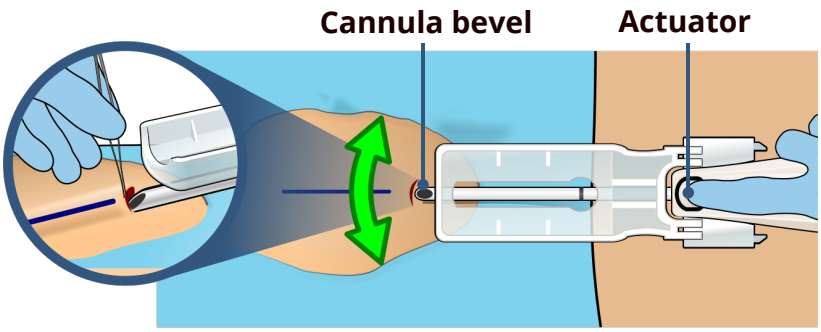
SUPPLIES NEEDED FOR THIS STEP:

- Loaded Implanter Tool from Step 3
- Adson tissue forceps

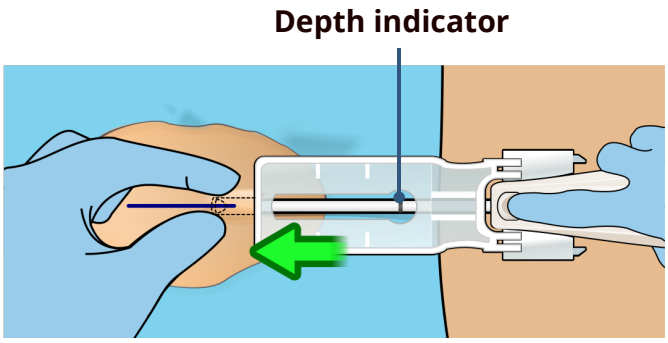
4.1 Insert cannula tip

a. Grasp handle of implanter tool and rest index finger on back of actuator.

b. Make sure cannula bevel is up. While lifting edge of incision with Adson forceps, insert cannula tip with a slight twist.



RECOMMENDATION: Use your free hand to palpate and guide the insertion.

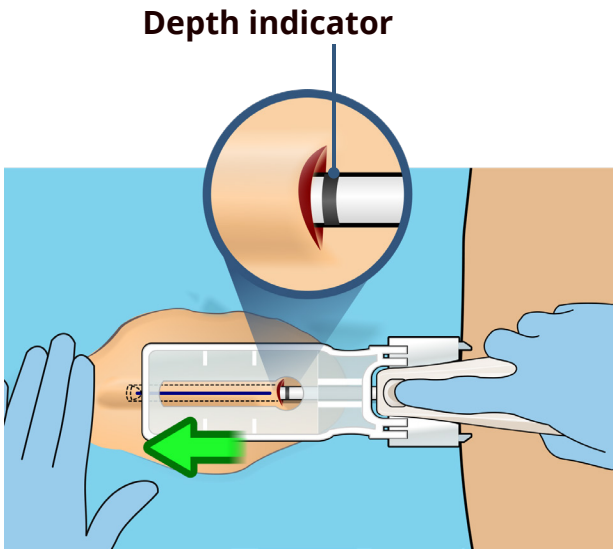


4.2 Slide cannula through the pocket

CAUTION: Keep implanter steady. **DO NOT** push implant into muscle tissue.

a. The cannula tip should be slightly tilted upward so that the skin will be visibly raised (tented) at all times during insertion. This ensures deployment is in the subcutaneous space.

b. Use other hand to stretch skin in the same direction as the intended insertion path Advance cannula subcutaneously along implantation line until cannula depth indicator reaches incision.



4.3 Deploy implant

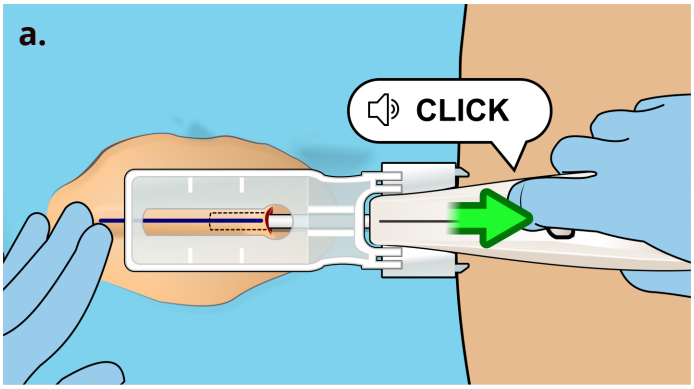
a. Hold implanter tool in position and slide actuator back until it stops with a click. Ensure the implant is released fully from the cannula.

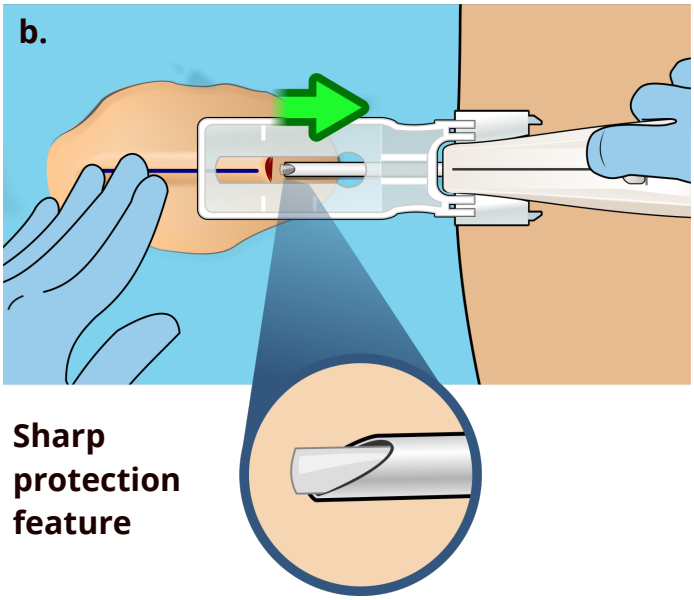
⚠ **CAUTION: DO NOT** move implanter tool until actuator is fully retracted with a click, to ensure correct positioning of the implant.

b. Gently press on deployed implant and carefully withdraw implanter tool from incision.

c. Palpate the marked track site to ensure the implant has been placed correctly under the skin.

ⓘ **NOTE:** When the cannula is retracted and in the locked position, the sharp protection feature is deployed (safe mode).

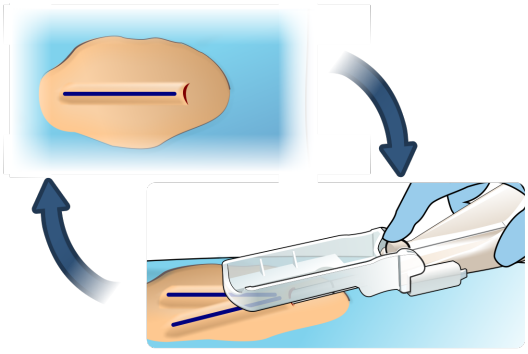




4.4 Insert additional implants if required:

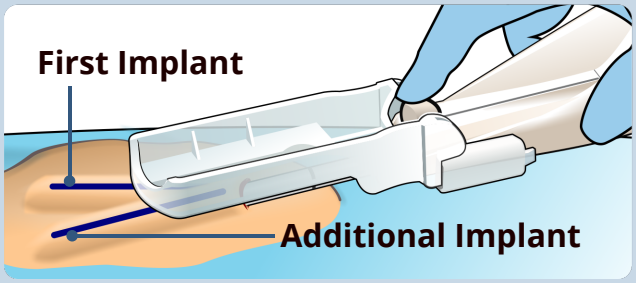
a. Fully extend cannula and ensure that actuator is titled in its most forward position.

b. **Repeat the prior two steps for each additional implant (Step 9 - Load Cannula, and Step 10 - Implant Insertion into site).**



To insert second implant, repeat Steps 4.

ⓘ **RECOMMENDATION:** The second or third implant can be inserted through the same incision and positioned in a fan-shaped layout.

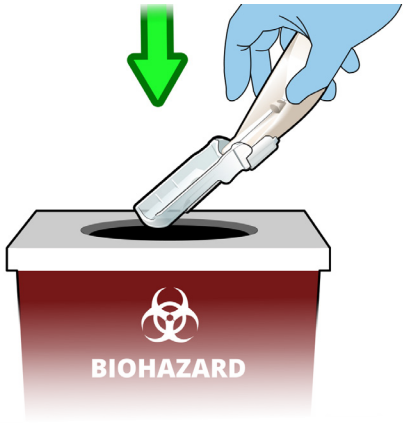


5 Complete Procedure

ⓘ SUPPLIES NEEDED FOR THIS STEP (BOX 1):

- Gauze sponges
- Transparent field dressing
- Suture
- Liquid adhesive
- Needle driver
- Wound closure strips

5.1 Discard implanter tool and vial in biohazard container.



5.2 Close incision

a. After removing implanter tool, press sterile gauze to the wound to stop the bleeding.

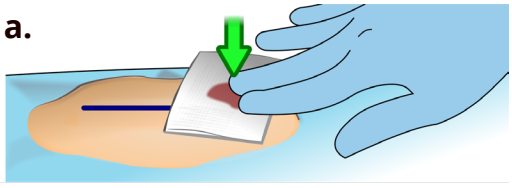
b. Clean insertion area using aseptic technique.

c. Close incision using the provided sutures and needle driver.

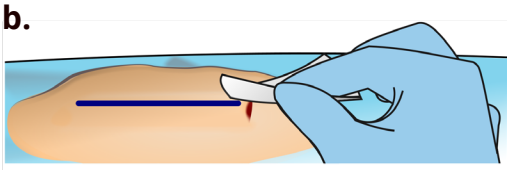
d. Cover incision with transparent field dressing and gauze sponges.

e. Wait a few minutes before leaving patient's bedside to make sure there are no signs of bleeding.

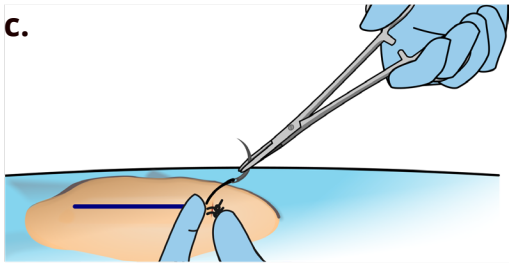
a.



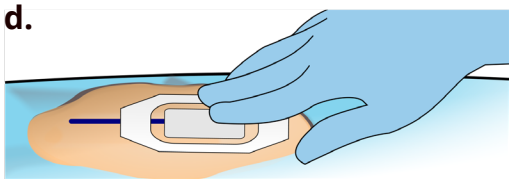
b.



c.



d.



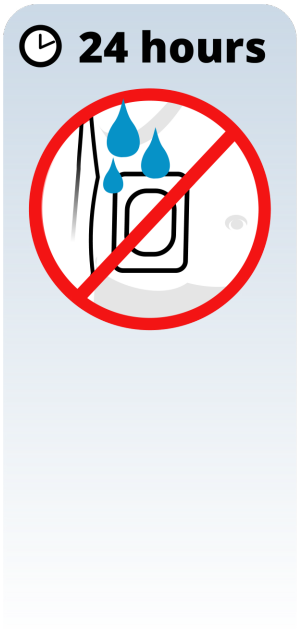
5.3 After-procedure care

a. Patient should keep insertion site clean and dry for 24 hours.

b. Patient should avoid heavy lifting and strenuous physical activity for 48 hours.

c. Make follow-up appointment to check the incision site after 14 days. If the incision has healed, remove sutures and apply liquid adhesive. After 30 seconds of drying the liquid adhesive, apply wound closure strips.

d. Inform patient to call their healthcare provider for any questions or concerns.



Delpor

EXPLANT PROCEDURE

NOTE: A new surgical kit will be used to perform explant and replacement procedures.

1 Prepare Explant Site

SUPPLIES NEEDED FOR THIS STEP (BOX 1):

- Marking pen
- Antiseptic
- Fenestrated drape
- 20G x 0.5” needle
- 30 mL syringe
- 25G x 1.5” needle
- Lidocaine HCl 2% with epinephrine

1.1 Wash hands

a. Perform proper surgical hand scrub.

1.2 Put on latex-free gloves

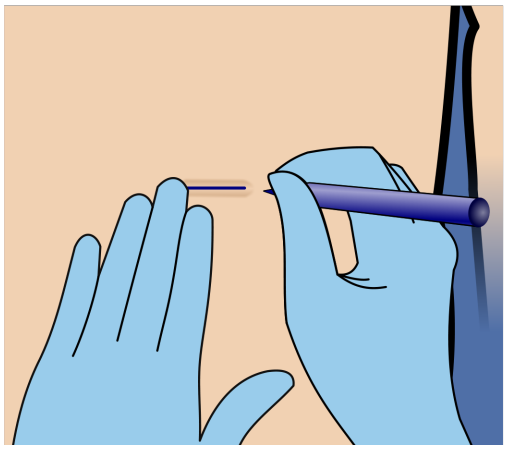
a. Perform appropriate hand hygiene technique and put sterile gloves on both hands

1.3 Locate implant

a. Inspect site by palpating location of implant

b. Mark position of the implant(s) with marking pen.

CAUTION: If unable to palpate the implant(s) prior to removal, do not attempt removal. Refer to a radiologist to help locate the implant. Attempt removal only after the depth and location of the implant can be determined.

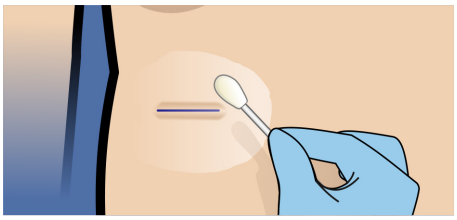


1.4 Clean removal site

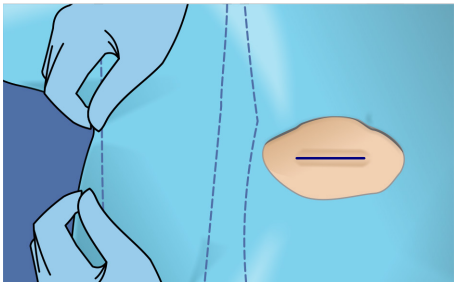
a. Using repeated back-and-forth strokes, swab the implantation site with ChloraPrep for 30 seconds before letting the site air dry for 30 seconds. If the implantation site is moist, increase swab time to 2 minutes and air dry for 1 minute.

b. Drape patient's abdomen with fenestrated drape.

a.



b.



1.5 Apply anesthetic

ⓘ **RECOMMENDATION:** It is recommended that local anesthesia is applied following the procedure described below, but the method of application is at the discretion of the health care provider.

⚠ **CAUTION:** Check for any known allergies to lidocain before injecting anesthetic.

a. Starting at one end of the marked line, insert entire length of needle along the marked line.

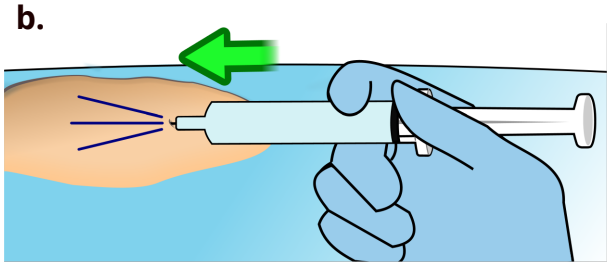
b. Slowly pull the needle out while depressing syringe to inject lidocaine. Anesthetization of the implantation site(s) and incision site may be performed with two or three needle reentries.

⚠ **CAUTION:** Take care not to puncture the implant membranes when inserting needle.

c. Determine that anesthesia is adequate. 10mL of lidocaine is recommended for complete anesthetization.

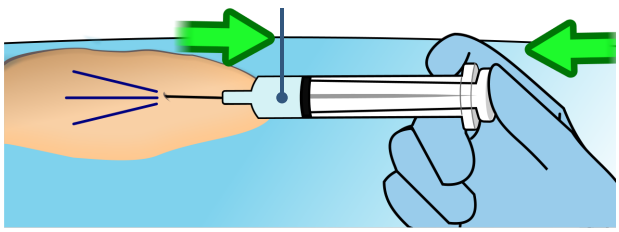
d. Repeat steps for each implant.

b.



c.

Inject Lidocaine along implantation path



2 Remove Implant Device

SUPPLIES NEEDED FOR THIS STEP (BOX 1):

- Hemostat forceps
- Scalpel
- Allis grasping forceps

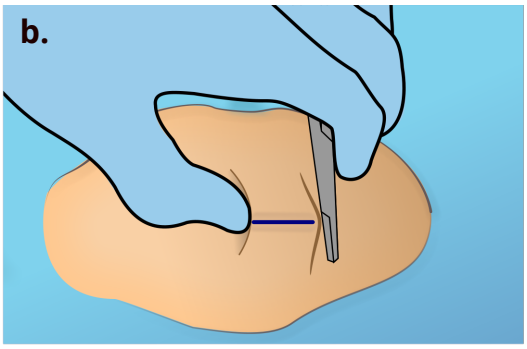
2.1 Make incision with forceps support

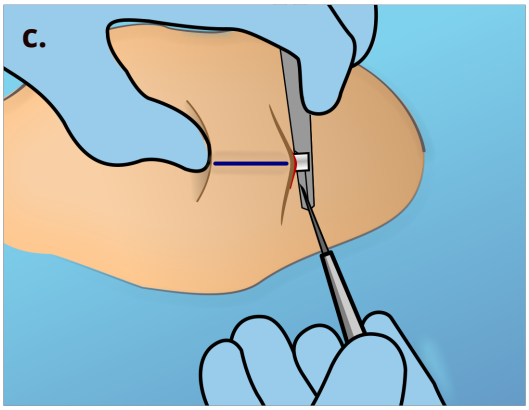
CAUTION: Be careful not to nick the implant membrane

a. Using the flat face of the tip of the hemostat forceps, depress the skin just in front of the end of the implant device.

b. Use fingers from one hand to gently depress the forceps into the skin and use the thumb from the same hand to push the implant towards and over the forceps tenting the skin under the raised tip of the device.

c. Using the other hand make an incision at the tented end until the device is visible (the titanium/metallic finish makes it easily distinguishable from tissue). Cut through the fibrous capsule if needed to release the end of the device.

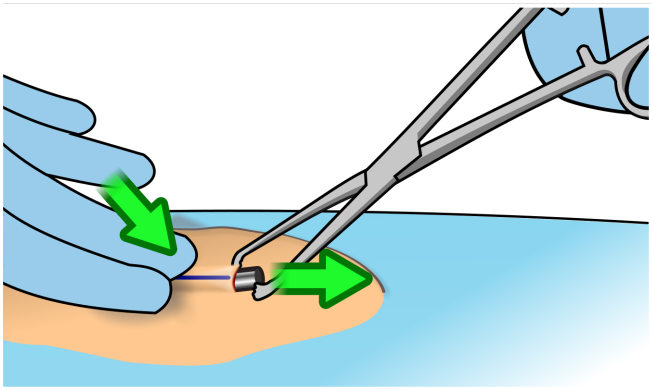




2.2 Remove Implant with grasping forceps

a. Continue to push the implant towards the forceps.

b. Allis forceps may be used to pull out the implant. Be sure not to damage the membrane at the end of the implant to avoid additional exposure to drug.



3 Complete Procedure

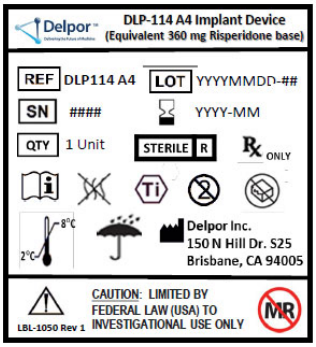
3.1 Discard implant device in biohazard container.

3.2 Following proper wound closing method, close the incision. The method of wound closing is at the discretion of the health care provider.

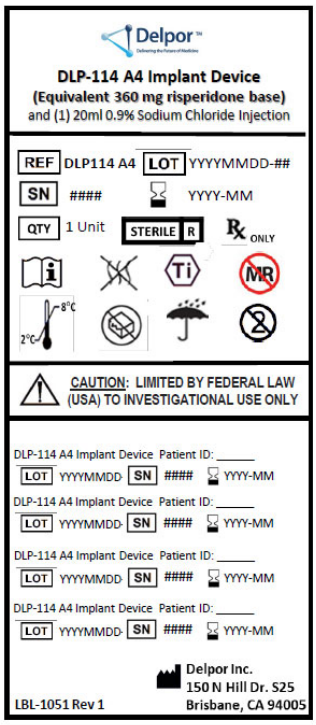
For Investigational Use Only
Instructions for Use
Risperidone Implant, DLP-114

26.6 APPENDIX 6. DLP-114 Labels

DLP-114 A4
Implant Device Pouch Label

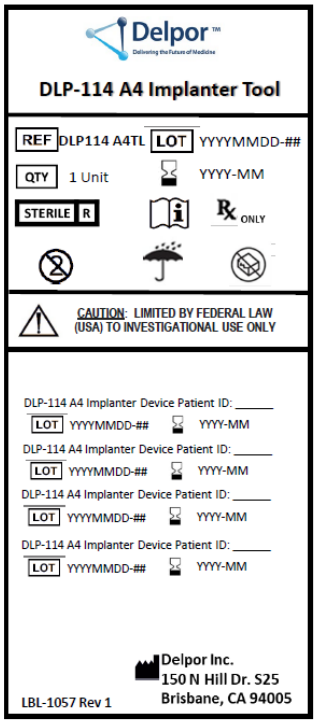


DLP-114 A4
Implant Device Box Label

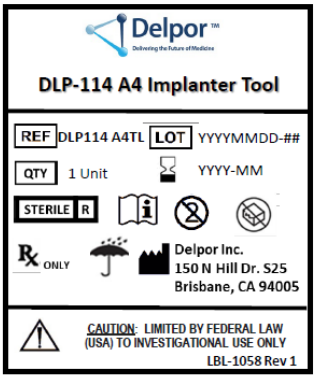


DLP-114 A4
Implant Device Vial Label

DLP-114 A4TL
Implanter Tool Pouch Label



DLP-114 A4TL
Implanter Tool Box Label



DLP-114 SK
Delpor Surgical Kit Box Label