NCT ID: 02899000

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Clinical Study Protocol

PROTOCOL NUMBER: GLI.04.SPR.US10355

Title	EFFICACY AND SAFETY OF ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL PLUS DOXYCYCLINE IN SEVERE INFLAMMATORY ACNE (NON-NODULOCYSTIC) SUBJECTS
Phase	4
CCI [redacted]	
Investigational Study Products	Adapalene 0.3% / Benzoyl Peroxide 2.5% gel plus oral Doxycycline 200 mg
Version No.	1.0
Final Date	28 Jun 2016
Sponsor:	Galderma Laboratories, LP 14501 North Freeway Fort Worth TX 76177 817-961-5000
Sponsor Contact	PPD
Sponsor's Responsible Medical Monitor	PPD RX Medical Director PPD

[redacted]

SIGNATURE PAGE

EFFICACY AND SAFETY OF ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL PLUS DOXYCYCLINE IN SEVERE INFLAMMATORY ACNE (NON-NODULOCYSTIC) SUBJECTS

Protocol Number GLI.04.SPR.US10355

Sponsor Approvals:

Signature: PPD Date: PPD

Galderma Laboratories, LP

Signature: PPD Date: PPD

Galderma Laboratories, LP

Signature: PPD Date: PPD

Galderma Laboratories, LP

Signature: PPD Date: PPD

Galderma Laboratories, LP

Signature: PPD Date: PPD

Galderma Laboratories, LP

Investigator Agreement:

I have read the protocol and agree to conduct the study as outlined herein.

Signature: _____ Date: _____

Name
(print):

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1.0 PROTOCOL SYNOPSIS

TITLE OF STUDY	EFFICACY AND SAFETY OF ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL PLUS DOXYCYCLINE IN SEVERE INFLAMMATORY ACNE (NON-NODULOCYSTIC) SUBJECTS
STUDY CENTERS	No more than 25 sites
PHASE	4
STUDY OBJECTIVE	Demonstrate that a daily treatment regimen of adapalene 0.3% / benzoyl peroxide 2.5% gel + oral Doxycycline 200 mg is an effective and safe alternative to oral isotretinoin in severe inflammatory acne with less than 3 nodules or cysts (non-nodulocystic) during a 12-week treatment period.
STUDY DESIGN	This is a Phase 4, 12-week, single-arm, open-label, multi-center investigational study in subjects with severe inflammatory acne. Male and female subjects, 12 years of age or older, presenting with severe inflammatory facial acne vulgaris, who have up to 2 nodules on the face, are evaluated with a score of 4 (severe) on the IGA scale, and who in the opinion of the Investigator are candidates for oral isotretinoin, are to be enrolled. Up to 25 independent study centers will participate in the study, and approximately 180 subjects will be enrolled. Subjects who meet the inclusion criteria and none of the exclusion criteria at the Screening visit will return to the clinic on Week 0 for baseline measures and to start treatment which will continue for a period of up to 12 weeks. Subjects who do not need to undergo a wash-out period (Section 6.2.2) may combine the Screening visit and Baseline visit and thus attend 4 clinic visits. Screened subjects requiring a wash-out period (up to 4 weeks) prior to baseline measurements and beginning treatment will attend a total of 5 visits. Following the Baseline (Week 0) visit, all subjects will report to the clinic for efficacy and safety evaluations at Weeks 4, 8, and 12. Subjects will be provided with Cetaphil Gentle Skin Cleanser and Cetaphil Daily Facial Moisturizer SPF15 throughout the study to help minimize potential irritation.
PLANNED SAMPLE SIZE	Approximately 180 subjects will be enrolled to complete approximately 150 subjects.
KEY SUBJECT SELECTION CRITERIA	**Inclusion Criteria:** 1. Male or female subjects, 12 years of age or older at Screening visit.

	2. Subjects with a clinical diagnosis of severe inflammatory acne (IGA score of 4) who, in the opinion of the Investigator, are candidates for oral isotretinoin at Screening and Baseline. 3. Subjects with ≤ 2 nodules on the face, < 1 cm in diameter. 4. Subjects willing to be photographed at study visits. Photographs may be used for research, marketing, promotional, and/or scientific purposes. 5. Female subjects of child-bearing potential able and willing to use a highly effective method of contraception associated with a barrier form of contraception from one month before beginning treatment to one month after treatment discontinuation. A highly effective method of contraception is defined as: bilateral tubal ligation; combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to baseline; hormonal intra-uterine device (IUD) inserted at least 1 month prior to baseline; vasectomized partner for at least 3 months prior to baseline and this male is the sole partner for that subject. Barrier forms of contraception include diaphragms, latex condoms, and cervical caps; each must be used with a spermicide. *For minors not yet sexually active, abstinence is an acceptable form of birth control. 6. Subjects able to follow instructions and likely to complete all required visits. 7. Subjects 18 years of age or older must read and sign the Informed Consent Form, which includes Photography Consent and HIPAA authorization, prior to any participation in the study. Consent will be obtained prior to any study-related procedures. Subjects under the age of 18 years must sign an Assent to Participate Form to participate in the study and must have one parent or guardian read and sign the Informed Consent Form prior to any study-related procedure. (The parent or guardian is not required to attend the following visits unless requested.) **Exclusion Criteria:** 1. Subjects with nodulocystic or conglobate acne, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc.). 2. Subjects with ≥ 3 acne nodules or cysts on the face at Screening and Baseline visits. 3. Female subjects who are pregnant, nursing, or planning a pregnancy during the study. 4. Subjects who have used any systemic therapy directed at improving acne, including antibiotics, within 30 days prior to

	Baseline visit. 5. Subjects who have previously used oral isotretinoin. 6. Subjects who have received topical treatment on the face by: a. Hydroquinones, peels, photodynamic therapy, laser therapy, microdermabrasion, deep chemical peel, or plastic surgery within 4 weeks prior to baseline. b. Corticosteroids, antibiotics, antibacterials, antiseptics, retinoids, azelaic acid, dapsone, other anti-inflammatory drugs, other acne treatments, or light therapy within 2 weeks prior to baseline. c. Zinc-containing products, or cosmetic procedures (facials, comedone extractions, etc.) within 1 week prior to baseline. 7. Subjects who have received systemic treatment by corticosteroids, antibiotics, or spironolactone within 4 weeks prior to baseline. Note: No washout period is required for oral vitamin A up to the recommended daily dose (4000 - 5000 IU). 8. Subjects who have started taking medications to treat a concurrent medical condition for which the type and dose has not been stable in the opinion of the Investigator for at least 90 days prior to signing the Informed Consent Form and/or is expected to change during the course of the study. 9. Subjects with a condition or circumstance which, in the Investigator's opinion, may put the subject at risk (e.g., a history of significant renal disease with impairment of renal function), confound the study results, or interfere with the subject's participation in the study. 10. Subjects who are at risk in terms of precautions, warnings, and contraindications for the investigational study drugs (see Appendix 14.1 for package inserts for adapalene 0.3% / benzoyl peroxide 2.5% gel and doxycycline hyclate tablets). 11. Subjects with a known allergy to any of the components of the study products and/or a known hypersensitivity to adapalene, benzoyl peroxide, and/or tetracycline class antibiotics. 12. Subjects with a skin condition which, in the Investigator's opinion, may interfere with study assessments. 13. Subjects who will be exposed to intensive ultraviolet (UV) radiation during the study (mountain sports, sunbathing, tanning beds, etc.). 14. Subjects who have participated in an interventional investigational study within 30 days of signing the Informed Consent Form, participated in biologic investigational studies within 90 days of signing the Informed Consent Form, or who plan to participate in any other interventional clinical research study while participating

	in this trial. 15. Sponsor and study site staff, relatives of staff members, or other individuals who would have access to the clinical study protocol.
TREATMENTS	**Investigational Study Drugs:** • Topical adapalene 0.3% / benzoyl peroxide 2.5% emulsion gel (one application daily for 12 weeks) • Oral doxycycline hyclate, 200 mg per day (two 50-mg tablets twice daily for 12 weeks) **Non-investigational Study Products:** • Cetaphil Gentle Skin Cleanser (twice daily) • Cetaphil Daily Facial Moisturizer SPF15 (at least once daily, and as needed)
EFFICACY PARAMETERS	Efficacy parameters to be assessed at Weeks 4, 8, and 12: • Investigator's Global Assessment (IGA) • Inflammatory and Non-inflammatory Lesion Counts
EFFICACY ASSESSMENTS	• Investigator Global Assessment: Evaluates acne severity on 0-4 scale • Lesion Count: Enumerates inflammatory and non-inflammatory lesions • Oral Isotretinoin Evaluation: Determines if, in the opinion of the Investigator, the subject is a candidate for oral isotretinoin
EFFICACY ENDPOINTS	**Primary efficacy endpoint:** • Reduction in number of inflammatory lesions at Week 12 **Secondary efficacy endpoints:** • IGA Success Rate at Weeks 4, 8, and 12 • Percent reduction in total, inflammatory, and non-inflammatory lesions at Weeks 4, 8, and 12 • Number and percent of subjects who, in the opinion of the Investigator, are candidates for oral isotretinoin at Weeks 0, 4, 8, and 12 • Reduction in number of total, inflammatory, and non-inflammatory lesions at Weeks 4, 8, and 12 • Subject Assessment of Acne Improvement at Week 12
SAFETY PARAMETERS	Safety parameter to be assessed for all subjects at Baseline and at every subsequent visit: • Incidence of Adverse Events (AEs)
SAFETY ASSESSMENTS	• Adverse Events: Enumeration and details of all AEs

	• Local Tolerability: Measures of erythema, scaling, drying, and stinging/burning on a 0-3 scale
CCI	
STATISTICAL ANALYSES	**Analysis Populations:** The Intent-to-Treat (ITT) Population consists of the entire population enrolled at baseline. All efficacy data will be analyzed for the ITT Population. The Safety Population consists of the ITT Population after exclusion of subjects who never took the treatment with certainty, based on monitoring reports. All safety analyses will be summarized for the Safety Population. **General Statistical Methods:** All efficacy variables will be summarized at each visit for the ITT Population. Categorical variables will be summarized by counts and percentages for each response category (N, %). Continuous variables will be summarized using number of subjects, means, standard deviations (SD), medians, minimums, and maximums for the data collected at each visit. Confidence intervals (CI) will be presented as appropriate. All evaluations (including CIs) will be reported for exploratory purposes and will be interpreted as such. No formal statistical tests will be performed. Subject demographics and baseline characteristics will be summarized with descriptive statistics. Subject disposition will be summarized with the number of subjects in the Safety Population, the number and percentage of subjects who complete the study, and the number and percentage of subjects who do not complete the study for each discontinuation reason. The primary endpoint is the reduction in the number of inflammatory lesions at Week 12, and is the change in the lesion count from Baseline to Week 12. The reduction in lesion count will be summarized with descriptive statistics, with a 95% CI for the reduction in lesions. The IGA Success Rate is defined as the number and percent of subjects rated as Clear (Grade 0) or Almost Clear (Grade 1), and will be summarized at Weeks 4, 8, and 12 with a 95% CI for the Success Rate. The number and percent of subjects who are candidates for oral isotretinoin will be summarized at Weeks 0, 4, 8, and 12, with a 95%

	CI. The Subject Assessment of Acne Improvement at Week 12 will be summarized with counts and percentages for each category. The data will be summarized as observed, with no imputation for missing values. A last observation carried forward (LOCF) approach will be used as a sensitivity analysis.
	
	Exposure to investigational study drugs and compliance will be summarized using descriptive statistics. AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence of treatment-emergent AEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the Safety Population. Additional summary tables will be provided for AEs considered related to the investigational study drug, and for AEs leading to discontinuation. The symptoms of local tolerability (erythema, scaling, dryness, and stinging/burning) will be summarized by frequency and percentage for each response category for each visit. Complete listings of all data represented on the electronic case report form (eCRF) will be provided as an appendix to the final study report to facilitate further investigation of tabulated values and to allow for clinical review of all parameters.
FINAL DATE **Version 1.0**	**28 JUN 2016**

2.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse Event
BPO	Benzoyl Peroxide (C14H10O4)
CCI	[redacted]
CDMS	Clinical Data Management System
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
CCI	[redacted]
DMP	Data Management Plan
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
e.g.	For Example (Latin: *exempli gratia*)
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
N or n	Number
N/A	Not Applicable
OTC	Over-the-Counter

Abbreviation or Term	Definition/Explanation
PT	Preferred Term
PV	Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIN	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SPF	Sun Protection Factor
UPT	Urine Pregnancy Test
US	United States
UV	Ultraviolet
WHO	World Health Organization

3.0 BACKGROUND AND RATIONALE

3.1 Medical Background and Brief Rationale for the Trial

Acne vulgaris is a chronic inflammatory disease affecting approximately 80% of young adults and adolescents.[1-4] Four main pathogenic factors are known to lead to its development: follicular hyperkeratosis, increased sebaceous gland activity with hyperseborrhoea, microbial hypercolonization with *Propionibacterium acnes* (*P. acnes*), and inflammation and immunological host reaction. The traditional acne treatment paradigm is directed toward these factors: initial treatment is with topical agents, followed by courses of antibiotics (preferably combined with topical agents), and hormonal treatment in women. For management of severe nodulocystic acne that has been proven unresponsive to these conventional therapies, including systemic therapy, the treatment of choice is isotretinoin.[5-7]

Isotretinoin (13-cis-retinoic acid), an isomer of retinoic acid, was first introduced as a treatment for acne vulgaris and various other skin disorders in the 1980s. In the last decade, it is estimated that over 11.2 million courses of isotretinoin have been dispensed worldwide; 81 million grams of isotretinoin were dispensed from 2000 through 2009 (IMS Health, MIDAS Database, MAT Dec 2000–MAT Dec 2009).[8,9]

The success of isotretinoin as a treatment for the most severe acne can be ascribed to the fact that it targets all four pathogenic factors. It reduces the secretion of sebum, decreases the size of the sebaceous glands, prevents the development of comedones, decreases the colonization with *P. acnes*, possesses anti-inflammatory properties, and reduces the levels of metalloproteinases in sebum.[8-16]

The major limitation of isotretinoin use has been its well-documented adverse effects. Isotretinoin is one of the strongest known teratogens among prescription medications, with the overall risk of birth defects estimated to be up to 30%. In addition, by interacting with many of the biologic systems of the body, it produces a pattern of significant adverse effects similar to that seen in hypervitaminosis A. Side effects have been observed in the mucocutaneous, musculoskeletal, ophthalmic, and central nervous systems.[14,16-20] In addition to teratogenesis, these side effects include headaches, elevations in triglyceride and cholesterol levels, liver enzyme elevations, potential skeletal abnormalities during long-term use, and depression or suicide. Most of the adverse effects are temporary, and resolve after the drug is discontinued.

Therapy must be individualized for each patient based on clinical presentation, preferences and acceptability of adverse effects, monitoring parameters, and potential risks. However, the serious adverse effects are of great concern, and have led to more stringent and restrictive regulation regarding the use of isotretinoin.[18] Despite this, a trend toward the use of isotretinoin for less severe forms of acne is emerging. Therefore, there is a growing need for an alternative safe and effective treatment for acne vulgaris.

A medication which can help meet this need is Adapalene-Benzoyl Peroxide (C14H10O4; BPO) gel, a unique antibiotic-free combination of adapalene 0.3%, a well-tolerated and efficacious topical retinoid, and BPO 2.5%, a well-established antimicrobial agent. The complementary modes of action, and the positive efficacy and safety profiles of these two agents, make adapalene-BPO gel the most logical choice for once-daily treatment for all types of acne but the most severe. Adapalene possesses anticomedogenic, comedolytic, and anti-inflammatory

properties[21-24], and BPO is the most potent bactericidal agent against *P. acnes*.[25,26] Because neither retinoids nor BPO create selective pressure for resistance, this combination may be expected to decrease the incidence of epidermal bacterial resistance relative to antibiotics.[27]

Adapalene-BPO gel has been evaluated in clinical trials as a treatment for acne, and has demonstrated significant efficacy in several large clinical studies.[28-30] As a result, adapalene-BPO gel has been granted marketing authorization in Canada under the trade name of Tactuo® (Galderma). It has also been shown that adapalene-BPO provides higher efficacy when more lesions are presented at baseline.[31] The efficacy of adapalene-BPO gel could be explained by the synergistic effect of adapalene and BPO when used together.[30]

Recently, a study in severe acne, following current international guidelines, showed that treatment with adapalene-BPO in combination with the antibiotic doxycycline resulted in a three-fold increase in success rate compared to treatment with oral antibiotic alone.[32] Doxycycline is a member of the tetracycline class of antibiotics, broad-spectrum bacteriostatic agents which are the most commonly prescribed oral antibiotics for moderate to severe inflammatory acne. Notably, the incidence of significant adverse effects with antibiotic use is low, with the main drawbacks being gastrointestinal distress and dose-dependent photosensitivity.[15,18,32-35]

While oral isotretinoin is an excellent treatment for severe nodular acne, it may not be appropriate in some cases, for example, due to current or expected pregnancy or previous adverse reaction to this class of drugs. Combination therapy consisting of adapalene-BPO plus an oral antibiotic is the logical and recommended first alternative.[36,37]

The gel formulation of adapalene 0.3% / benzoyl peroxide 2.5% (see Appendix 14.1 for a product insert) has been shown to be effective and safe, and represents a more potent combination product to treat severe acne vulgaris.

The overall objective of this Phase 4 trial is to determine the extent to which daily treatment with adapalene 0.3% / benzoyl peroxide 2.5% gel plus oral Doxycycline 200 mg for 12 weeks may be an effective and safe alternative to oral isotretinoin in subjects 12 years of age and older having severe inflammatory acne with less than 3 nodules or cysts (non-nodulocystic/non-conglobate).

4.0 CLINICAL TRIAL OBJECTIVE AND CLINICAL HYPOTHESIS

4.1 Clinical Trial Objective

The clinical trial objective is to demonstrate that a daily treatment regimen of adapalene 0.3% / benzoyl peroxide 2.5% gel + oral Doxycycline 200 mg is an effective and safe alternative to oral isotretinoin in subjects 12 years of age and older having severe inflammatory acne with less than 3 nodules or cysts (non-nodulocystic/non-conglobate) during a 12-week treatment period.

4.2 Clinical Hypothesis

The proposed clinical efficacy hypothesis is based on the current Acne Treatment Guidelines for severe inflammatory acne from the American Academy of Dermatology/American Academy of Dermatology Association.[37,38]

According to these Guidelines, first-line therapy for severe inflammatory acne is an oral antibiotic + topical combination therapy consisting of Benzoyl Peroxide (BPO) + Antibiotic *or* Retinoid + BPO *or* Retinoid + BPO + Antibiotic. Thus, daily combination therapy with adapalene 0.3% / benzoyl peroxide 2.5% gel and Doxycycline 200 mg is a recommended first-line therapy for severe inflammatory acne; the hypothesis of this study is that this combination is an effective therapy alternative for oral isotretinoin.

5.0 STUDY DESIGN

This is a Phase 4, 12-week, single-arm, open-label, multi-center investigational study in subjects with severe inflammatory acne.

This study will enroll male and female subjects, 12 years of age or older, presenting with severe inflammatory facial acne vulgaris with up to 2 nodules on the face and a score of 4 (severe) on the IGA scale, and who are, in the opinion of the Investigator, candidates for oral isotretinoin. If, at screening, the inclusion/exclusion criteria regarding the IGA score and nodule counts are not met, the subject should be screen-failed and will not complete a baseline evaluation. Re-screening will not be allowed during the trial.

Up to 25 independent study centers will participate in the study, and approximately 180 subjects will be enrolled. Subjects who meet the inclusion criteria and none of the exclusion criteria at the Screening visit will return to the clinic on Week 0 for baseline measures and to start treatment, which will continue for a period of up to 12 weeks. Those screened subjects who do not need to undergo a wash-out period (Table 1; Section 6.2.2) may combine the Screening and Baseline visits, and thus attend 4 clinic visits. Screened subjects requiring a wash-out period (up to 4 weeks) prior to baseline measurements and beginning treatment will attend a total of 5 clinic visits. Following the Baseline (Week 0) visit, all subjects will report to the clinic for efficacy and safety evaluations at Week 4, Week 8, and Week 12.

Lesion Counts and Investigator Global Assessments (IGAs) for a given subject are to be performed by the same Investigator throughout the study, from Week 0 through Week 12/Early Termination (ET) visits.

A urine pregnancy test (UPT) will be required at the Screening, Baseline, Week 4, Week 8, and Week 12/ET visits for all females of childbearing potential. The decision may be made by the Investigator to perform additional UPTs during the course of the study.

Subjects will be provided with Cetaphil Gentle Skin Cleanser and Cetaphil Daily Facial Moisturizer Sun Protection Factor SPF 15 as needed during the study. To prevent dry skin, subjects will be requested to use a moisturizer throughout the study. If a subject experiences persistent dryness or irritation, the Investigator may consider a reduced application frequency for the investigational study drug gel, as required for the symptomatic relief of skin dryness or irritation.

A summary of the Study Schedule is provided in Table 1.

Table 1. Schedule of Study Assessments

PROCEDURES	Screening [h]	Week 0 (Baseline)	Week 4 (±3 days)	Week 8 (±3 days)	Week 12 [k] (±3 days)
Informed Consent with HIPAA / Assent (for minors)	X	X [i]			
Demographics / Medical History	X	X			
Previous Therapies and Medications [a]	X	X			
Concomitant Medications / Therapies / Procedures	X	X	X	X	X
Inclusion / Exclusion Criteria	X	X			
Urine Pregnancy Test	X	X	X	X	X
Lesion Counts [b,l]		X	X	X	X
Investigator Global Assessment [c,l]	X	X	X	X	X
Oral Isotretinoin Evaluation	X	X	X	X	X
Local Tolerability [d]		X [j]	X	X	X
Adverse Events [e]		X	X	X	X
Subject Satisfaction Questionnaire					X
Subject Assessment of Acne Improvement					X
Acne QoL [f]		X			X
CCI					
Photographs		X	X		X
Study Treatments Dispensed		X	X	X	
Study Treatments Returned			X	X	X
Exit Form					X

a Acne treatment for the previous 6 months and all other therapies for the previous 4 weeks. Therapy that continues after baseline should be recorded on the Concomitant Medication Form of the eCRF.

b Inflammatory lesion and non-inflammatory lesion counts.

c Assessment is to be conducted on the face only. See Section 9.1.1, Point 6.

d The Investigator must record and grade the severity of the signs and record the assessment of symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) at each visit. A symptom which requires a dose modification or concomitant medications/therapy should be recorded as an AE.

e AE onsets after subject signature of the ICF should be recorded on the AE Form of the eCRF.

f Only for subjects aged 13 years or older at Informed Consent.

CCI

h In the event a wash-out period is required, the visit with the original Informed Consent Form (ICF) signature will be considered to be the Screening visit; the Baseline visit is to be scheduled as appropriate after the wash-out period. If no wash-out period is necessary, the Baseline visit is to be performed immediately (on the same day) as the Screening visit..

i If Screening and Baseline visits are combined, the ICF does not have to be signed again. See Section 9.1.2 for a complete list of assessments required.

j Stinging/burning at the Baseline visit is to be assessed as None (0). See Section 9.1.2, Point 7.

k Week 12 visit procedures are to be performed for early termination/exit visit.

l These 2 evaluations are to be performed for a given subject by the same Investigator (or designee) throughout the study. See Section 8.1.

5.1 Study Duration

The planned clinical trial duration from the start of subject screening (i.e., Informed Consent Form [ICF] signature by the first subject) to last subject out (i.e., completion of the last clinical trial visit by the last subject) is anticipated to be approximately 8 months. The study duration for each subject is expected to be from 12 to 16 weeks (12-week treatment, plus a wash-out period of up to 4 weeks for some subjects).

Galderma Laboratories, LP (Galderma) may decide to prematurely terminate or suspend the participation of a particular clinical trial center (e.g., for non-inclusion or non-compliance with clinical trial protocol, regulations, or Good Clinical Practice [GCP]), or to prematurely suspend the clinical trial (e.g., for safety, study drug quality, regulatory, efficacy, or logistical reasons) at any time with appropriate notification.

6.0 SELECTION AND DISPOSITION OF SUBJECTS

6.1 Number of Subjects

It is estimated that the screen failure rate will be 20%; therefore, approximately 225 subjects will be screened in order to enroll approximately 180 subjects and to complete approximately 150 subjects.

6.2 Clinical Trial Population Characteristics

In order to be eligible for the clinical trial, subjects must fulfill all of the following criteria. Some criteria are to be checked at the Screening visit and/or at the Baseline visit, as specified.

Male and female subjects of any race, 12 years of age or older, with acne vulgaris who meet all of the Inclusion criteria and none of the Exclusion criteria will be enrolled.

6.2.1 Inclusion Criteria

Potential study participants must meet all of the following criteria to be eligible for inclusion in the study:

1. Male or female subjects, 12 years of age or older at Screening visit.
2. Subjects with a clinical diagnosis of severe inflammatory acne (IGA score of 4) who, in the opinion of the Investigator, are candidates for oral isotretinoin at Screening and Baseline.
3. Subjects with ≤ 2 nodules on the face, < 1 cm in diameter.
4. Subjects willing to be photographed at study visits. Photographs may be used for research, marketing, promotional, and/or scientific purposes.
5. Female subjects of child-bearing potential able and willing to use a highly effective method of contraception associated with a barrier form of contraception from one month before beginning treatment to one month after treatment discontinuation.

   A highly effective method of contraception is defined as: bilateral tubal ligation; combined oral contraceptives (estrogens and progesterone) or implanted or injectable

contraceptives with a stable dose for at least 1 month prior to baseline; hormonal intra-uterine device (IUD) inserted at least 1 month prior to baseline; vasectomized partner for at least 3 months prior to baseline and this male is the sole partner for that subject.

Barrier forms of contraception include diaphragms, latex condoms, and cervical caps; each must be used with a spermicide.

*For minors not yet sexually active, abstinence is an acceptable form of birth control.

6. Subjects able to follow instructions and likely to complete all required visits.
7. Subjects 18 years of age or older must read and sign the Informed Consent Form, which includes Photography Consent and HIPAA authorization, prior to any participation in the study. Consent will be obtained prior to any study-related procedures.

   Subjects under the age of 18 years must sign an Assent to Participate Form to participate in the study and must have one parent or guardian read and sign the Informed Consent Form prior to any study-related procedure. (The parent or guardian is not required to attend the following visits unless requested.)

6.2.2 Exclusion Criteria

Potential study participants who meet any of the following criteria must be excluded from the study:

1. Subjects with nodulocystic or conglobate acne, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc.).
2. Subjects with ≥ 3 acne nodules or cysts on the face at Screening and Baseline visits.
3. Female subjects who are pregnant, nursing, or planning a pregnancy during the study.
4. Subjects who have used any systemic therapy directed at improving acne, including antibiotics, within 30 days prior to Baseline visit.
5. Subjects who have previously used oral isotretinoin.
6. Subjects who have received topical treatment on the face by:
   a. Hydroquinones, peels, photodynamic therapy, laser therapy, microdermabrasion, deep chemical peel, or plastic surgery within 4 weeks prior to baseline.
   b. Corticosteroids, antibiotics, antibacterials, antiseptics, retinoids, azelaic acid, dapsone, other anti-inflammatory drugs, other acne treatments, or light therapy within 2 weeks prior to baseline.
   c. Zinc-containing products, or cosmetic procedures (facials, comedone extractions, etc.) within 1 week prior to baseline.
7. Subjects who have received systemic treatment by corticosteroids, antibiotics, or spironolactone within 4 weeks prior to baseline.

   Note: Oral vitamin A up to the recommended daily dose (4000 - 5000 IU) is acceptable.
8. Subjects who have started taking medications to treat a concurrent medical condition for which the type and dose has not been stable in the opinion of the Investigator for at least 90 days prior to signing the Informed Consent Form and/or is expected to change during the course of the study.

9. Subjects with a condition or circumstance which, in the Investigator's opinion, may put the subject at risk (e.g., a history of significant renal disease with impairment of renal function), confound the study results, or interfere with the subject's participation in the study.
10. Subjects who are at risk in terms of precautions, warnings, and contraindications for the investigational study drugs (see Appendix 14.1 for package inserts for adapalene 0.3% / benzoyl peroxide 2.5% gel and doxycycline hyclate tablets).
11. Subjects with known allergy to any of the components of the study products and/or a known hypersensitivity to adapalene, benzoyl peroxide, or tetracycline class antibiotics.
12. Subjects with a skin condition which, in the Investigator's opinion, may interfere with study assessments.
13. Subjects who will be exposed to intensive ultraviolet (UV) radiation during the study (mountain sports, sunbathing, tanning beds, etc.).
14. Subjects who have participated in an interventional investigational study within 30 days of signing the Informed Consent Form, participated in biologic investigational studies within 90 days of signing the Informed Consent Form, or who plan to participate in any other interventional clinical research study while participating in this trial.
15. Sponsor and study site staff, relatives of staff members, or other individuals who would have access to the clinical study protocol.

6.3 Previous and Concomitant Therapies

6.3.1 Definitions

Previous therapies are defined as therapies for the treatment of acne vulgaris that have been taken within the previous 6 months, and all other therapies or procedures that have been taken within the 4 weeks preceding the Screening visit. Subjects who have previously been exposed to oral isotretinoin will be excluded from participating in the study.

Immunomodulators, biologics, and retinoids prescribed for indications other than acne during the previous 6 months must be reported.

Concomitant therapies are defined as:

- Any existing therapies ongoing at the time of the Screening visit.
- Any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical trial.
- Any new therapies received by the subject since the Screening visit.

6.3.2 Categories

Previous and concomitant therapies for the treatment of acne vulgaris fall into two categories:

- Drugs/therapies including, but not limited to: prescription, OTC, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines and supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to: laser/radiation procedures, dermal fillers, X-rays.

Previous and concomitant therapies are to be recorded on the form for drugs/therapies and/or on the form for medical/surgical procedures in the electronic case report form (eCRF).

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an Adverse Event (AE). A corresponding AE Form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

6.3.3 Authorized Concomitant Therapies

Unless listed under the Exclusion Criteria (Section 6.2.2) or in Prohibited Concomitant Therapies (Section 6.3.4), all therapies are authorized.

Subjects will be instructed to use Cetaphil Gentle Skin Cleanser twice daily and to apply Cetaphil Daily Facial Moisturizer SPF15 at least once daily; liberal application of moisturizer should be encouraged. Moisturizers should not be applied within 2 hours (before or after) of the application of study drug. The use of a moisturizer will be documented as a Concomitant Therapy. Use of moisturizer will not constitute an AE. Cleanser should not be used for at least 4 hours after study drug application.

Higher SPF sunscreens (> SPF15) are permitted when discussed with/approved by the Investigator, if the subject needs additional sunscreen for outdoor activities.

6.3.4 Prohibited Concomitant Therapies

No topical medication treatment other than the study drug, cleanser, moisturizer, and sunscreen will be permitted on the face. The following therapies are prohibited because they may interfere with the efficacy and/or safety (e.g., interaction with the study medication metabolism) assessment of the study medication. Specific interfering therapies include the medications listed in Exclusion Criteria (Section 6.2.2) and the following:

- Alpha hydroxyl acid products
- Medicated shaving creams
- Antibacterial soaps
- Astringents
- Preparations with alcohol
- Drugs that are prescribed off-label for the treatment of acne vulgaris

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, the medical monitor should be notified to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical trial, the medical monitor should be notified to discuss the pertinence and the modalities for the subject to continue in the trial.

6.3.5 Procedures/Reasons for Subject Discontinuation/Withdrawal

Although the importance of completing the entire clinical trial should be explained to the subject by the clinical trial personnel, any subject is free to discontinue participation in this clinical trial at any time and for whatever reason, specified or unspecified, and without prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated. Any subject who does not complete the clinical trial will be fully assessed, if such assessment is possible. The procedures designated for the Week 12/ET visit should be completed for all subjects discontinuing the clinical trial and the appropriate eCRF page should be completed when possible.

All discontinuations and the reasons for discontinuation are to be documented by the Investigator on the Exit Form in the EDC, and also on the Adverse Event Form for discontinuation due to an AE.

For discontinuation due to an AE, the Investigator should ensure that the subject receives suitable therapy for the AE.

An Investigator may decide to discontinue a subject from the clinical trial for safety reasons. Galderma may also decide to prematurely terminate or suspend a subject's participation in the clinical trial. Potential reasons for discontinuation, as listed on the Exit Form, are defined in Table 2.

Subjects who are discontinued or withdrawn will not be replaced.

Table 2. Exit Form Reasons for Discontinuation

Reason for Discontinuation	Action to be Taken at Discontinuation
Pregnancy	Withdraw the subject from the clinical trial, following the procedure described in Section 8.4.2.2.3.
Lack of Efficacy	Withdraw the subject from the clinical trial. This reason for discontinuation can be cited only by the Investigator, and is based on his judgment and therapeutic/disease state expectations. If only the subject feels there is "lack of efficacy", mark "Subject Request" as the reason and document in the comment section of the eCRF Exit Form.
Adverse Event	Complete an AE Form.
Subject Request[a]	Explain reason for withdrawal in the comment section of the eCRF Exit Form. (Reasons can include consent withdrawal, subject relocation, schedule conflicts, subject wants isotretinoin.)
Protocol Violation	Explain violation in the comment section of the eCRF Exit Form. (Major protocol violations, especially when subject safety is concerned, will lead to discontinuation.)
Lost to Follow-up	Explain situation in the comment section of the eCRF Exit Form. ("Lost to Follow-up" must be confirmed with two documented phone calls and a certified letter [delivery receipt requested] without answer.)
Other[a]	Explain reason for discontinuation in the comment section of the eCRF Exit Form. (This category is to be used for a subject who discontinues due to a reason other than those specified in the predefined categories above.)

[a] If reason for discontinuation is "subject request" or "other", the subject will be questioned to rule out the possibility of an AE. (This should be documented in the comment section of the eCRF Exit Form.)

7.0 CLINICAL SUPPLIES AND TREATMENT DESCRIPTION

7.1 Description and Use of Study Medications

Descriptions and use of the study medications, both the investigational drugs and the non-investigational products, are summarized in Table 3. Additional information is available in the package inserts for the investigational study drugs (Appendix 14.1).

Table 3. Description and Dispensing of Study Medications

Investigational Study Drug:	**Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel**
Form	Topical Emulsion (Gel)
Dose	Apply a thin film of adapalene 0.3% / benzoyl peroxide 2.5% gel to affected areas of the face once daily in the evening after washing. Use a pea-sized amount for each area of the face (e.g., forehead, right cheek, left cheek, chin, and nose). Avoid the eyes, lips, and mucous membranes.
Mode of Administration	Topical
Duration of Treatment	12 weeks
Quantity Supplied	1 bottle per visit (not Week 12/ET)
How Supplied	45 g bottle with pump
Storage and Handling	Store at 25°C. Excursions permitted to 15°C - 30°C. Protect from light and keep away from heat.
Investigational Study Drug:	**Doxycycline Hyclate**
Form	50 mg tablets
Dose	200 mg daily
Mode of Administration	Oral
Duration of Treatment	12 weeks
Quantity Supplied	2 bottles at Baseline, 1 bottle at each subsequent visit (not Week 12/ET)
How Supplied	120 tablets per bottle
Storage and Handling	Store at 25° C. Excursions permitted to 15°C – 30° C.
Non-Investigational Study Product:	**Cetaphil Gentle Cleanser**
Form	Viscous, slightly translucent, off-white lotion
Dose	Twice a day
Mode of Administration	Topical
Duration of Treatment	12 weeks
Quantity Supplied	1 bottle for duration of study, at Baseline visit
How Supplied	16 oz bottle
Storage and Handling	Room temperature
Non-Investigational Study Product:	**Cetaphil Daily Facial Moisturizer SPF 15**
Form	Lotion
Dose	As needed
Mode of Administration	Topical
Duration of Treatment	12 weeks
Quantity Supplied	1 bottle per visit (not Week 12/ET)
How Supplied	4 oz bottle
Storage and Handling	Room temperature (away from excessive heat and direct sun)

7.1.1 Subject Identification Number

A unique Subject Identification Number (SIN) will be assigned to each individual at the Screening visit. Subjects will be identified using the SIN for the duration of the clinical trial, for all documentation and discussion. Screen failures will be captured in the clinical database using the SIN.

7.1.2 Method of Treatment Assignment and Blinding

Not Applicable. This is an open-label study. All subjects will receive the same treatment.

7.1.3 Study Medication Kit Number

Not Applicable. No kits will be used.

7.1.4 Instructions for Use and Administration of Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel

Each subject will receive the investigational study drug adapalene 0.3% / benzoyl peroxide 2.5% gel in 45 g pump bottles during the course of the study (Table 3).

This study drug should be applied to dry skin once daily for 12 weeks, at night after washing with Cetaphil Gentle Skin Cleanser (provided by the Sponsor; Table 3). A pea-sized amount of adapalene 0.3% / benzoyl peroxide 2.5% gel should be put on the fingertip and applied to the forehead. The procedure is repeated with a pea-sized amount applied to each cheek and to the chin and nose, being careful to avoid application to the nostrils, mouth, lips, and eyelids. The objective is to cover the entire face with a thin film of the treatment, even if there are areas on the face that do not have acne. While there are five areas of the face to be treated (forehead, right cheek, left cheek, chin, and nose), four pea-sized amounts of the study drug are typically estimated to be enough for the entire face. Designated study personnel should demonstrate how to apply the study drug by using a moisturizer as a tool, to show the subject the amount of study drug to use daily and the method of application. The product should not be applied to cuts, abrasions, or eczematous or sunburned skin.

Signs and symptoms of local tolerability are possible during treatment (erythema, scaling, dryness, and stinging/burning). To prevent dry skin, subjects will be requested to use a moisturizer (Cetaphil Daily Facial Moisturizer SPF15, provided by the Sponsor) throughout the study as needed. If a subject experiences persistent dryness or irritation, the Investigator may consider a reduced application frequency of the investigational study drug gel as required for the symptomatic relief of skin dryness or irritation (Section 7.1.6).

Subjects should be instructed to store the adapalene 0.3% / benzoyl peroxide 2.5% gel at room temperature in a closed container, away from light, heat, and moisture. The study drug should not be refrigerated or frozen.

7.1.5 Instructions for Use and Administration of Doxycycline Hyclate

At the Baseline/Week 0 visit, each subject will receive two 120-count bottles of the investigational study drug doxycycline hyclate (50 mg tablets) and will be resupplied at each study visit (Week 4 and 8 only) with one new bottle (Table 3). During the Baseline/Week 0 visit, subjects will be instructed to take the first 100-mg dose of doxycycline hyclate at the same time as the adapalene 0.3% / benzoyl peroxide 2.5% gel treatment that evening (i.e., receiving only a 100-mg dose on Day 0). They will take the second 100-mg dose the next morning, beginning the 200 mg per day dosing regimen on Study Day 1. The subject will be instructed to completely use one bottle of doxycycline hyclate before starting a subsequent bottle.

For the 200 mg per day dosing regimen, each subject will take two 50-mg tablets of doxycycline hyclate in the morning and at night, for a total of four tablets (a total of 200 mg) daily for 12 weeks. The tablets should be swallowed, not chewed, should be taken with adequate amounts of fluid, and may be taken with food.

Subjects should be instructed to store doxycycline hyclate tablets at room temperature.

7.1.6 Dose Modification

If a subject experiences persistent dryness or irritation despite use of the moisturizers provided (Section 7.1.4), the Investigator may consider dose modification; i.e., reducing the once-daily treatment regimen to every other day. The Investigator should attempt to return the subject to once-daily treatment within two weeks.

If this dose modification occurs between Baseline Week 0 and Week 4, and lasts more than 2 weeks after the onset date of the dryness or irritation, the signs or symptoms of local tolerability should be recorded as an AE. After the Week 4 visit, the signs or symptoms related to this dose modification should be recorded as an AE, regardless of the duration of the dose modification.

7.1.7 Other Supplies

Galderma will supply the UPTs, Cetaphil® Daily Facial Moisturizer SPF15 or equivalent (Table 3), and Cetaphil® Gentle Skin Cleanser or equivalent (Table 3).

7.2 Investigational Study Drug Packaging and Labeling

Adapalene 0.3% / benzoyl peroxide 2.5% gel is packaged in a 45 g bottle with a pump. A representation of the package insert is provided in Appendix 14.1.

Doxycycline Hyclate 50 mg tablets are packaged in bottles of 120 tablets per bottle. A representation of the package insert is provided in Appendix 14.1.

7.3 Supplies Management

7.3.1 Study Medication Accountability

The Investigator or designee will maintain accurate records of the following:

- Reconciliation of all study medications (investigational study drugs and non-investigational study products; Table 3) delivered to/received at the clinical trial center
- Overall inventory for study medications at the clinical trial center
- Study medications dispensed to each subject
- Study medications returned by each subject to clinical trial center
- Used and unused investigational study drug returned to the Sponsor (or alternative disposal)

Upon receipt of the study medication, the clinical trial center personnel responsible for managing the supplies must conduct a complete inventory of all study medication and submit a signed copy of the *Transfer of Clinical Supply Record* (a.k.a. packing slip) received with the materials to The Coghlan Group via fax (512) 303-1390 or email RandyD@tcgsupplies.com.

None of the used or unused Cetaphil® moisturizers, Cetaphil® cleansers, or UPTs will be returned to the Sponsor.

All clinical investigational study drug (adapalene 0.3% / benzoyl peroxide 2.5% gel and doxycycline hyclate tablets) sent to the Investigator/Institution will be accounted for, and no unauthorized use is permitted.

7.3.2 Study Medication Storage

Study medication must be stored in a safe and secure area with restricted access, under the storage conditions specified by Galderma (Table 3; Sections 7.1.4 and 7.1.5).

7.3.3 Study Medication Dispensing and Return

Only qualified study personnel (as designated by the Principal Investigator) will be responsible for dispensing study medication. Upon dispensing, the designated study personnel will document on the medication bottles the date of dispensing, the SIN of the subject receiving the study medication, and the initials of the person responsible for dispensing the medication.

Full accountability, including the date of return and initials of the study personnel responsible for receipt, will be performed and documented for all study medications returned to the clinical study center as required.

Subjects will be instructed by study personnel on the importance of being compliant with the use of the study medication throughout the clinical trial, and about the importance of returning their investigational study drugs (used and/or unused) at each visit. Each subject will receive Cetaphil Gentle Skin Cleanser, Cetaphil Daily Facial Moisturizer SPF15, 45 g pumps of adapalene 0.3% / benzoyl peroxide 2.5% gel (to be weighed prior to dispensing and upon return) and 120-count bottles of 50 mg doxycycline hyclate (to be counted upon return) during the course of the study.

The adapalene 0.3% / benzoyl peroxide 2.5% gel and doxycycline hyclate will each be labeled with the protocol number and a four-digit bottle number. Study personnel should appropriately document the dispensation and return of study medication on the site's drug accountability log. At the appropriate visits, subjects will return their investigational study drug and will be dispensed new study drug; the process will be repeated throughout the subject's participation.

In the event of early termination/suspension of the clinical trial, a rapid recall of investigational study drug will be initiated. The Investigator or designee must immediately instruct the subjects to stop the study medication regimen and return the investigational study drug to the clinical trial center.

For subjects who do not complete the entire clinical trial, all used and unused investigational study drug should be returned by the subjects to the clinical trial center.

The Investigator will return the investigational study drug to The Coghlan Group at the end of the study when all subjects have exited the study. Coghlan will then reconcile the investigational study drug by counting the returned pumps and counting the number of tablets to create a report of all study drug accountability (pump and tablet counts); the report will be provided to the Sponsor.

7.4 Treatment Compliance Management and Records

Investigational study drug will be collected from subjects at Weeks 4, 8, and 12/ET visits. To assess subject compliance, the Study Personnel will weigh the adapalene 0.3% / benzoyl peroxide 2.5% gel bottle before dispensing and upon subject returning the study drug at each visit. The doxycycline hyclate tablets will be counted upon subject returning the study drug at each visit. (A count of the pumps of adapalene 0.3% / benzoyl peroxide 2.5% gel and doxycycline hyclate tablets will be confirmed by The Coghlan Group after receipt of the investigational study drugs from the site at the end of the study [Section 7.3.3].) Other than documentation of dispensing to the subjects, no additional accountability will be required for the non-investigational products (i.e., Cetaphil cleanser, Cetaphil moisturizer).

Subjects will be questioned regarding the investigational study drug gel application technique and use of any additional topical or systemic medications (including OTC products, and sunscreen usage for outdoor activities) which will be recorded in the Concomitant Medication Form. Subjects will also be questioned about the number of missed gel applications (if any) between study visits.

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

Throughout the study, the same Investigator will perform the IGA and lesion counts for a given individual subject (Section 8.2). The initials of the Investigator performing the assessment will be captured on the eCRF. In the event there is a change in the assigned Investigator for a given subject, the reason for change must be documented. Untrained evaluators are not allowed to perform these assessments. If it is not possible to use the same evaluator to follow a given subject, the Sponsor recommends that evaluations by the primary and subsequent Investigator overlap (both Investigators should examine the subject together and discuss findings) for at least one visit. This should be documented in the appropriate *Comments* section of the eCRF.

8.2 Efficacy Measurements

Efficacy assessments performed by the Investigator at Baseline and Weeks 4, 8, and 12 include IGA, Inflammatory Lesion Counts (papules and pustules), Non-inflammatory Lesion Counts (open and closed comedones), and Oral Isotretinoin Evaluation. Only the subject's face will be evaluated for IGA and Lesion Counts. The Subject's Assessment of Acne Improvement is an efficacy-related subject survey.

The same Investigator will evaluate a given subject at every visit throughout the study. The same Investigator will evaluate whether, in his opinion, the subject is suitable for an oral isotretinoin prescription at every study visit.

The IGA assessment should be performed before the lesion counting.

8.2.1 Investigator's Global Assessment (IGA)

A Board Certified Dermatologist will assess the subject's acne severity using the IGA scale at every visit, performing a static ("snap-shot") evaluation of acne severity. No reference to

baseline or other previous visits should be made by the Investigator when evaluating the subject's facial acne.

The IGA is dichotomized, such that Success is clearly defined as 0=Clear and 1=Almost Clear. The IGA Severity Scale is presented in Table 4.

Table 4. Investigator's Global Assessment Severity Scale

Severity Scale		Description
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present.

8.2.2 Lesion Counts

Lesion counts will be performed by the Investigator at baseline and each post-baseline visit. Each type of lesion will be counted separately and recorded on the appropriate eCRF page. The lesion counts will be taken from the forehead, right cheek, left cheek, chin, and nose (see Appendix 0).

The following lesion types will be counted:

- Inflammatory Lesions
  - Papule – a small, red, solid elevation equal to or less than 0.5 cm in diameter.
  - Pustule – a small, circumscribed elevation of the skin that contains yellow-white exudate.
- Non-inflammatory Lesions
  - Open Comedone – a pigmented dilated pilosebaceous orifice (blackhead).
  - Closed Comedone – a tiny white papule (whitehead).

Nodules/Cysts, defined as circumscribed, elevated, solid lesions generally more than 1 cm in diameter with palpable depth, are counted at Screening/Baseline visit only. No more than 2 nodules/cysts will be allowed for study participation (Exclusion Criterion #2, Section 6.2.2). Nodules/Cysts are not counted at post-Baseline visits.

8.2.3 Oral Isotretinoin Evaluation

At each study visit, subjects will be evaluated to determine if, in the opinion of the Investigator, they are still candidates for oral isotretinoin. Regardless of the results, subjects will not be exited from the study due to this evaluation, and will continue participation in the study.

8.3 Safety Assessments

Safety assessments will be conducted for all subjects at Baseline and at every subsequent visit.

8.4 Safety Measurements

Safety measurements include Local Tolerability Assessment and the Incidence of AEs.

8.4.1 Local Tolerability Assessment

Signs and symptoms of local tolerability (erythema, scaling, dryness, and/or stinging/burning) will be evaluated by the Investigator at baseline and each post-baseline visit.

The Investigator will record stinging/burning after discussion with the subject, based on the prior day's application. The Investigator will ask an open-ended question such as, "Have you experienced any sensations immediately following dosing)?" taking care not to influence the subject's answer.

Erythema, scaling, dryness, and stinging/burning will be graded (Table 5) at Baseline and each post-Baseline visit (face only).

Table 5. Local Tolerability Severity Scale

Severity		Description
Erythema – abnormal redness of the skin		
0	None	No erythema
1	Mild	Slight pinkness present
2	Moderate	Definite redness, easily recognized
3	Severe	Intense redness
Scaling – abnormal shedding of the stratum corneum		
0	None	No scaling
1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
2	Moderate	Obvious but not profuse shedding
3	Severe	Heavy scale production
Dryness – brittle and/or tight sensation		
0	None	No dryness
1	Mild	Slight but definite roughness
2	Moderate	Moderate roughness
3	Severe	Marked roughness
Stinging/Burning – prickling pain sensation immediately after (within 5 minutes) dosing		
0	None	No stinging/burning
1	Mild	Slight warm, tingling/stinging sensation; not really bothersome
2	Moderate	Definite warm, tingling/stinging sensation that is somewhat bothersome
3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort

Note: Stinging/Burning at the Baseline visit is to be assessed as none (0).

An AE will be recorded if the severity of the signs and symptoms is such that:

- The subject's participation in the study is interrupted at the subject's request or at the Investigator's request.
- The subject permanently discontinues the treatment at the subject's request or at the Investigator's request.
- The subject requires concomitant prescription or OTC therapy (other than moisturizers). Note: Need for increased moisturizer use does NOT constitute an AE.

Any new sign or symptom not included in the scheduled evaluation of tolerability should be recorded as an AE, including those of mild intensity.

8.4.2 Adverse Events

Throughout the course of the study, all AEs will be monitored and reported on the eCRF Adverse Event Form, disclosing any requested and known information. When AEs occur, the main concern is the safety of the study subjects.

8.4.2.1 Definitions

The following definitions of terms are guided by the International Conference on Harmonisation (ICH) and the U.S. Code of Federal Regulations (21 CFR 312.32).

8.4.2.1.1 Adverse Event

An AE can be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal/investigational product, whether or not related to the medicinal/investigational products or to the study procedures.

Thus any new sign, symptom or disease, or clinically significant increase in the intensity of an existing sign, symptom or disease, should be considered as an AE. All events that occur after signing of the subject ICF until the subject is off-study should be recorded.

Notes:

- Clinically significant worsening of the disease/condition being evaluated, which occurs during the study, is considered an AE.
- Any new signs or symptoms suffered by the subject which appear after accidental or intentional overdose or misuse should also be reported as an AE.

Pregnancy is not to be considered an AE, but must be reported promptly and followed up as described in Section 8.4.2.2.3.

Any AE, whether or not it is related to the investigational study products or to the study procedures, will be reported on the eCRF Adverse Event Form along with the diagnosis (preferably) or description of the signs/symptoms, the date of onset, the severity, the seriousness, the relationship and the action taken with the investigational product, the treatment given to treat the AE, and the final AE outcome.

Assessment of AE seriousness, severity, and causality will be based on specific definitions (see, respectively, Sections 8.4.2.1.2, 8.4.2.1.5, and 8.4.2.1.6).

Side effects may be expected during treatment with Adapalene-BPO Gel, the characteristics of which are described in this protocol (e.g., erythema, scaling, dryness, and stinging/burning). The course of these expected events will be assessed and reported on the tolerability assessments. An Adverse Event Form will be completed only if the severity of the expected signs and symptoms is such that an interruption of the Subject's participation in the study occurred at Investigator's decision and/or if a concomitant medication (except moisturizer) is prescribed to treat the sign/symptom.

8.4.2.1.2 Serious Adverse Event

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of a diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrollment in the clinical trial, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

8.4.2.1.3 Unexpected Adverse Drug Reaction

According to ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study medication information (e.g., Investigator's Brochure for an unapproved investigational drug or the package insert/summary of product characteristics for an approved product).

8.4.2.1.4 Adverse Event Reporting Period

The clinical trial period during which AEs must be reported is the period from the time the subject (or the subject's surrogate) signs the ICF to the end of the subject's participation.

The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has participated in a clinical trial, even after a subject has completed the clinical trial. The Investigator should be diligent in looking for possible latent safety effects that may appear after the medication has been discontinued.

8.4.2.1.5 Severity

Severity is a clinical determination of the intensity of an AE and not of a disease.

The Investigator is to classify the intensity of AEs using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by Galderma. For this classification, the Investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according his medical judgment.

Mild: Awareness of signs or symptom, but easily tolerated (acceptable)
Moderate: Discomfort, enough to cause interference with usual activity (disturbing)
Severe: Incapacitating, with inability to work or perform usual activity (unacceptable)

8.4.2.1.6 Relationship to the study treatment

The Investigator is to determine whether there is a reasonable causal relationship between the study treatment and the AE. Medical judgment should be used to determine the relationship, considering all relevant factors, including the pattern of reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by Galderma:

Reasonable possibility:
According to the reporting Investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between the study treatment (investigational product) and the AE.

No reasonable possibility:
No suggestive evidence or arguments can be identified regarding a causal relationship between the study treatment or the clinical trial protocol procedure and the AE.

8.4.2.2 Reporting Procedures

8.4.2.2.1 Procedures for reporting adverse events

The collection of AEs will occur from the time that a subject (or the subject's surrogate) signs the ICF to his final visit. Any AE occurring during the AE reporting period, whether it is related to the study treatment or not, will be recorded immediately in the source document, and described on the Adverse Event Form of the eCRF along with the date of onset, severity, relationship to the study treatment, and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances. AEs assessed as related to the treatment will be monitored until they are completely or satisfactorily resolved. Other AEs will be monitored until the last visit if they are not resolved or satisfactorily resolved.

The Investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up

of the subject. If necessary, the Investigator will contact the subject's personal physician or hospital staff to obtain further details.

For SAEs (see Section 8.4.2.2.2), and pregnancies (see Section 8.4.2.2.3), the event must be reported by facsimile or scan and sent by e-mail within 24 hours (contact details in Section 8.4.2.2.2).

If the Subject discontinues due to an AE, the AE and Exit Forms must be completed.

8.4.2.2.2 Procedure for reporting a Serious Adverse Event

For an SAE occurring during the period of the clinical trial, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the Investigator must do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority. Additional contact details are provided in the Investigator's site file.
2. Complete the Adverse Event Form provided in the eCRF as fully as possible.
3. Ensure that the event is classified as an SAE.
4. Complete the Serious Adverse Event Form (available in the Study Reference Manual). Send the completed form within 24 hours to Advanced Clinical (AC) Pharmacovigilance (PV) by fax (847-919-4677), or scan the completed form and send within 24 hours by e-mail (drugsafetypv@advancedclinical.com). Include any other relevant information or medical records (e.g., physical examination findings).

   AC PV will inform Galderma of the SAE by fax (682-831-9197) and by e-mail (PharmacovigilanceUS@galderma.com) within 24 hours. The minimum information that must be provided is identifiable coded subject, identifiable reporter, study treatment, description of the event (diagnosis). The demographics, medical history, previous and concomitant therapies, and AE pages of the eCRF must be completed and available for review in the Electronic Data Capture (EDC) system at the time of the report.
5. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, complete or update a Serious Adverse Event Form, and then fax or scan; send by e-mail all additional follow-up information to the AC PV within 24 hours. SAEs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.

   Report SAEs to:

   Advanced Clinical Pharmacovigilance
   SAE eFax: 847-919-4677
   SAE Hotline: 1-855-225-2340
   Email: drugsafetypv@advancedclinical.com
6. Inform AC PV of the final outcome of the event. Send a revised or updated Serious Adverse Event Form and Adverse Event Form, if appropriate.
7. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the regulatory authority(ies), Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and other pharmaceutical companies (as appropriate).

8.4.2.2.3 Procedures for reporting pregnancies

Pregnancies occurring during the screening period are considered screen failures and do not require reporting. Any pregnancy occurring during a clinical trial, in which the fetus could have been exposed to the study medication, must be reported in the same manner as an SAE (within 24 hours, as described in Section 8.4.2.2.2) and monitored until its final outcome in order to ensure the complete collection of safety data for Galderma products.

The Sponsor's Pharmacovigilance Department has instituted a Pregnancy Exposure Follow-up program that allows for the follow-up of all exposures in pregnant women. Pregnancy exposure is defined as an exposure to the investigational study drug during the subject's pregnancy.

If a subject becomes pregnant, the Investigator is to do the following:

1. Withdraw the subject from the clinical trial
2. Complete appropriate final visit evaluations and eCRF pages.

Upon the report of a pregnancy occurring during the study, the Sponsor's Pharmacovigilance Department will contact the Investigator to gather additional information and provide more information about the Pregnancy Exposure Follow-up Program.

If the pregnancy leads to an abortion (voluntary, spontaneous, or therapeutic), ectopic pregnancy, in-utero death, or congenital anomaly, the Investigator will follow the procedure for declaration of an SAE (see Section 8.4.2.2.2).


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8.6 Appropriateness of Measurements

The measurements to be used for assessment of efficacy in this clinical trial are recommended by the Food and Drug Administration (FDA) in *Guidance for Industry, Acne Vulgaris: Developing Drugs for Treatment* (2005)[38], and are widely accepted clinical endpoints in studies evaluating treatments for acne vulgaris.

Change from Baseline in Inflammatory and Non-inflammatory Lesion Counts at Week 12 is a commonly used practice to assess severity of acne. All lesions will be counted, including those on the nose.

An IGA will also be performed, using a 5-point scale to evaluate acne severity. As recommended by the Agency, IGA Success is defined as Clear (Grade 0) or Almost Clear (Grade 1) at a specified time point. Therefore, IGA Success Rate for this study is defined as the number and percent of subjects rated as Clear or Almost Clear; Success Rate will be summarized at Weeks 4, 8, and 12.

[redacted]

Collection of AEs and SAEs is a standard-of-care medical assessment for safety monitoring of patients participating in clinical trials.

9.0 CLINICAL TRIAL VISITS

9.1 Description of Clinical Trial Visits

Please refer to the Schedule of Assessments (Table 1).

A written, signed ICF (signed Assent Form for minors) which includes Photography Consent and HIPAA authorization must be obtained prior to performing any clinical trial-related evaluations and/or procedures.

9.1.1 Screening Visit

The following procedures will be performed at the Screening visit.

1. Review and explain the nature of the study to subject and parent/legal representative (as applicable).

2. Obtain the appropriate approved ICF (which contains Photography Consent and HIPAA authorization), and Assent form, if needed. Provide signed copies of all forms to the subject and parent/legal representative (as applicable).
3. Assign a SIN to the subject after the ICF is signed. This number will be used to identify the subject throughout the study.
4. Collect information regarding demographics, relevant medical history, and previous and ongoing medication/therapy use.
5. Verify Inclusion/Exclusion Criteria and evaluate the subject for entry into the study.
6. Perform a UPT on all females of child-bearing potential.
7. Verify that the subject is not wearing makeup. In the event the subject is wearing make-up, the appointment may be rescheduled, or the subject can be instructed to wash the face with a Gentle Skin Cleanser; wait for 30 minutes prior to beginning the IGA.
8. Evaluate acne on the face only, using IGA scale.
9. Determine if, in the opinion of the Investigator, the subject is a candidate for oral isotretinoin.
10. If no wash-out is required, Screening and Baseline visits can be combined.

    If Screening and Baseline visits need to occur on separate days (i.e., for subjects who have received, applied, or taken treatments as noted in Exclusion Criteria 6 and 7) and additional time for wash-out is required, schedule a return appointment for the Baseline visit according to the wash-out period for that medication (maximal 28 ± 3 days after Screening). Instruct the subject to arrive at the site for the visit without make-up.

    If Screening and Baseline visits will occur same day, complete the Baseline assessments.

9.1.2 Baseline Visit

The following procedures will be performed at the Baseline visit.

If Screening and Baseline visits occur on separate days, begin Baseline assessments at Step 1 and complete all assessments listed. If Screening and Baseline visits occur on the same day, begin Baseline assessments at Step 7, after completion of Screening assessments and a UPT for all females of child-bearing potential (Step 3 below).

Note: The Investigator/Evaluator for a particular subject should remain the same for the duration of the study.

1. Assess concomitant medication/therapy/procedures and verify required wash-out period has been completed for any previous medications/therapies.
2. Re-confirm Inclusion/Exclusion Criteria and re-evaluate the subject for entry into the study. If the subject no longer meets eligibility criteria, no further assessments are required. Enter the subject into EDC as a screen failure.
3. Perform a UPT on all females of child-bearing potential.
    - Urine pregnancy testing is mandatory for all females of child-bearing potential.
    - For a subject with a pre-menstrual status at the previous visit, confirm that her childbearing potential status has not changed (began menses). If her status has changed, follow the pregnancy testing schedule for females of child-bearing potential correlating to the visit that menses began. Confirm that the subject agrees to use two effective

forms of birth control while in the study, until at least one month after the last study drug application.

4. Verify that the subject is not wearing makeup. In the event the subject is wearing make-up, the appointment may be rescheduled, or the subject should be instructed to wash the face with a Gentle Skin Cleanser; wait for 30 minutes prior to beginning the evaluations.
5. Evaluate acne on the face only, using IGA scale (see Section 8.2.1).
6. Determine if, in the opinion of the Investigator, the subject is a candidate for oral isotretinoin (see Section 8.2.3).
7. Conduct the facial Lesion Counts (see Section 8.2.2).
8. Perform the Baseline Local Tolerability Assessment (erythema, dryness, scaling, stinging/burning; see Section 8.4.1). Note: Stinging/burning at the Baseline visit is to be assessed as None (0).
9. Question the subject about AEs by asking an open-ended question, taking care not to influence the subject's answer, such as: "Have you had any new symptoms, injuries, illness or side-effects or worsening of pre-existing conditions?" Record all events as appropriate on the corresponding AE eCRF pages (see Section 8.4.2).
10. Have the subject (if 13 years of age or older at the time of Informed Consent) complete the Acne QoL form (see Section 8.5.5). Subjects 12 years of age at Informed Consent will not complete the form. Confirm that all questions have been answered prior to the subject leaving the office.

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12. Obtain photographs of facial acne (see Section 8.5.1).
13. Weigh the adapalene 0.3% / benzoyl peroxide 2.5% gel and record the pre-dispensed weight in drug accountability record and/or source documentation.
14. Dispense study medications as listed below to the subject:

Product	**Quantity**
Cetaphil Daily Gentle Cleanser	1 bottle
Cetaphil Daily Facial Moisturizer SPF 15	1 bottle
Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel	1 bottle with pump
Doxycycline Hyclate	2 bottles

Give verbal and written (Galderma Protocol GLI.04.SPR.US10355 Subject Instruction Sheet) instructions to the subject (or parent/legal representative, as appropriate) regarding when and how to properly apply and take the study drugs. Instructions are to include the use of cleansers and moisturizers, sunscreens, and other concomitant treatments or medications. Demonstrate how to apply the study drug gel by using moisturizer, to show the subject the amount of study drug gel to use daily and the method of application.

Instruct the subject to bring the investigational study drugs to all study visits for review. (Subjects do not need to bring the cleanser and moisturizer to the study visits.)

15. Remind the subject to use a cleanser and moisturizer, throughout the duration of the study (e.g., Cetaphil Gentle Skin Cleanser and Cetaphil Daily Facial Moisturizer SPF15 or equivalent). Liberal application of moisturizers should be encouraged.
16. Schedule a return appointment for the Week 4 Visit (a visit window of ± 3 days will be allowed), and remind the subject to bring the investigational study drugs to the next scheduled visit and to arrive at the site for the visit without make-up.

9.1.3 Week 4 Visit (± 3 days)

The following procedures will be performed at the Week 4 visit.

1. Perform a UPT on all females of child-bearing potential.
   - Urine pregnancy testing is mandatory for all females of child-bearing potential.
   - For a subject with a pre-menstrual status at the previous visit, confirm that her childbearing potential status has not changed (began menses). If her status has changed, follow the pregnancy testing schedule for females of child-bearing potential correlating to the visit that menses began. Confirm that the subject agrees to use an effective form of birth control while in the study, until at least one month after the last study drug application.
2. Assess concomitant medication/therapy/procedures.
3. Verify that the subject is not wearing makeup. In the event the subject is wearing make-up, the appointment may be rescheduled, or the subject should be instructed to wash the face with a Gentle Skin Cleanser; wait for 30 minutes prior to beginning the evaluations.
4. Evaluate acne on the face only, using IGA scale (see Section 8.2.1).
5. Conduct the facial Lesion Counts (see Section 8.2.2).
6. Determine if, in the opinion of the Investigator, the subject is still a candidate for oral isotretinoin (see Section 8.2.3).
7. Perform the Local Tolerability Assessment (erythema, dryness, scaling, stinging/burning; see Section 8.4.1).
8. Question the subject about the occurrence of AEs and record all events as appropriate on the corresponding AE eCRF pages (see Section 8.4.2).
9. Obtain photographs of facial acne (see Section 8.5.1).
10. Collect returned Investigational Study Drugs (used and unused) and perform accountability evaluations as described in Section 7.4. Discuss any concerns with compliance and note discussion in source documentation.
11. Obtain a new bottle of the adapalene 0.3% / benzoyl peroxide 2.5% gel, weigh, and document the weight in drug accountability record and/or source documentation.

12. Dispense study medications as listed below to the subject.

Product	Quantity
Cetaphil Daily Facial Moisturizer SPF 15	1 bottle
Adapalene 0.3% / benzoyl peroxide 2.5% gel	1 bottle with pump
Doxycycline Hyclate - new bottle	1 bottle
Doxycycline Hyclate – redispense bottle with unused medication from previous visit	1 bottle

Provide verbal and/or written instructions (Galderma Protocol GLI.04.SPR.US10355 Subject Instruction Sheet – if needed) to the subject (or parent/legal representative, as appropriate) on when and how to properly apply and take the study drugs.

13. Schedule a return appointment for the Week 8 Visit (a visit window of ± 3 days will be allowed), and remind the subject to bring the investigational study drugs to the next scheduled visit and to arrive at the site for the visit without make-up.

9.1.4 Week 8 Visit (± 3 days)

The following procedures will be performed at the Week 8 visit.

1. Perform a UPT on all females of child-bearing potential.
   - Urine pregnancy testing is mandatory for all females of child-bearing potential.
   - For a subject with a pre-menstrual status at the previous visit, confirm that her childbearing potential status has not changed (began menses). If her status has changed, follow the pregnancy testing schedule for females of child-bearing potential correlating to the visit that menses began. Confirm that the subject agrees to use two effective forms of birth control while in the study, until at least one month after the last study drug application.
2. Assess concomitant medication/therapy/procedures.
3. Verify that the subject is not wearing makeup. In the event the subject is wearing make-up, the appointment may be rescheduled, or the subject should be instructed to wash the face with a Gentle Skin Cleanser; wait for 30 minutes prior to beginning the evaluations.
4. Evaluate acne using IGA scale on the face (see Section 8.2.1)
5. Conduct the facial Lesion Counts (see Section 8.2.2).
6. Determine if, in the opinion of the Investigator, the subject is still a candidate for oral isotretinoin (see Section 8.2.3).
7. Perform the Local Tolerability Assessment (erythema, dryness, scaling, stinging/burning; see Section 8.4.1).
8. Question the subject about the occurrence of AEs and record all events as appropriate on the corresponding AE eCRF pages (see Section 8.4.2).
9. Collect returned Investigational Study Drugs (used and unused) and perform accountability evaluations as described in Section 7.4. Discuss any concerns with compliance and note discussion in source documentation.
10. Obtain a new bottle of the adapalene 0.3% / benzoyl peroxide 2.5% gel, weigh, and

document the weight in drug accountability record and/or source documentation.

11. Dispense study medications as listed below to the subject:

Product	Quantity
Cetaphil Daily Facial Moisturizer SPF 15	1 bottle
Adapalene 0.3% / Benzoyl Peroxide 2.5% Gel	1 bottle with pump
Doxycycline Hyclate – new bottle	1 bottle
Doxycycline Hyclate – redispense bottle with unused medication from previous visit	1 bottle

Again give verbal and/or written instructions (Galderma Protocol GLI.04.SPR.US10355 Subject Instruction Sheet) to the subject (or parent/legal representative, as appropriate) on when and how to properly apply and take the study drugs, if needed.

12. Schedule a return appointment for the Week 12 Visit (a visit window of ± 3 days will be allowed), and remind the subject to bring all study medications (both investigational study drugs and non-investigational study products) to the next scheduled visit and to arrive at the site for the visit without make-up.

9.1.5 Week 12/Early Termination Visit (± 3 days)

The following procedures will be performed at the Week 12/ET visit.

1. Perform a UPT on all females of child-bearing potential.
   - Urine pregnancy testing is mandatory for all females of child-bearing potential.
   - For a subject with a pre-menstrual status at the previous visit, confirm that her childbearing potential status has not changed (began menses). If her status has changed, follow the pregnancy testing schedule for females of child-bearing potential correlating to the visit that menses began. Confirm that the subject agrees to use two effective forms of birth control while in the study, until at least one month after the last study drug application.
2. Assess concomitant medication/therapy/procedures.
3. Verify that the subject is not wearing makeup. In the event the subject is wearing make-up, the appointment may be rescheduled, or the subject should be instructed to wash the face with a Gentle Skin Cleanser; wait for 30 minutes prior to beginning the evaluations.
4. Evaluate acne using IGA scale on the face (see Section 8.2.1).
5. Conduct the facial Lesion Counts (see Section 8.2.2).
6. Determine if, in the opinion of the Investigator, the subject is still a candidate for oral isotretinoin (see Section 8.2.3).
7. Perform the Local Tolerability Assessment (erythema, dryness, scaling, stinging/burning; see Section 8.4.1).
8. Question subject about the occurrence of AEs and record all events as appropriate on the corresponding AE eCRF pages (see Section 8.4.2).
9. Ask subject to complete the Subject Satisfaction Questionnaire (see Section 8.5.4).

10. Ask subject to complete the Subject Assessment of Acne Improvement form (see Section 8.5.2).

13. Obtain photographs of facial acne (see Section 8.5.1).
14. Collect returned Investigational Study Medications (used and unused) and perform accountability evaluations as described in Section 7.4. Discuss any concerns with compliance and note discussion in source documentation.
15. Complete the Study Exit Form.

9.2 Additional Instructions for Subjects

There are no dietary or activity requirements; however, subjects should avoid excess sun exposure. Each subject will be given both oral and written instructions for use of investigational study drugs, cleanser, and moisturizer according to protocol. Subjects will be instructed to bring their study medications to each visit as noted in Sections 9.1.2 – 9.1.5.

10.0 PLANNED STATISTICAL ANALYSES AND STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be developed and finalized prior to database lock. The SAP will contain detailed descriptions of data conventions and statistical procedures for executing the analyses that are specified in the trial protocol below.

Any deviation(s) from the SAP will be described and justified in the clinical study report.

10.3 Analysis Populations

The Intent-to-Treat (ITT) Population consists of the entire population enrolled at baseline. All efficacy data will be analyzed for the ITT population.

The Safety Population consists of the Intent-to-Treat population, after exclusion of subjects who never took the treatment with certainty, based on monitoring report. All safety analyses will be summarized for the Safety Population.

10.4 Statistical Analysis

10.4.1 General Methods

All efficacy variables will be summarized at each visit for the ITT Population. Categorical variables will be summarized by counts and percentages for each response category (N, %). Continuous variables will be summarized using number of subjects, means, standard deviations, medians, minimums, and maximums for the data collected at each visit. Confidence intervals (CI) will be presented as appropriate. All evaluations (including CIs) will be reported for exploratory purposes and will be interpreted as such. No formal statistical tests will be performed.

10.4.2 Demographics and Subject Disposition

Subject demographics and baseline characteristics will be summarized with descriptive statistics. Subject disposition will be summarized with the number of subjects in each population, the number and percentage of subjects who complete the study, along with the number and percentage of subjects who do not complete the study for each discontinuation reason as specified on the eCRFs.

10.4.3 Efficacy Analysis

10.4.3.1 Primary Efficacy Endpoint

The primary endpoint is the reduction in the number of inflammatory lesions at Week 12, and is the change in the inflammatory lesion count from Baseline to Week 12. The reduction in lesion count will be summarized with descriptive statistics. A 95% CI for the reduction in lesions will be presented.

The data will be summarized as observed, with no imputation for missing values. A last observation carried forward (LOCF) approach will be used as a sensitivity analysis.

10.4.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- IGA Success Rate at Weeks 4, 8, and 12
- Percent reduction in total, inflammatory, and non-inflammatory lesions at Weeks 4, 8, and 12
- Number and percent of subjects who, in the opinion of the Investigator, are candidates for oral isotretinoin at Weeks 0, 4, 8, and 12

- Reduction in number of total, inflammatory, and non-inflammatory lesions at Weeks 4, 8, and 12
- Subject Assessment of Acne Improvement at Week 12

The IGA Success Rate is defined as the number and percent of subjects rated as Clear (Grade 0) or Almost Clear (Grade 1). It will be summarized at Weeks 4, 8, and 12 with a 95% CI for the Success Rate.

The reduction in lesion count (both percent and number of lesions) at Weeks 4, 8, and 12 will be summarized with descriptive statistics and a 95% CI for the reduction in lesions.

The number and percent of subjects who are candidates for oral isotretinoin will be summarized at Weeks 0, 4, 8, and 12, and a 95% CI will be provided.

The Subject Assessment of Acne Improvement at Week 12 will be summarized with counts and percentages for each category (ranging from 0 = Complete Improvement to 5 = Worse).

All data will be summarized as observed with no imputation for missing values. LOCF will be performed as a sensitivity analysis.

A pharmaco-economic analysis will be performed.

10.4.4 Safety Analysis

10.4.4.1 Study Drug Exposure

Exposure to investigational study drugs and compliance will be summarized using descriptive statistics.

10.4.4.2 Adverse Events

AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as any AE with onset or (worsening of a pre-existing condition) after the first dose of study drug through the end of participation in the study. AEs

with partial dates will be assessed using the available date information to determine if treatment-emergent. AEs with completely missing dates will be assumed to be treatment-emergent.

Incidence of treatment-emergent AEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the Safety Population. If a subject has more than one AE with same PT, the subject will be counted only once for that PT. Additional summary tables will be provided for AEs considered related to the study drug, and AEs leading to discontinuation.

All AEs will be displayed in data listings.

10.4.4.3 Local Tolerability

The symptoms of local tolerability (erythema, scaling, dryness and stinging/burning) will be summarized by frequency and percentage for each response category for each visit. Scores range from 0 = None to 3 = Severe.

10.4.4.4 Previous and Concomitant Medications, Therapies, and Procedures

Previous and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary. Prior medications are defined as those ending prior to the first dose of investigational study drug. Concomitant medications are defined as those ongoing at the time of the first dose of study drug or started after the first dose.

11.0 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

11.1 Institutional Review Board or Independent Ethics Committee

This clinical trial protocol and all amendments will be reviewed and approved by the appropriate IRBs/IECs.

11.2 Ethical Conduct of the Clinical Trial

This clinical trial will be conducted according to the protocol, and the ethical principles that have their origin in the Declaration of Helsinki (1964; Appendix 14.7) and subsequent amendments, U.S. and international standards of GCP (FDA regulations 21 CFR 312 for Investigational New Drug (IND) studies and FDA Guidance E6), and applicable regulatory requirements. To ensure ethical conduct of this clinical study, Investigators will be expected to adhere to the basic principles in recognized guidelines such the Belmont Report and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

11.3 Informed Consent

All subjects who participate in this clinical trial are required to be fully informed about the clinical trial in accordance with GCP guidelines, federal regulations, and HIPAA, and in accordance with local requirements.

The ICF (which contains Photography Consent and HIPAA authorization) and the Assent approved by an IRB/IEC will be fully explained to the subject (or parent/legal representative, if applicable).

Prior to enrollment into the clinical trial, the subject, and as applicable, the subject's parent/legal representative when the subject is a minor, will sign and date the consent form(s). The Investigator is responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject, or the subject's parent or legal representative (for minors), with a copy of the signed and dated consent form(s).

11.4 Contractual Requirements

A contractual agreement will be signed between the Sponsor/Contract Research Organization (CRO) and each Investigator/Institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical trial schedule, third party responsibility, and publication rights.

12.0 REGULATORY/ADMINISTRATIVE PROCEDURES AND DOCUMENTATION

12.1 Quality Assurance and Audits/Inspections

The study will be conducted under the sponsorship of Galderma in compliance with all applicable international and local regulatory requirements and applicable ICH guidelines, and in accordance with the SOPs for clinical trial conduct and monitoring from Galderma and/or the CRO.

Audits of clinical trial centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IRBs/IECs before, during, or after the clinical trial.

The Investigator will allow and assist the CRO/Sponsor's representatives, IRBs/IECs, and any regulatory agency to have direct access to all requested clinical trial-related records.

For the audits performed by, or on behalf of, Galderma auditors, audit certificate(s) will be provided by Quality Assurance.

12.2 Protocol Compliance and Protocol Deviations

With the exception of eliminating an immediate hazard to a subject, the Investigator should not deviate from the clinical trial protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical trial protocol are authorized. The Investigator should document and explain any deviation from the clinical trial protocol.

12.3 Protocol Amendments

The Sponsor may modify the clinical trial protocol at any time for ethical, medical, or scientific reasons.

No amendment can be implemented at clinical trial centers, unless to eliminate an immediate hazard to the subjects, without having been submitted to the FDA or any appropriate Regulatory

Authority for its review and having obtained approval from the IRB/EC with responsibility for review and approval of the clinical trial.

12.4 Data Collection and Electronic Case Report Forms (eCRFs)

The Investigator must maintain all required records for all subjects. Data for this clinical trial will be recorded in the subject's source documents and on the eCRFs provided by the Sponsor. All data should be recorded on the eCRFs completely and promptly.

12.5 Source Documentation

The Investigator must keep accurate separate records (other than the CRFs) of all subject visits, being sure to include all pertinent clinical trial-related information. A statement should be made indicating that the subjects have been included in this clinical trial and have provided signed written Informed Consent and Assent to Participate as applicable. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical trial should also be included in the source documentation.

12.6 Study Initiation and Personnel Training

An Investigator's Meeting will be conducted. It is recommended that all Investigators, other Evaluators, study coordinators, or other applicable personnel attend. During this meeting, participants will be trained on the protocol, ICH-GCP, study-specific procedures, and eCRF completion. Site personnel are expected to attend the Investigator Meeting and receive on-site training prior to participating in the procedures and evaluations in this study. Each study center will have a training record as part of the site file and Trial Master File.

Study initiation will be conducted for each study center prior to the enrollment of any subjects. The Investigator Meeting may serve as the initiation visit. In the event the Primary Investigator does not attend the Investigator Meeting but site personnel attend, the Investigator may be initiated and trained via telephone/WebEx. If a site is not represented at the Investigator Meeting and no personnel are present, an on-site initiation visit will be required.

Clinical Research Associates (CRAs) and other applicable personnel will be trained prior to study initiation to familiarize the CRAs with the disease, the Standard Operating Procedures (SOPs)/study procedures, the protocol, and other study-specific items. Team organization, communication, and operational issues will also be discussed.

An Investigator's Site File will be provided to each study center.

12.7 Clinical Monitoring

The conduct of the clinical trial will be closely monitored by representatives of Advanced Clinical to verify adherence to the clinical trial protocol, ICH-GCP guidelines, and applicable SOPs/study procedures.

The Investigator will allow the CRO/Sponsor's representatives, to have direct access to all clinical trial records, eCRFs, corresponding subject medical records, study medication

dispensing records, study medication storage area, clinical trial facilities, and any other documents considered source documentation.

12.8 Data Management

All data management procedures will be detailed in a Data Management Plan (DMP).

The DMP will describe the Clinical Data Management System (CDMS) that will be used to collect data via EDC, and whether the data management activities are performed internally or outsourced. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data clarifications are resolved. The data will be exported to be stored in SAS datasets. After all data clarifications are resolved, coding is approved, and subject's evaluability is determined, the database will be locked.

12.9 Study Documentation and Retention of Records

All pertinent data, samples, photographs, correspondence, and reports, the original or amended clinical trial protocol, and all other material relating to the clinical trial will be maintained securely in Sponsor/CRO/Investigator/Institution archives for the legally required duration for archiving.

The Investigator/Institution should maintain the essential clinical trial documents as specified in Section 8 of ICH-GCP, and according to the applicable regulatory requirements.

The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

If the Principal Investigator retires, relocates, or withdraws from the responsibility of keeping the clinical trial records for any other reasons, custody must be transferred to a person who will accept the responsibility. The Sponsor/CRO must be notified in writing of the name and address of the new custodian.

12.10 Insurance

A certificate attesting Third Party coverage of Sponsor/CRO will be provided upon request.

13.0 REFERENCES

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14.0 APPENDICES

14.1 PACKAGE INSERTS FOR ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL AND DOXYCYCLINE HYCLATE TABLETS

Package Insert for ADAPALENE 0.3% / BENZOYL PEROXIDE 2.5% GEL

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPIDUO FORTE gel safely and effectively. See full prescribing information for EPIDUO FORTE gel.

EPIDUO® FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is for topical use
Initial U.S. Approval: XXXX

----------INDICATIONS AND USAGE----------
EPIDUO FORTE gel, is a combination of adapalene, a retinoid, and benzoyl peroxide, and, is indicated for the topical treatment of acne vulgaris. (1)

----------DOSAGE AND ADMINISTRATION----------
EPIDUO FORTE gel is not for oral, ophthalmic, or intravaginal use. (2)
Apply a thin layer of EPIDUO FORTE gel to affected areas of the face and/or trunk once daily after washing. Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips, and mucous membranes. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Gel, 0.3%/2.5% in 15-g, 30-g, 45-g, 60-g and 70-g pumps

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Ultraviolet Light and Environmental Exposure: Avoid exposure to sunlight and sunlamps. Wear sunscreen when sun exposure cannot be avoided. (5.1)
- Erythema, scaling, dryness, stinging/burning, irritant and allergic contact dermatitis may occur with use of EPIDUO FORTE gel and may necessitate discontinuation. (5.2)

----------ADVERSE REACTIONS----------
Most commonly reported adverse reactions (≥1%) in patients treated with EPIDUO FORTE gel were skin irritation, eczema, atopic dermatitis, and skin burning sensation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Reference ID: 3792009

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EPIDUO FORTE gel is indicated for the topical treatment of acne vulgaris.

2 DOSAGE AND ADMINISTRATION

For topical use only. EPIDUO FORTE gel is not for oral, ophthalmic, or intravaginal use.

Apply a thin layer of EPIDUO FORTE gel to affected areas of the face and/or trunk once daily after washing. Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips and mucous membranes.

3 DOSAGE FORMS AND STRENGTHS

Each gram of EPIDUO FORTE gel contains 3 mg (0.3%) adapalene and 25 mg (2.5%) benzoyl peroxide in a white to very pale yellow, opaque gel. EPIDUO FORTE is available in pumps containing 15 g, 30 g, 45 g, 60 g or 70 g.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Ultraviolet Light and Environmental Exposure

Exposure to sunlight, including sunlamps, should be minimized during the use of EPIDUO FORTE gel. Patients with high levels of sun exposure and those with inherent sensitivity to sun should exercise particular caution. Use of sunscreen products and protective apparel (e.g., hat) are recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, may be irritating to patients under treatment with EPIDUO FORTE gel.

5.2 Local Cutaneous Reactions

Erythema, scaling, dryness, and stinging/burning may be experienced with use of EPIDUO FORTE gel. These are most likely to occur during the first four weeks of treatment, are mostly mild to moderate in intensity, and usually lessen with continued use of the medication. Irritant and allergic contact dermatitis may occur. Depending upon the severity of these adverse reactions, patients should be instructed to use a moisturizer, reduce the frequency of the application of EPIDUO FORTE gel, or discontinue use. The product should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, use of "waxing" as a depilatory method should be avoided on skin treated with EPIDUO FORTE gel.

Avoid concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics that have strong skin-drying effect and products with high concentrations of alcohol, astringents, spices, or limes).

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

During the Phase 3 clinical trial, 217 subjects were exposed to EPIDUO FORTE gel. A total of 197 subjects with acne vulgaris, 12 years and older, were treated once daily for 12 weeks. Adverse reactions reported within 12 weeks of treatment in at least 1% of subjects treated with EPIDUO FORTE gel and for which the rate with EPIDUO FORTE gel exceeded the rate for the vehicle gel are presented inTable 1:

Table 1. Adverse Reactions Occurring in ≥1% of Subjects with Acne Vulgaris in a 12-week Clinical Trial

	EPIDUO FORTE Gel (N=217)	Adapalene and Benzoyl Peroxide Gel, 0.1%/2.5% (N=217)	Vehicle Gel (N=69)
Skin irritation	4%	<1%	0%
Eczema	1%	0%	0%
Dermatitis atopic	1%	0%	0%
Skin burning sensation	1%	0%	0%

Local tolerability evaluations presented in Table 2, were conducted at each study visit in the clinical trial by assessment of erythema, scaling, dryness, and stinging/burning, which peaked at Week 1 of therapy and decreased thereafter.

Table 2. Incidence of Local Cutaneous Irritation in 12-week Clinical Trial in Subjects with Acne Vulgaris

	Maximum Severity During Treatment		End of Treatment Severity (Final Score)	
	Moderate	Severe	Moderate	Severe
EPIDUO FORTE Gel (N=213)				
Erythema	20%	1%	4%	<1%
Scaling	17%	1%	1%	<1%
Dryness	15%	2%	3%	<1%
Stinging/burning	19%	6%	1%	1%
Adapalene and Benzoyl Peroxide Gel, 0.1%/2.5% (N=212)				
Erythema	15%	1%	2%	<1%
Scaling	12%	<1%	2%	0%
Dryness	13%	1%	2%	0%
Stinging/burning	14%	9%	3%	0%
Vehicle Gel (N=68)				
Erythema	6%	1%	1%	0%
Scaling	6%	0%	1%	0%
Dryness	4%	1%	1%	0%
Stinging/burning	3%	1%	0%	0%

6.2 Post-Marketing Experience

There is no post-marketing experience with EPIDUO FORTE gel.

The following adverse reactions have been identified during post-approval use of EPIDUO gel, a similar drug containing 0.1% adapalene and 2.5% benzoyl peroxide as the active ingredients: eyelid edema, sunburn, blister, pain of skin, pruritus, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness and allergic contact dermatitis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7. DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with EPIDUO FORTE gel.

Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with EPIDUO FORTE gel. Animal reproduction studies have not been conducted with the combination gel. Furthermore, such studies are not always predictive of human response; therefore, EPIDUO FORTE gel should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No teratogenic effects were observed in rats treated with oral doses of 0.15 to 5.0 mg adapalene/kg/day,up to 8 times (mg/m^2/day) the maximum recommended human dose (MRHD) of 2 grams of EPIDUO FORTE gel. However, teratogenic changes were observed in rats and rabbits when treated with oral doses of ≥ 25 mg adapalene/kg/day representing 41 and 81 times MRHD, respectively. Findings included cleft palate, microphthalmia, encephalocele, and skeletal abnormalities in rats; and umbilical hernia, exophthalmos, and kidney and skeletal abnormalities in rabbits.

Dermal teratology studies conducted in rats and rabbits at doses of 0.6-6.0 mg adapalene/kg/day (9.7-19.5 times MRHD) exhibited no fetotoxicity and only minimal increases in supernumerary ribs in both species and delayed ossification in rabbits.

8.3 Nursing Mothers

It is not known whether adapalene or benzoyl peroxide is excreted in human milk following use of EPIDUO FORTE gel. Because many drugs are excreted in human milk, caution should be exercised when EPIDUO FORTE gel is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of EPIDUO FORTE gel in pediatric patients under the age of 12 have not been established.

8.5 Geriatric Use

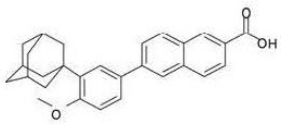
Clinical studies of EPIDUO FORTE gel did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is a white to very pale yellow, opaque gel for topical use containing adapalene 0.3% and benzoyl peroxide 2.5%.

Adapalene, a synthetic retinoid, is a naphthoic acid derivative with retinoid-like properties. The chemical name for adapalene is (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid). It has the following structural formula:

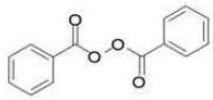
Adapalene:



Molecular formula: $C_{28}H_{28}O_3$ Molecular weight: 412.5

Benzoyl Peroxide is a highly lipophilic oxidizing agent that localizes in both bacterial and keratinocyte cell membranes. The chemical name for benzoyl peroxide is dibenzoyl peroxide. It has the following structural formula:

Benzoyl Peroxide:



Molecular formula: $C_{14}H_{10}O_4$ Molecular weight: 242.23

EPIDUO FORTE gel contains the following inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, poloxamer 124, polysorbate 80, propylene glycol, purified water, and sorbitan oleate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adapalene

Adapalene binds to specific retinoic acid nuclear receptors but does not bind to cytosolic receptor protein. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. However, the significance of these findings with regard to the mechanism of action of adapalene for the treatment of acne is unknown.

Benzoyl peroxide

Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects.

12.2 Pharmacodynamics

Pharmacodynamics of EPIDUO FORTE gel is unknown.

12.3 Pharmacokinetics

A pharmacokinetic study was conducted in 26 adult and adolescent subjects (12 to 33 years of age) with severe acne vulgaris who were treated with once-daily applications during a 4-week period with, on average, 2.3 grams/day (range1.6 - 3.1 grams/day) of EPIDUO FORTE gel applied as a thin layer to the face, shoulders, upper chest, and upper back. After a 4-week treatment, 16 subjects (62%) had quantifiable adapalene plasma concentrations above the limit of quantification of 0.1 ng/mL, with a mean C_{max} of 0.16 ± 0.08 ng/mL and a mean $AUC_{0\text{-}24hr}$ of 2.49 ± 1.21 ng.h/mL. The most exposed subject had adapalene C_{max} and $AUC_{0\text{-}24hr}$ of 0.35 ng/mL and 6.41 ng.h/mL, respectively. Excretion of adapalene appears to be primarily by the biliary route.
Benzoyl peroxide is absorbed by the skin where it is converted to benzoic acid and eliminated in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, photocarcinogenicity, genotoxicity, or fertility studies were conducted with EPIDUO FORTE gel.

Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day (1.2, 3.9, 12 mg/m^2/day), and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day (0.9, 3.0, and 9.0 mg/m^2/day). In terms of body surface area, the highest dose levels are 3.2 (mice) and 2.4 (rats) the MRHD of 2 grams of EPIDUO FORTE gel. In the rat study, an increased incidence of benign and malignant pheochromocytomas reported in the adrenal medulla of male rats was observed.

No significant increase in tumor formation was observed in rodents topically treated with 15-25% benzoyl peroxide carbopol gel (6-10 times the concentration of benzoyl peroxide in EPIDUO FORTE gel) for two years. Rats received maximum daily applications of 138 (males) and 205 (females) mg benzoyl peroxide/kg. In terms of body surface area, these levels are 27-40 times the MRHD. Similar results were obtained in mice topically treated with 25% benzoyl peroxide carbopol gel for 56 weeks followed by intermittent treatment with 15% benzoyl peroxide carbopol gel for rest of the 2 year study period, and in mice topically treated with 5% benzoyl peroxide carbopol gel for two years.

The role of benzoyl peroxide as a tumor promoter has been well established in several animal species. The significance of this finding in humans is unknown.

In a photocarcinogenicity study conducted with 5% benzoyl peroxide carbopol gel, no increase in UV-induced tumor formation was observed in hairless mice topically treated for 40 weeks.

No photocarcinogenicity studies were conducted with adapalene. However, animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the

laboratory or sunlight. Although the significance of these findings to humans is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial irradiation sources.

Adapalene did not exhibit mutagenic or genotoxic effects *in vitro* (Ames test, Chinese hamster ovary cell assay, or mouse lymphoma TK assay) or *in vivo* (mouse micronucleus test).

Bacterial mutagenicity assays (Ames test) with benzoyl peroxide has provided mixed results; mutagenic potential was observed in a few but not in a majority of investigations. It has been shown to produce single-strand DNA breaks in human bronchial epithelial and mouse epidermal cells, caused DNA-protein cross-links in the human cells, and also induced a dose-dependent increase in sister chromatid exchanges in Chinese hamster ovary cells.

In rat oral studies, 20 mg adapalene/kg/day did not affect the reproductive performance and fertility of F_0 males and females, or the growth, development and reproductive function of F_1 offspring.

No fertility studies were conducted with benzoyl peroxide.

14 CLINICAL STUDIES

The safety and efficacy of EPIDUO FORTE gel applied once daily for 12 weeks for the treatment of acne vulgaris were assessed in a multicenter, randomized, double-blind, vehicle-controlled study, comparing EPIDUO FORTE gel to vehicle gel in subjects with acne vulgaris. The study also evaluated adapalene and benzoyl peroxide gel, 0.1%/2.5%, a lower strength product than EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5%. In this study, 217 subjects were treated with EPIDUO FORTE gel, 217 subjects with adapalene and benzoyl peroxide, gel, 0.1%/2.5% and 69 subjects with the vehicle gel.

Treatment response was defined as the percent of subjects who were rated "clear" or "almost clear' at Week 12 with at least a two-grade improvement based on the Investigator's Global Assessment (IGA), and mean absolute change from baseline at Week 12 in both inflammatory and non-inflammatory lesion counts. An IGA score of 'Clear' corresponded to clear skin with no inflammatory or non-inflammatory lesions. An IGA score of "almost clear" corresponded to a few scattered comedones and a few small papules.

At baseline, 50% of subjects were graded as "moderate" (IGA Grade 3) and 50% were graded as "severe" (IGA Grade 4) on the IGA scale. Subjects had an average of 98 (range 51-226) total lesions of which the mean number of inflammatory lesions was 38 (range: 20-99) and the mean number of non-inflammatory lesions was 60 (range 30-149). Subjects ranged in age from 12 to 57 years, with 273 (54%) of subjects 12 to 17 years of age. Approximately equal number of males (48%) and females (52%) were enrolled.

The IGA success rate, mean reduction, and percent reduction in acne lesion counts from baseline after 12 weeks of treatment are presented in the following table.

Table 3. Clinical Efficacy of EPIDUO FORTE Gel at Week 12 in Subjects with Acne Vulgaris

	EPIDUO FORTE Gel(N=217)	Adapalene and Benzoyl Peroxide Gel, 0.1%/2.5% (N=217)*	Vehicle Gel (N=69)
IGA: two-grade improvement and "clear" or "almost clear"	33.7%	27.3%	11.0%
Inflammatory lesions: mean absolute (percent) reduction	27.8 (68.7%)	26.5 (69.3%)	13.2 (39.2%)
Non-inflammatory lesions: mean absolute (percent) reduction	40.5 (68.3%)	40.0 (68.0%)	19.7 (37.4%)

* This study was not designed or powered to compare the efficacy of EPIDUO FORTE to the lower strength adapalene and benzoyl peroxide gel, 0.1%/2.5%, nor to compare the lower strength adapalene and benzoyl peroxide gel, 0.1%/2.5% to the vehicle control.

In subjects graded as "severe" (IGA Grade 4), efficacy was observed in the EPIDUO FORTE group.

16 HOW SUPPLIED/STORAGE AND HANDLING

EPIDUO FORTE (adapalene and benzoyl peroxide) gel 0.3% / 2.5% is white to very pale yellow in color and opaque in appearance, and is supplied as follows:

15 gram pump	NDC 0299-5906-15
30 gram pump	NDC 0299-5906-30
45 gram pump	NDC 0299-5906-45
60 gram pump	NDC 0299-5906-60
70 gram pump	NDC 0299-5906-70

Storage and handling

- Store at controlled room temperature 20 – 25°C (68 – 77°F) with excursions permitted to 15° – 30°C (59° – 86°F) [see USP controlled room temperature].
- Protect from light.
- Keep out of reach of children.
- Keep away from heat.

17 PATIENT COUNSELING INFORMATION

[See FDA Approved Patient Labeling (Patient Information)]

Information for Patients

- Advise patients to cleanse the area to be treated with a mild or soapless cleanser; pat dry. Apply EPIDUO FORTE gel as a thin layer, avoiding the eyes, lips and mucous membranes.
- Advise patients not to use more than the recommended amount and not to apply more than once daily as this will not produce faster results, but may increase irritation.
- EPIDUO FORTE gel may cause irritation such as erythema, scaling, dryness, stinging or burning.
- Advise patients to minimize exposure to sunlight, including sunlamps.
- Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided.
- EPIDUO FORTE gel may bleach hair and colored fabric.

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

GALDERMA is a registered trademark.
XXXXX-X

Reference ID: 3792009

Patient Information
EPIDUO® FORTE (Ep-E-Do-Oh For-Tay)
(adapalene and benzoyl peroxide) gel 0.3%/2.5%

Important information: EPIDUO FORTE gel is for use on the skin only (topical). Do not use EPIDUO FORTE gel in or on your mouth, eyes, or vagina.

What is EPIDUO FORTE gel?

EPIDUO FORTE gel is a prescription medicine used on the skin (topical) to treat acne vulgaris.

It is not known ~~if~~ whether EPIDUO FORTE gel is safe and effective in children under 12 years of age.

Before using EPIDUO FORTE gel, tell your doctor about all of your medical conditions, including if you:

- have other skin problems, including cuts or sunburn
- are pregnant or plan to become pregnant. It is not known if EPIDUO FORTE gel can harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if EPIDUO FORTE gel passes into your breast milk and if it can harm your baby. Talk to your doctor about the best way to feed your baby if you use EPIDUO FORTE gel.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using other topical acne products may increase the irritation of your skin when used with EPIDUO FORTE gel.

How should I use EPIDUO FORTE gel?

- Use EPIDUO FORTE gel exactly as your doctor tells you to use it.
- Apply EPIDUO FORTE gel 1 time a day.
- Do not use more EPIDUO FORTE gel than you need to cover the treatment area. Using too much EPIDUO FORTE gel or using it more than 1 time a day may increase your chance of skin irritation.

Applying EPIDUO FORTE gel:

- Wash the area where the gel will be applied with a mild or soapless cleanser and pat dry.
- EPIDUO FORTE gel comes in a pump. Depress the pump to dispense a small amount (about the size of a pea) of EPIDUO FORTE gel and spread a thin layer over the affected area.
- Wash your hands after applying the gel.

What should I avoid while using EPIDUO FORTE gel?

- Avoid spending time in sunlight or artificial sunlight, such as tanning beds or sunlamps. EPIDUO FORTE gel can make your skin sensitive to sun and the light from tanning beds and sunlamps. Use sunscreen and wear a hat and clothes that cover the areas treated with EPIDUO FORTE gel if you have to be in sunlight.
- Cold weather and wind may irritate skin treated with EPIDUO FORTE gel.
- Avoid applying EPIDUO FORTE gel to cuts, abrasions, and sunburned skin.
- Avoid skin products that may dry or irritate your skin such as medicated or harsh soaps, astringents, cosmetics that make your skin dry, and products containing high levels of alcohol, spices, or limes.
- Avoid the use of "waxing" as a hair removal method on skin treated with EPIDUO FORTE gel.
- EPIDUO FORTE gel may bleach your clothes or hair. Allow EPIDUO FORTE gel to dry completely before dressing to prevent bleaching of your clothes.

What are the possible side effects of EPIDUO FORTE gel?

EPIDUO FORTE gel may cause serious side effects including:

Local skin reactions. Local skin reactions are most likely to happen during the first 4 weeks of treatment and usually lessen with continued use of EPIDUO FORTE gel. Signs and symptoms of local skin reactions include redness, scaling, dryness, stinging, or burning.

Tell your doctor right away if these side effects continue for longer than 4 weeks or get worse, you may have to stop using EPIDUO FORTE gel.

These are not all the possible side effects of EPIDUO FORTE gel. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to GALDERMA LABORATORIES, L.P. at 1-866-735-4137

Reference ID: 3792009

How should I store EPIDUO FORTE gel?

- Store EPIDUO FORTE gel at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep EPIDUO FORTE gel out of light and away from heat.

Keep EPIDUO FORTE gel and all medicines out of the reach of children.

General information about the safe and effective use of EPIDUO FORTE gel

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EPIDUO FORTE gel for a condition for which it was not prescribed. Do not give EPIDUO FORTE gel to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about EPIDUO FORTE gel that is written for health professionals.

What are the ingredients in EPIDUO FORTE gel?

Active ingredient: adapalene and benzoyl peroxide

Inactive ingredients: acrylamide/sodium acryloydimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, polaxamer 124, polysorbate 80, propylene glycol, purified water and sorbitan oleate

Marketed by: GALDERMA LABORATORIES, L.P., Fort Worth, Texas 76177 USA
GALDERMA is a registered trademark. XXXXX-X

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 07/2015

Reference ID: 3792009

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Reference ID: 3792009

Package Insert for DOXYCYCLINE HYCLATE TABLETS

DORYX- doxycycline hyclate tablet, delayed release
Mayne Pharma

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DORYX® (doxycycline hyclate delayed-release tablets) safely and effectively. See Full Prescribing Information for DORYX Tablets.

DORYX® (doxycycline hyclate delayed-release tablets) Oral use.
Initial U.S. Approval: 1967
To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate and other antibacterial drugs, DORYX Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1)

RECENT MAJOR CHANGES

Warnings and Precautions (5.5)	02/2015

INDICATIONS AND USAGE
DORYX is a tetracycline-class antibacterial indicated for:
- Rickettsial infections (1.1)
- Sexually transmitted infections (1.2)
- Respiratory tract infections (1.3)
- Specific bacterial infections (1.4)
- Ophthalmic infections (1.5)
- Anthrax, including inhalational anthrax (post-exposure) (1.6)
- Alternative treatment for selected infections when penicillin is contraindicated (1.7)
- Adjunctive therapy in acute intestinal amebiasis and severe acne (1.8)
- Prophylaxis of malaria (1.9)

DOSAGE AND ADMINISTRATION
- Adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. (2.1)
- For children above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used. (2.1)

DOSAGE FORMS AND STRENGTHS
Tablets: 50 mg and 200 mg (3)

CONTRAINDICATIONS
Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

WARNINGS AND PRECAUTIONS
- The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (5.1)
- *Clostridium difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.2)
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Limit sun exposure. (5.3)
- Overgrowth of non-susceptible organisms, including fungi, may occur. Re- evaluate therapy if superinfection occurs. (5.4)

ADVERSE REACTIONS
Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticaria, and hemolytic anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (7.1)
- Avoid co-administration of tetracyclines with penicillin (7.2)
- Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations (7.3)
- Concurrent use of tetracycline may render oral contraceptives less effective (7.4)
- Barbiturates, carbamazepine and phenytoin decrease the half-life of doxycycline (7.5)

USE IN SPECIFIC POPULATIONS

- Pregnancy Category D (8.1)
- Tetracyclines are excreted in human milk; however, the extent of absorption of doxycycline in the breastfed infant is not known. Doxycycline use during nursing should be avoided if possible. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORYX and other antibacterial drugs, DORYX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Doxycycline is a tetracycline-class antibacterial indicated in the following conditions or diseases:

1.1 Rickettsial infections

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by *Rickettsiae*.

1.2 Sexually transmitted infections

Uncomplicated urethral, endocervical or rectal infections caused by *Chlamydia trachomatis*.

Nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Granuloma inguinale caused by *Klebsiella granulomatis*.

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.

Chancroid caused by *Haemophilus ducreyi*.

1.3 Respiratory tract infections

Respiratory tract infections caused by *Mycoplasma pneumoniae*. Psittacosis (ornithosis) caused by *Chlamydophila psittaci*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following micro-organisms, when bacteriological testing indicates appropriate susceptibility to the drug:

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract infections caused by *Klebsiella* species.

Upper respiratory infections caused by *Streptococcus pneumoniae*.

1.4 Specific bacterial infections

Relapsing fever due to *Borrelia recurrentis*.

Plague due to *Yersinia pestis*.

Tularemia due to *Francisella tularensis*.

Cholera caused by *Vibrio cholerae*.

Campylobacter fetus infections caused by *Campylobacter fetus*.

Brucellosis due to *Brucella* species (in conjunction with streptomycin).

Bartonellosis due to *Bartonella bacilliformis*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:

Escherichia coli

Enterobacter aerogenes

Shigella species

Acinetobacter species

Urinary tract infections caused by *Klebsiella* species.

1.5 Ophthalmic infections

Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

1.6 Anthrax including inhalational anthrax (post-exposure)

Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

1.7 Alternative treatment for selected infections when penicillin is contraindicated

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pallidum* subspecies *pertenue*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

1.8 Adjunctive therapy for acute intestinal amebiasis and severe acne

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne, doxycycline may be useful adjunctive therapy.

1.9 Prophylaxis of malaria

Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [*see Dosage and Administration (2.2) and Patient Counseling Information (17)*].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage and Administration

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours), followed by a maintenance dose of 100 mg daily. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For pediatric patients above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline-class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6.1)*].

If gastric irritation occurs, doxycycline may be given with food or milk [*see Clinical Pharmacology (12)*].

When used in streptococcal infections, therapy should be continued for 10 days.

Uncomplicated urethral, endocervical, or rectal infection caused by *Chlamydia trachomatis*: 100 mg by mouth twice a day for 7 days. As an alternate dosing regimen for uncomplicated urethral or endocervical infection caused by *Chlamydia trachomatis*, administer 200 mg by mouth once-a-day for 7 days.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose.

Nongonococcal urethritis (NGU) caused by *U. urealyticum*: 100 mg by mouth twice-a- day for 7 days.

Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice-a-day for 2 weeks.

Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice-a-day for 4 weeks.

Acute epididymo-orchitis caused by *C. trachomatis*: 100 mg, by mouth, twice-a-day for at least 10 days.

2.2 For prophylaxis of malaria

For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1 or 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

2.3 Inhalational anthrax (post-exposure)

ADULTS: 100 mg, of doxycycline, by mouth, twice-a-day for 60 days.

CHILDREN: weighing less than 45 kg, 2.2 mg/kg of body weight, by mouth, twice-a-day for 60 days. Children weighing 45 kg or more should receive the adult dose.

2.4 Sprinkling the tablet over applesauce

DORYX Tablets may also be administered by carefully breaking up the tablet and sprinkling the tablet contents (delayed-release pellets) on a spoonful of applesauce. The delayed-release pellets must not be crushed or damaged when breaking up the tablet. Any loss of pellets in the transfer would prevent using the dose. The applesauce/DORYX mixture should be swallowed immediately without chewing and may be followed by a glass of water if desired. The applesauce should not be hot, and it should be soft enough to be swallowed without chewing. In the event that a prepared dose of applesauce/DORYX Tablet cannot be taken immediately, the mixture should be discarded and not stored for later use.

3 DOSAGE FORMS AND STRENGTHS

DORYX (doxycycline hyclate delayed-release tablets, USP), 50 mg are white, oval tablets containing yellow pellets and debossed with "DV" on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 50 mg of doxycycline.

DORYX (doxycycline hyclate delayed-release tablets), 200 mg are white, oval scored tablets containing yellow pellets and debossed with "D|D" on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 200 mg of doxycycline.

4 CONTRAINDICATIONS

The drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

5 WARNINGS AND PRECAUTIONS

5.1 Tooth Development

The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Doxycycline should not be used in this age group, except for anthrax, including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated.

5.2 Clostridium difficile associated diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including DORYX Tablets, and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

5.4 Superinfection

As with other antibacterial preparations, use of DORYX may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibacterial should be discontinued and appropriate therapy instituted.

5.5 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline including DORYX. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Avoid concomitant use of isotretinoin and Doryx because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

5.6 Skeletal Development

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus.

5.7 Antianabolic Action

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

5.8 Malaria

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium*

strains.

Doxycycline does not suppress *P. falciparum's* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

5.9 Development of Drug-Resistant Bacteria

Prescribing DORYX in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.10 Laboratory Monitoring for Long-Term Therapy

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The safety and efficacy of DORYX Tablets, 200 mg as a single daily dose was evaluated in a multicenter, randomized, double-blind, active-controlled study. DORYX Tablets, 200 mg was given orally once-a-day for 7 days and compared to doxycycline hyclate capsules 100 mg given orally twice daily for 7 days for the treatment of men and women with uncomplicated urogenital *C. trachomatis* infection.

Adverse events in the Safety Population were reported by 99 (40.2%) subjects in the DORYX Tablets, 200 mg treatment group and 132 (53.2%) subjects in the doxycyclinehyclate capsules reference treatment group. Most AEs were mild in intensity. The most commonly reported adverse events in both treatment groups were nausea, vomiting, diarrhea, and bacterial vaginitis, Table 1.

Table 1: Adverse Reactions Reported in Greater than or Equal to 2% of Subjects

	DORYX Tablets, 200 mg N = 246
Preferred Term	**n (%)**
Subjects with any AE	99 (40.2)
Nausea	33 (13.4)
Vomiting	20 (8.1)
Headache	5 (2.0)
Diarrhea	8 (3.3)
Abdominal Pain Upper	5 (2.0)
Vaginitis Bacterial	8 (3.3)
Vulvovaginal Mycotic Infection	5 (2.0)

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not always reflect the rates observed in practice.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of doxycycline. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate a causal relationship to drug exposure.

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly

diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline- class. Most of these patients took medications immediately before going to bed [*see Dosage and Administration (2.1)*].

Skin: Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme have been reported. Photosensitivity is discussed above [*see Warnings and Precautions (5.3)*].

Renal: Rise in BUN has been reported and is apparently dose-related [*see Warnings and Precautions (5.7)*].

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline [*see Warnings and Precautions (5.5)*]

Thyroid Gland Changes: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

7 DRUG INTERACTIONS

7.1 Anticoagulant Drugs

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

7.2 Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

7.3 Antacids and Iron Preparations

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations.

7.4 Oral Contraceptives

Concurrent use of tetracycline may render oral contraceptives less effective.

7.5 Barbiturates and anti-epileptics

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

7.6 Penthrane

The concurrent use of tetracycline and Penthrane® (methoxyflurane) has been reported to result in fatal renal toxicity.

7.7 Drug/Laboratory Test Interactions

False elevations of urinary catecholamines may occur due to interference with the fluorescence test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category D:

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for the treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk.[1]

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (that is, in the second and third months of gestation), with the exception of a marginal relationship with neural tube defect based on only two-exposed cases.[2]

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.[3]

Nonteratogenic effects: [*see Warnings and Precautions (5.1, 5.6)*].

8.3 Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated. The effects of prolonged exposure to doxycycline in breast milk are unknown[4]. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [*see Warnings and Precautions (5.1, 5.6)*].

8.4 Pediatric use

Because of the effects of drugs of the tetracycline-class on tooth development and growth, DORYX should not be used in pediatric patients to the age of 8 years, unless the potential benefits are expected to outweigh the risks such as for anthrax, or when other drugs are not likely to be effective or are contraindicated [*see Warnings and Precautions (5.1, 5.6) and Dosage and Administration (2.1, 2.3)*].

8.5 Geriatric use

Clinical studies of DORYX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

DORYX 50 mg tablets contain 3 mg (0.131 mEq) of sodium.

DORYX 200 mg tablets contain 12 mg (0.522 mEq) of sodium.

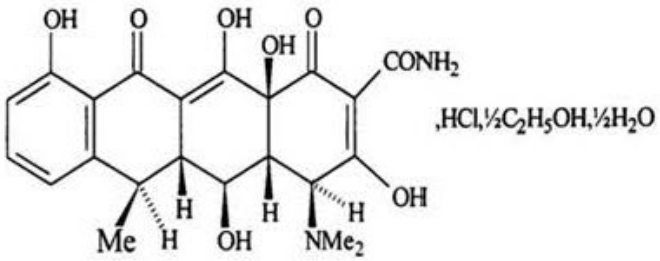
10 OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

11 DESCRIPTION

DORYX (doxycycline hyclate delayed-release tablets), for oral administration, contain specially coated pellets of doxycycline hyclate, a broad-spectrum antibacterial synthetically derived from oxytetracycline, in a delayed-release formulation for oral administration.

The structural formula for doxycycline hyclate is:



with a molecular formula of $C_{22}H_{24}N_2O_8$, HCl, ½ C_2H_6O, ½ H_2O and a molecular weight of 512.9. The chemical designation for doxycycline hyclate is [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6- methyl-1,11-deoxonaphthacene-2-carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form. Inactive ingredients in the tablet formulation are: lactose monohydrate; microcrystalline cellulose; sodium lauryl sulfate; sodium chloride; talc; anhydrous lactose; corn starch; crospovidone; magnesium stearate; cellulosic polymer coating.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is an antibacterial drug [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

Doxycycline is virtually completely absorbed after oral administration. Following single and multiple-dose administration of DORYX Tablets, 200 mg to adult volunteers, average peak plasma doxycycline concentration (C_{max}) was 4.6 mcg/mL and 6.3 mcg/mL, respectively with median t_{max} of 3 hours; the corresponding mean plasma concentration values 24 hours after single and multiple doses were 1.5 mcg/mL and 2.3 mcg/mL, respectively. The mean C_{max} and AUC $_{0-\infty}$ of doxycycline are 24% and 13% lower, respectively, following single dose administration of DORYX Tablets, 100 mg with a high fat meal (including milk) compared to fasted conditions. The mean C_{max} of doxycycline is 19% lower and the AUC $_{0-\infty}$ is unchanged following single dose administration of DORYX Tablets, 150 mg with a high fat meal (including milk) compared to fasted conditions. The clinical significance of these decreases is unknown. Doxycycline bioavailability from DORYX Tablets, 200 mg was not affected by food, but the incidence of nausea was higher in fasted subjects. The 200 mg tablets may be administered without regard to meals.

When DORYX Tablets are sprinkled over applesauce and taken with or without water, the extent of doxycycline absorption is unchanged, but the rate of absorption is increased slightly.

Tetracyclines are concentrated in bile by the liver and excreted in the urine and feces at high concentrations and in a biologically active form. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with a creatinine clearance of about 75 mL/min. This percentage may fall as low as 1-5%/72 hours in individuals with a creatinine clearance below 10 mL/min.

Studies have shown no significant difference in the serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life.

12.4 Microbiology

Mechanism of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram- negative bacteria. Cross-resistance between tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for DORYX Tablets [*see Indications and Usage (1)*].

Gram-Negative Bacteria

Acinetobacter species

Bartonella bacilliformis

Brucella species

Campylobacter fetus

Enterobacter aerogenes

Escherichia coli

Francisella tularensis

Haemophilus ducreyi

Haemophilus influenzae

Klebsiella granulomatis

Klebsiella species

Neisseria gonorrhoeae

Shigella species

Vibrio cholerae

Yersinia pestis

Gram-Positive Bacteria *Bacillus anthracis Streptococcus pneumoniae*

Anerobic Bacteria *Clostridium* species *Fusobacterium fusiforme Propionibacterium acnes*

Other Bacteria

Borrelia recurrentis

Chlamydophila psittaci

Chlamydia trachomatis

Mycoplasma pneumoniae

Norcardiae and other aerobic Rickettsiae

Treponema pallidum

Treponema pertenue

Ureaplasma urealyticum

Parasites

Balantidium coli

Entamoeba species *Plasmodium falciparum*[1]

---

1 Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar)[5,6,8]. The MIC values should be interpreted according to the criteria provided in Table 2.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. Zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standard test method[5,7,8]. This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of bacteria to doxycycline. The disk diffusion interpretive criteria are provided in Table 2.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method[9]. The MIC values obtained should be interpreted according to the criteria provided in Table 2.

Table 2: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

Bacteria*	**Minimal Inhibitory Concentration (mcg/mL)**			**Zone Diameter (mm)**			**Agar Dilution (mcg/mL)**		
	S	**I**	**R**	**S**	**I**	**R**	**S**	**I**	**R**
Acinetobacter spp.									
Doxycycline	≤4	8	≥16	≥13	10-12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
Bacillus anthracis†									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Brucella species†									
Doxycycline	≤1	-	-	-	-	-	-	-	-

Tetracycline	≤1	-	-	-	-	-	-	-	-
Enterobacteriaceae									
Doxycycline	≤4	8	≥16	≥14	11-13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
Francisella tularensis†									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
Haemophilus influenzae									
Tetracycline	≤2	4	≥8	≥29	26-28	≤25	-	-	-
Mycoplasma pneumoniae									
Tetracycline	-	-	-	-	-	-	≤2	-	-
Nocardiae and other aerobic *Actinomyces* species*†									
Doxycycline	≤1	2-4	≥8	-	-	-			
Neisseria gonorrhoeae‡									
Tetracycline	-	-	-	≥38	31-37	≤30	≤0.25	0.5-1	≥2
Streptococcus pneumoniae									
Doxycycline	≤0. 25	0.5	≥1	≥28	25-27	≤24	-	-	-
Tetracycline	≤1	2	≥4	≥28	25-27	≤24	-	-	-
Vibrio cholerae									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
Yersinia pestis									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
Ureaplasma urealyticum									
Tetracycline	-	-	-	-	-	-	≤1		≥2

* Organisms susceptible to tetracycline are also considered susceptible to doxycycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

† The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

‡ Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC greater than or equal to 16 mcg/mL).

A report of *Susceptible* (S) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the bacteria is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually

achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test[5,6,7,8,9,10,11]. Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 3. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 3 should be achieved.

Table 3: Acceptable Quality Control Ranges for Susceptiblity Testing for Doxycycline and Tetracycline

QC Strain	Minimal Inhibitory Concentration (mcg/mL)	Zone Diameter (mm)	Agar Dilution (mcg/mL)
Enterococcus faecalis ATCC 29212			
Doxycycline	2 - 8	-	-
Tetracycline	8 - 32	-	-
Escherichia coli ATCC 25922			
Doxycycline	0.5 - 2	18 - 24	-
Tetracycline	0.5 - 2	18 - 25	-
Eubacteria lentum ATCC 43055			
Doxycycline	2-16		
Haemophilus influenzae ATCC 49247			
Tetracycline	4 - 32	14 - 22	-
Neisseria gonorrhoeae ATCC 49226			
Tetracycline	-	30 - 42	0.25 - 1
Staphylococcus aureus ATCC 25923			
Doxycycline	-	23 - 29	-
Tetracycline	-	24 - 30	-
Staphylococcus aureus ATCC 29213			
Doxycycline	0.12 - 0.5		-
Tetracycline	0.12 - 1		-
Staphylococcus pneumoniae ATCC 49619			
Doxycycline	0.015 - 0.12	25 - 34	-
Tetracycline	0.06 - 0.5	27 - 31	-
Bacteroides fragilis ATCC 25285			
Tetracycline	-	-	0.125 - 0.5
Bacteroides thetaiotaomicron ATCC 29741			
Doxycycline	2-8	-	
Tetracycline	-	-	8 - 32
Mycoplasma pneumoniae ATCC 29342			
Tetracycline	0.06 - 0.5	-	0.06 - 0.5
Ureaplasma urealyticum ATCC 33175			

Tetracycline	-	-	≥8

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibacterials (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

13.2 Animal Toxicology and/or Pharmacology

Hyperpigmentation of the thyroid has been produced by members of the tetracycline- class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl, were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline); in chickens (chlortetracycline); and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

14 CLINICAL STUDIES

This was a randomized, double-blind, active-controlled, multicenter trial which enrolled 495 subjects, between 19 to 45 years of age with a confirmed diagnosis of urogenital *C. trachomatis* infection less than 14 days prior to enrollment, or partner(s) of a subject with a known positive test for urogenital *C. trachomatis* infection.

The primary purpose of this study was to evaluate the efficacy and safety of DORYX Tablets, 200 mg once daily versus doxycycline hyclate capsules, 100 mg twice daily for seven days for the treatment of uncomplicated urogenital *C. trachomatis* infection. The primary efficacy objective was to demonstrate non-inferiority of the DORYX Tablets, 200 mg once daily treatment regimen versus the doxycycline 100 mg twice daily treatment regimen for the indication using a negative nucleic acid amplification test (NAAT) at the test of cure visit (day 28) in the mITT population (subjects who were positive at baseline and took at least one day of study drug).

Table 4: Primary Efficacy Outcome – Microbiological Cure of C. trachomatis at Day 28

mITT Population		DORYX Tablets, 200 mg once daily Cure Rate (%)	Doxycycline hyclate capsules, 100 mg twice daily Cure Rate (%)	Difference (%)
	N	188	190	

	Microbiological Cure, n (%)	163 (86.7)	171 (90.0)	-3.3%
	95% Confidence Interval for Cure Rate			-10.3, 3.7

15 REFERENCES

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4. Hale T. *Medications and Mothers Milk*. 9th edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.

5. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational* Supplement, CLSI document M100–S24. CLSI document M100S24, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2014.

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11. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline*. CLSI document M43-A, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne Pennsylvania 19087, USA, 2011.

16 HOW SUPPLIED/STORAGE AND HANDLING

DORYX® (doxycycline hyclate delayed-release tablets), 50 mg are white, oval tablets containing yellow pellets and debossed with "DV" on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 50 mg of doxycycline.

Bottles of 120 tablets **NDC** 51862-557-12

DORYX® (doxycycline hyclate delayed-release tablets), 200 mg are white, oval scored tablets containing yellow pellets and debossed with "D|D" on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 200 mg of doxycycline.

Bottles of 60 tablets **NDC** 51862-558-06

Store at 25° C (77° F); excursions permitted to 15 – 30° C (59 – 86° F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container (USP).

17 PATIENT COUNSELING INFORMATION

Patients taking doxycycline for malaria prophylaxis should be advised:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (for example, staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- that doxycycline prophylaxis:
  - should begin 1 to 2 days before travel to the malarious area,
  - should be continued daily while in the malarious area and after leaving the malarious area,
  - should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area,
  - should not exceed 4 months.

All patients taking doxycycline should be advised:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (for example, skin eruptions, etc.) occurs. Sunscreen or sunblock should be considered [*see Warnings and Precautions (5.3)*].
- to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6.1)*].
- that the absorption of tetracyclines is reduced when taken with foods, especially those that contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk [*see Drug Interactions (7.3)*].
- that the absorption of tetracyclines is reduced when taken with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations [*see Drug Interactions (7.3)*].
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

Diarrhea is a common problem caused by antibacterials which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of antibacterial. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including DORYX should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When DORYX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DORYX or other antibacterial drugs in the future.

Rx only

Distributed by:

Mayne Pharma
Greenville, NC 27834
1-844-825-8500

Manufactured by:
Mayne Pharma International Pty Ltd
Salisbury South, SA 5106
Australia

501331/1

PRINCIPAL DISPLAY PANEL - 60 Tablet Bottle Label

N 51862-558-06

DORYX®
(doxycycline hyclate
delayed-release tablets)

200 mg

R_x only
Each tablet contains specially
coated pellets of doxycycline hyclate
equivalent to 200 mg of doxycycline.

60 TABLETS

mayne pharma

PRINCIPAL DISPLAY PANEL - 120 Tablet Bottle Label

N 51862-557-12

R_x only

DORYX®
(doxycycline hyclate
delayed-release tablets)

50 mg

Do not chew or crush tablets.
Each tablet contains specially
coated pellets of doxycycline hyclate

equivalent to 50 mg of doxycycline.

mayne pharma

120 TABLETS

DORYX

doxycycline hyclate tablet, delayed release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51862-558
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
doxycycline hyclate (UNII: 19XTS3T51U) (doxycycline anhydrous - UNII:334895S862)	doxycycline anhydrous	200 mg

Inactive Ingredients	
Ingredient Name	Strength
Lactose Monohydrate (UNII: EWQ57Q8I5X)	
Cellulose, microcrystalline (UNII: OP1R32D61U)	
sodium lauryl sulfate (UNII: 368GB5141J)	
sodium chloride (UNII: 451W47IQ8X)	
talc (UNII: 7SEV7J4R1U)	
anhydrous lactose (UNII: 3SY5LI9PMK)	
starch, corn (UNII: O8232NY3SJ)	
crospovidone (UNII: 68401960MK)	
magnesium stearate (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (containing yellow pellets)	Score	2 pieces
Shape	OVAL	Size	19mm

Flavor		**Imprint Code**	D;D
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-558-06	60 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:51862-558-00	1 in 1 CARTON		
2		3 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050795	04/13/2015	

DORYX

doxycycline hyclate tablet, delayed release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:51862-557
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
doxycycline hyclate (UNII: 19XTS3T51U) (doxycycline anhydrous - UNII:334895S862)	doxycycline anhydrous	50 mg

Inactive Ingredients

Ingredient Name	Strength
Lactose Monohydrate (UNII: EWQ57Q815X)	
Cellulose, microcrystalline (UNII: OP1R32D61U)	
sodium lauryl sulfate (UNII: 368GB5141J)	
sodium chloride (UNII: 451W47IQ8X)	
talc (UNII: 7SEV7J4R1U)	
anhydrous lactose (UNII: 3SY5LH9PMK)	
starch, corn (UNII: O8232NY3SJ)	
crospovidone (UNII: 68401960MK)	
magnesium stearate (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE (containing yellow pellets)	**Score**	no score
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	D;V

Contains				

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51862-557-12	120 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:51862-557-00	1 in 1 CARTON		
2		6 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA050795	05/26/2015	

Labeler - Mayne Pharma (962128943)

Establishment

Name	Address	ID/FEI	Business Operations
Mayne Pharma International Pty Ltd		756003745	MANUFACTURE(51862-558, 51862-557) , ANALYSIS(51862-558, 51862-557)

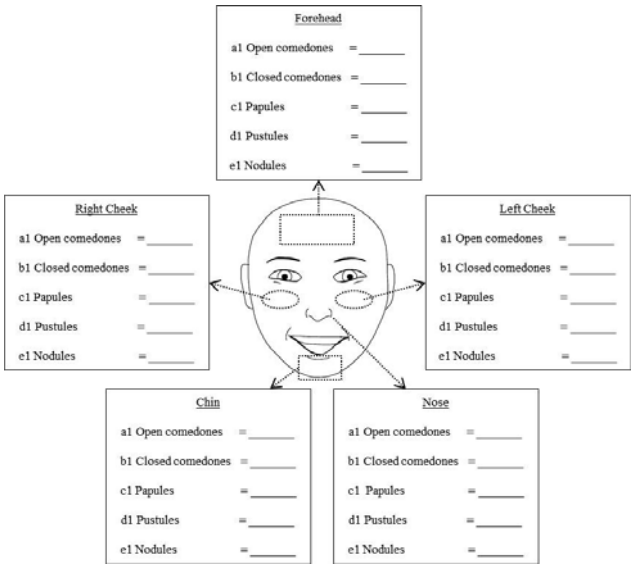
Establishment

Name	Address	ID/FEI	Business Operations
Hovione PharmaScience Limited		854974342	API MANUFACTURE(51862-558, 51862-557)

Revised: 6/2015 Mayne Pharma

14.2 PROCEDURE FOR FACIAL LESION COUNTS

1. If the skin is very greasy, blot off the sebum with a paper towel before counting lesions.
2. Instruct subjects to attend with a clean face and no make-up (foundation, powder, concealer, blush), or remove makeup completely with Cetaphil® Gentle Skin Cleanser as soon as they arrive, and wait for 30 minutes prior to beginning assessments. Let the skin color return to normal before counting.
3. Always use a lamp (and glasses, if needed), but do not routinely use a magnifying lens. Use the same room and constant lighting conditions for every evaluation. Avoid shadows.
4. Position the subject in the same place every time. Make sure the subject is comfortable. The subject's seat should be fairly high, so that the evaluator can view the facial skin comfortably (without excessive bending).
5. Each subject should be assessed at all visits by the same evaluator (Investigator or designee):
   - Practice: count-recount (minimizes intra-rater variability).
   - Make your decision promptly - hesitation leads to confusion.
   - Evaluate the subject after visual inspection and palpation of the skin. Use palpation to assess the depth of the spots and to locate ones that are not obvious.
   - Do not stretch the skin; this alters the profile of the spots.
   - Where many lesions are present, stroke the skin from left to right or from top to bottom to avoid counting some spots more than once and others not at all.
   - Count the different types of lesions separately. Spots of any size should be counted, however small.
   - If it appears difficult to count accurately in a particular area, make a note and exclude this region every time for a given subject. If stubble is very obvious, it is best to avoid counting in the beard area.
   - Record any problems and how they were dealt with in the subject's notes.
6. Lesions should routinely be counted on the whole face, area by area:
   - The face is defined by the hairline and edge of the jaw (mandibular lines).
   - Use the following template to divide the face into five areas to be evaluated: forehead, right cheek, left cheek, chin, and nose (see CRF).
   - Nodules/cysts are counted only at Screening/Baseline visit.



7. The exact number of each lesion should be recorded on the appropriate CRF page. The lesion counts will be electronically added together to obtain a total lesion count.

The following definitions describe the lesions to be counted:

Non-inflammatory lesions

- Open Comedone - A mass of sebaceous material that is impacted behind an open follicular orifice (blackhead).

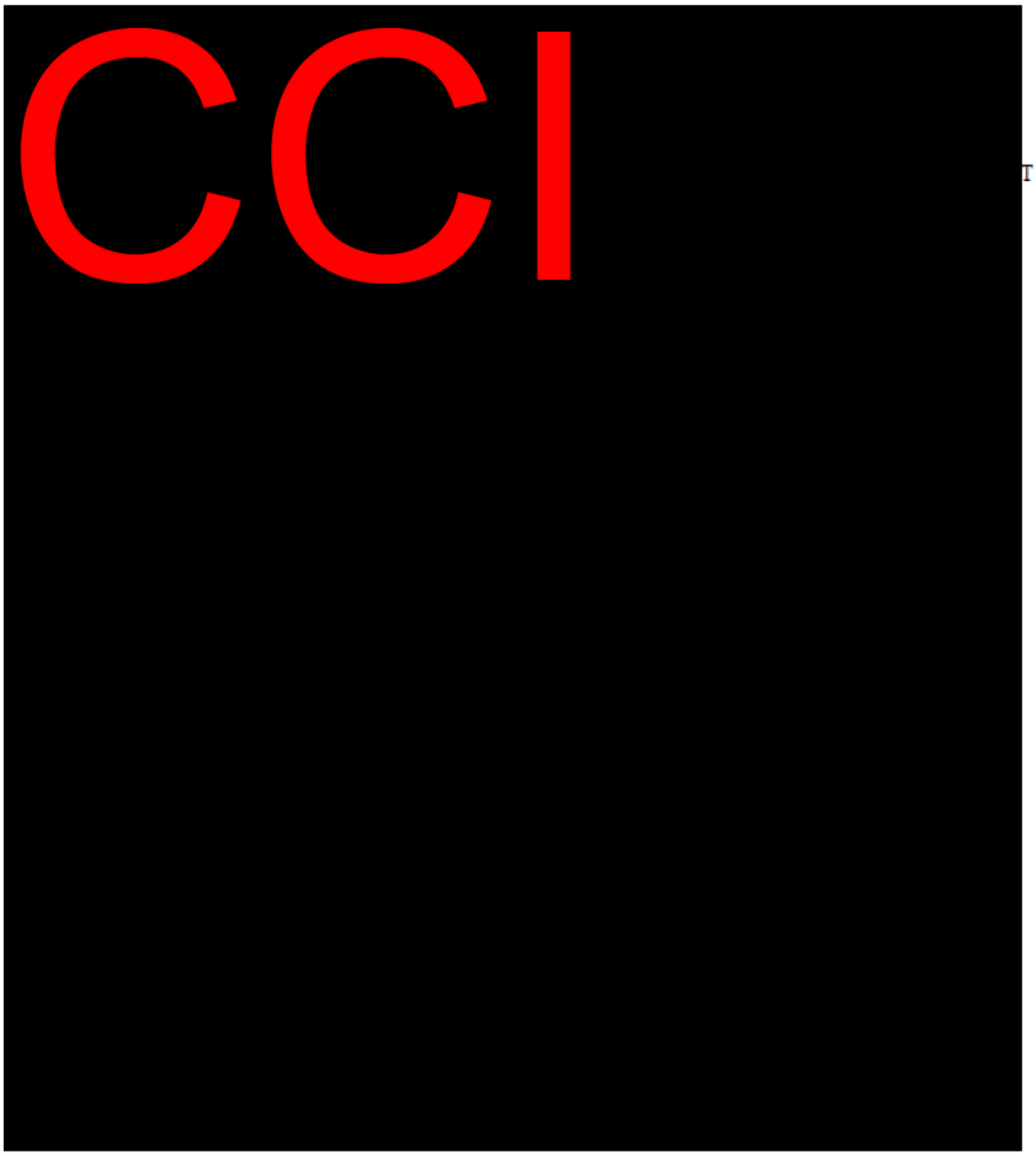
- Closed Comedone - A mass of sebaceous material that is impacted behind a closed follicular orifice (white head).

Inflammatory lesions

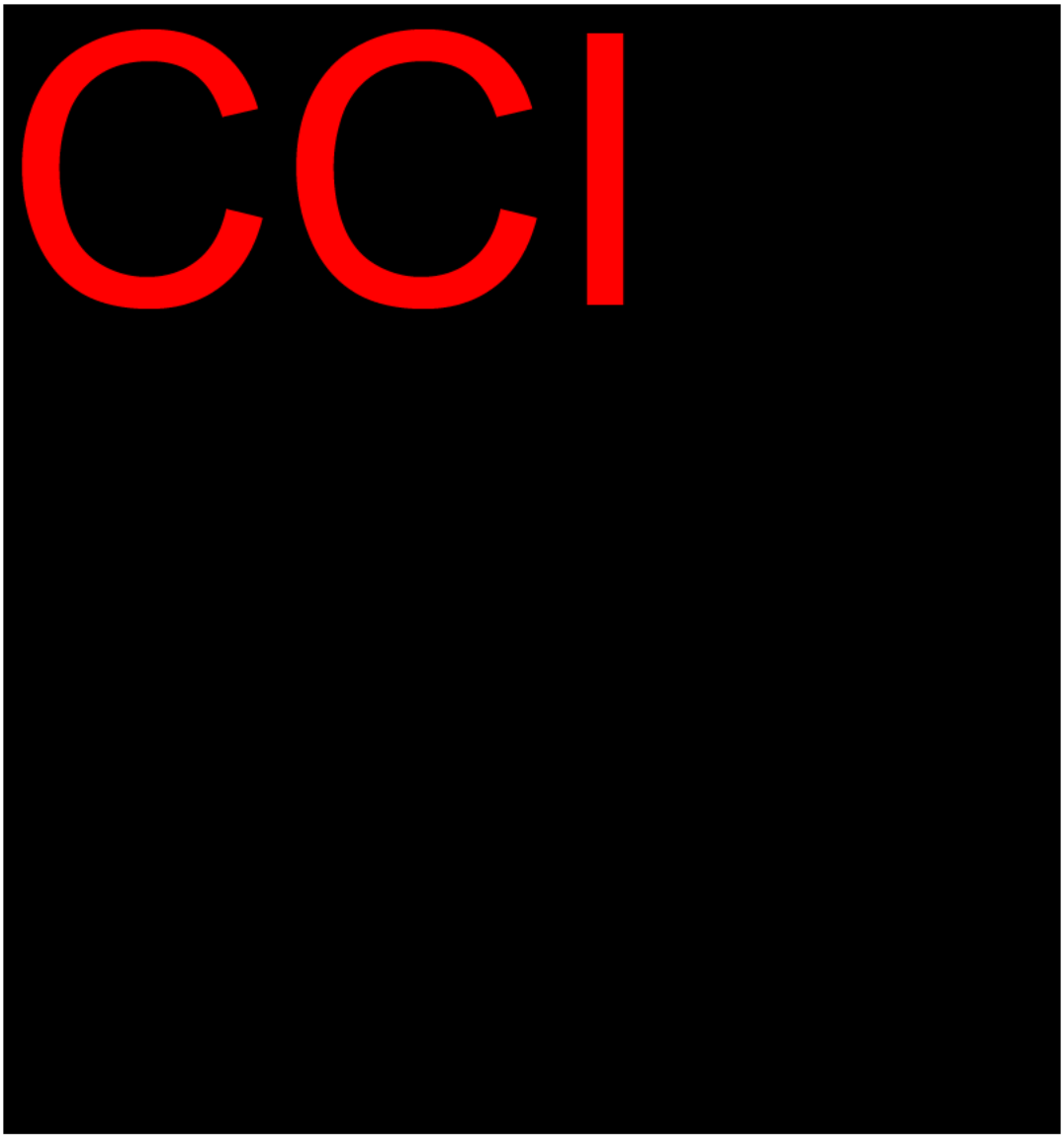
- Papules - A small, solid, red elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.

- Pustules - A small, circumscribed red elevation of the skin which contains yellow-white exudates.

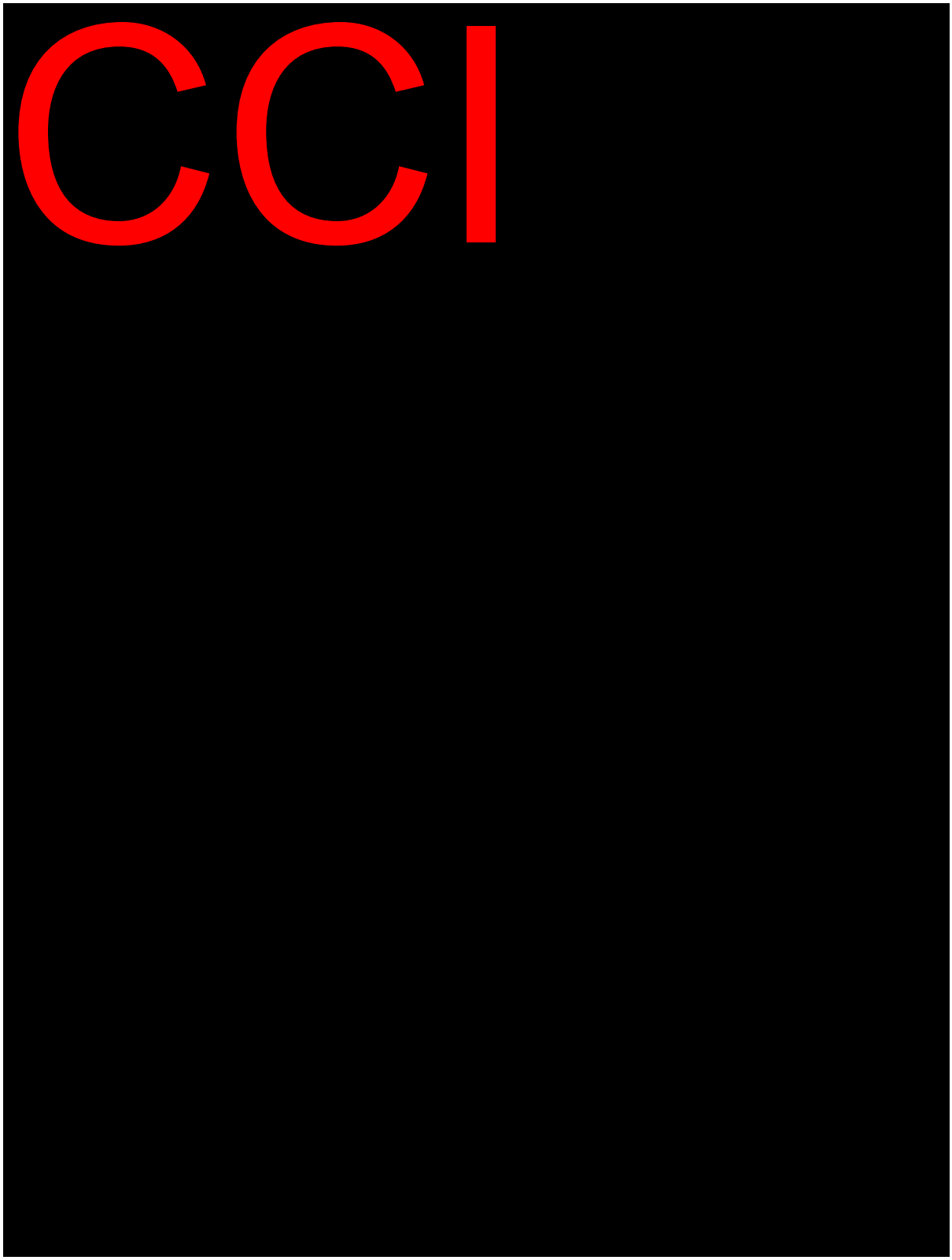
Nodules/Cysts, defined as circumscribed, elevated, solid lesions generally more than 1 cm in diameter with palpable depth, are counted at the Screening/Baseline visit only. No more than 2 nodules/cysts will be allowed for study participation (Exclusion Criterion #2, Section 6.2.2). Nodules/Cysts are not counted at post-Baseline visits.



T



AY Finlay, GK Khan, April 1992. This must not be copied without the permission of the authors.


CCI

Please check that you have answered EVERY question. Thank you.

14.5 SUBJECT SATISFACTION QUESTIONNAIRE

INSTRUCTIONS:

Please complete this questionnaire regarding the study treatments you have been using in this study.

Your answers will help us to better understand your needs and expectations.

This questionnaire has been designed so that it can be completed quickly and easily. Please use black pen to complete this questionnaire. Please give only ONE answer per question.

There are no "Right" or "Wrong" answers.

If you are unsure how to answer a question, please give the best answer you can.

If you need to make a change, draw a line through the answer you would like to change, record your new response with a checkmark, and put your initials and today's date next to your correction.

Your answers will not affect your participation in the study and no prejudice will be shown towards you for completing this document.

1. How bothered were you by the treatment side effects?

[ ]1 Not bothered at all

[ ]2 Bothered somewhat

[ ]3 Bothered

[ ]4 Bothered a great deal

2. How satisfied were you with the time it took for treatment to work?

[ ]1 Very satisfied

[ ]2 Satisfied

[ ]3 Somewhat satisfied

[ ]4 Not satisfied

3. How satisfied were you with the effectiveness of the treatment?

[ ]1 Very satisfied

[ ]2 Satisfied

[ ]3 Somewhat satisfied

[ ]4 Not satisfied

4. How do you feel about yourself, since starting your treatment?

[ ]1 Very much better

[ ]2 A lot better

[ ]3 A little better

[ ]4 Worse

5. Overall, are you satisfied with the treatment?

[ ]1 Very satisfied

[ ]2 Satisfied

[ ]3 Somewhat satisfied

[ ]4 Not satisfied

6. Would you consider using this treatment again?

[ ]1 Yes

[ ]2 No

7. Did you use the provided moisturizing lotion?

[ ]1 Yes

[ ]2 No

a. If yes, would you say (check as many answers as you wish)

[ ]1 The moisturizer helps to reduce irritation

[ ]2 The moisturizer helps you to be adherent to study treatments

[ ]3 The moisturizer was pleasant to use

[ ]4 None of the above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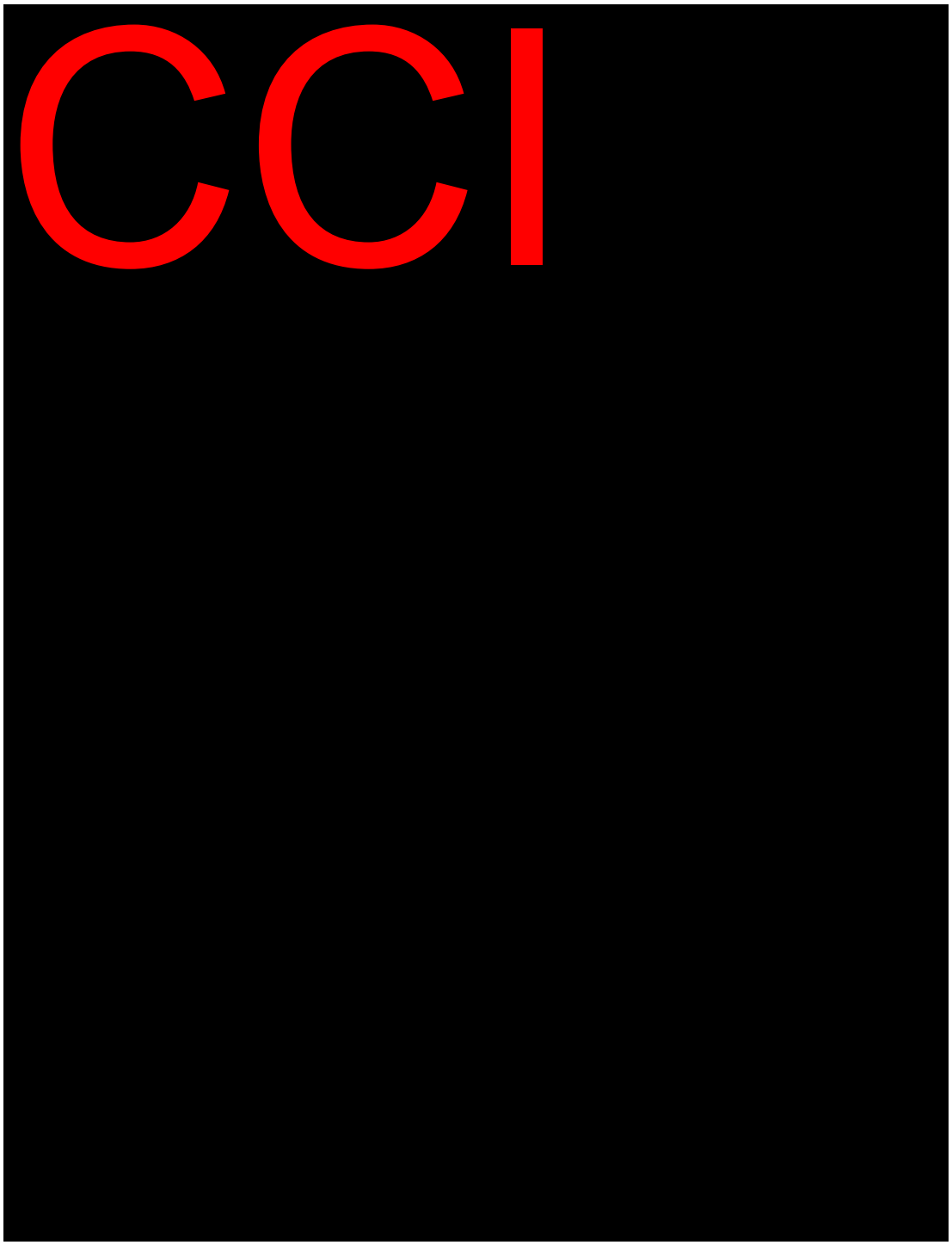
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14.7 DECLARATION OF HELSINKI

Clinical Review & Education

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

ARTICLE INFORMATION

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