APPLICATION NUMBER:

209269Orig1s000

CLINICAL REVIEW(S)
CLINICAL REVIEW

Application Type: NDA
Application Number(s): 209269
Priority or Standard: Standard
Submit Date(s): July 8, 2016
Received Date(s): July 8, 2016
PDUFA Goal Date: May 8, 2017
Division / Office: DDDP/ODEIII
Reviewer Name(s): Patricia C. Brown, MD
Review Completion Date: April 5, 2017
Established Name: Minocycline hydrochloride
(Proposed) Trade Name: Minolira™
Therapeutic Class: Acne agent
Applicant: Dr Reddy’s Laboratories, LTD
Formulation(s): extended-release tablets
Dosing Regimen: Approximately 1 mg/kg once daily for 12 weeks
Indication(s): Only inflammatory lesions of non-nodular moderate to severe acne vulgaris
Intended Population(s): Patients 12 years and older

Reference ID: 4080447
Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT ................................. 7
  1.1 Recommendation on Regulatory Action .............................................. 7
  1.2 Risk Benefit Assessment ................................................................. 7
  1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .................................................................................. 8
  1.4 Recommendations for Postmarket Requirements and Commitments ............................................................................................... 8

2 INTRODUCTION AND REGULATORY BACKGROUND ............................ 8
  2.1 Product Information ............................................................................. 8
  2.2 Tables of Currently Available Treatments for Proposed Indications ........ 9
  2.3 Availability of Proposed Active Ingredient in the United States .......... 11
  2.4 Important Safety Issues with Consideration to Related Drugs .......... 12
  2.5 Summary of Presubmission Regulatory Activity Related to Submission .. 13
  2.6 Other Relevant Background Information ........................................... 16

3 ETHICS AND GOOD CLINICAL PRACTICES ........................................ 16
  3.1 Submission Quality and Integrity ............................................................ 17
  3.2 Compliance with Good Clinical Practices ............................................ 17
  3.3 Financial Disclosures ........................................................................... 18

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES ......................................................................... 19
  4.1 Chemistry Manufacturing and Controls ............................................... 19
  4.2 Clinical Microbiology .......................................................................... 24
  4.3 Preclinical Pharmacology/Toxicology .................................................. 24
  4.4 Clinical Pharmacology ......................................................................... 28
    4.4.1 Mechanism of Action ................................................................... 29
    4.4.2 Pharmacodynamics ..................................................................... 29
    4.4.3 Pharmacokinetics ........................................................................ 29

5 SOURCES OF CLINICAL DATA .............................................................. 33
  5.1 Tables of Studies/Clinical Trials ............................................................ 33
  5.2 Review Strategy .................................................................................. 33
  5.3 Discussion of Individual Studies/Clinical Trials .................................... 34

6 REVIEW OF EFFICACY ........................................................................ 37

7 REVIEW OF SAFETY ............................................................................. 38
  Safety Summary ....................................................................................... 38
  7.1 Methods ............................................................................................. 38
    7.1.1 Studies/Clinical Trials Used to Evaluate Safety .............................. 39
    7.1.2 Categorization of Adverse Events ................................................... 39
Minolira™ (minocycline hydrochloride) extended-release tablets

8.2 Lactation ............................................................................................................62
8.3 Females and Males of Reproductive Potential ..................................................63
8.4 Pediatric Use .....................................................................................................63

12 CLINICAL PHARMACOLOGY ................................................................................63
  12.3 Pharmacokinetics ..............................................................................................63

17 PATIENT COUNSELING INFORMATION ........................................................................65
  9.3 Advisory Committee Meeting.............................................................................67
# Table of Tables

Table 1: Currently Available Treatments for Acne ............................................................... 10
Table 2: Oral Acne Products .................................................................................................. 10
Table 3: Quantitative Composition of MINOLIRA™ Tablets ............................................. 20
Table 4: PK parameters (mean + SD) Trial 007 ................................................................. 30
Table 5: PK parameters (mean + SD) Trial 008 ................................................................. 30
Table 6: Summary of Relative BA Results Trials 007 and 008 ........................................... 31
Table 7: Demographic Summary (Trial 007) ..................................................................... 34
Table 8: Demographic Summary (Trial 008) ..................................................................... 35
Table 9: Summary of Subject Disposition (Trial 007) ....................................................... 36
Table 10: Summary of Subject Disposition (Trial 008) ...................................................... 37
Table 11: Exposure (Trials 006, 007, 008) ..................................................................... 40
Table 12: Demographics of Safety Population (All Subj. Dosed: Trials 0006, 007, 008) .......... 41
Table 13: Race and Ethnicity Compared with US Population (Trials 007 & 008) .............. 42
Table 14: TEAE’s Trial DFD-10-CD-006 ............................................................................ 44
Table 15: TEAE Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) and Those of Moderate Severity Noted: Trial 007 .................... 45
Table 16: TEAE Frequency by Treatment – Number of Subjects Reporting Events (% of Subjects Dosed): Trial 007 ...................................................................................... 46
Table 17: TEAE Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) and One of Moderate Severity Noted: Trial 008 ......................... 47
Table 18: TEAE Frequency by Treatment – Number of Subjects Reporting Events (% of Subjects Dosed): Trial 008 ...................................................................................... 48
1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Review of the pharmacokinetic trials, DFD-10-CD-007 and DFD-10-CD-008, has demonstrated that MINOLIRA™ (minocycline hydrochloride) extended-release tablets are bioequivalent to the listed drug SOLODYN® (minocycline HCl) 135 mg Extended Release Tablets. Based on these findings, this reviewer recommends approval of MINOLIRA™ (minocycline hydrochloride) extended-release tablets to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

1.2 Risk Benefit Assessment

Minocycline Hydrochloride has been marketed since FDA approval in 1971. It is currently available under the tradenames SOLODYN®, MINOCIN®, and ARESTIN® in multiple strengths as oral capsules (immediate release), extended release tablets, sterile powder for injection, and extended release powder (microspheres in unit dose cartridges). Generic formulations include immediate release oral tablets and capsules and extended release tablets, all in a variety of strengths.

The applicant, Dr. Reddy’s Laboratories Limited, is submitting for approval, a new formulation, MINOLIRA™, an extended release oral tablet formulation of minocycline hydrochloride using a single score line, which allows splitting of the tablet into two equal halves. When split along the score line, each tablet of 105 mg and 135 mg will break into two equal halves, each half representing a dose of 52.5 mg from the 105 mg tablet and 67.5 mg from the 135 mg tablet. SOLODYN® is currently marketed as 55 mg, 65 mg, 80 mg, 105 mg, and 115 mg tablets.

The recommended dose for MINOLIRA™ and SOLODYN is approximately 1mg/kg. MINOLIRA will have a dose range of 0.76-1.17 mg/kg with the proposed strengths while SOLODYN, as currently marketed has a dose range of 0.92-1.11 mg/kg. SOLODYN was originally approved in 3 strengths (45 mg, 90 mg, and 135 and no longer marketed) with a dose range of 0.76-1.48 mg/kg* which includes the proposed MINOLIRA dose range. *From SOLODYN labeling approved May 8, 2006.

For this 505(b)(2) application, safety and efficacy are established through reliance on the Agency’s findings of safety and efficacy for the listed drug SOLODYN® (minocycline hydrochloride) extended-release tablets.
HCl) Extended Release Tablets. The scientific justification for this reliance is provided by data from two relative bioavailability/bioequivalence trials performed in humans, trials 007 and 008.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The standard risk management procedures of prescription status, professional labeling, and spontaneous adverse event reporting are adequate risk management activities for this drug at this time. A risk evaluation and mitigation strategy is not necessary for this 505 (b)(2) application for which the adverse event profile is well known.

1.4 Recommendations for Postmarket Requirements and Commitments

No recommendations are made for postmarket requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant, Dr. Reddy’s Laboratories, Inc., has submitted a 505(b)2 application for MINOLIRA™ (minocycline hydrochloride) extended-release tablets 105 mg and 135 mg and “indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.” This is a new formulation (extended-release tablets) that is functionally scored. This NDA refers to the listed drug SOLODYN® (minocycline HCl) Release Tablets, 135 mg of Medicis Pharmaceutical Corporation, the holder of the approved application (NDA 50808). SOLODYN® was approved May 8, 2006.

This NDA is not appropriate for submission as an ANDA under section 505 (j) of the Federal Food, Drug, and Cosmetic Act because there is a change in formulation from extended-release tablets to extended-release tablets that are functionally scored.

The ANDA process requires drugs that are the same as a listed drug. According to CFR Title 21 part 314 Subpart C §314.92:

For determining the suitability of an abbreviated new drug application, the term “same as” means identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which
approval cannot be granted because of exclusivity or an existing patent may be omitted.

This NDA relies on the Agency’s findings of safety and effectiveness for the listed drug SOLODYN®. The scientific justification for this reliance is provided by data from two relative bioavailability/bioequivalence (BA/BE) trials performed in humans, “the clinical bridge.” For an oral product, safety and efficacy are a function of systemic exposure. Bioequivalence is defined in 21 CFR 320.1 as; “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in appropriately designed study.” If bioequivalence is established, then the active moiety of both SOLODYN® and MINOLIRA™ will be available at the site of drug action without a significant difference in rate or extent. One can infer then that there would not be a significant difference between SOLODYN® and MINOLIRA™ extended-release tablets in induction of adverse events and efficacy when used to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

Minocycline hydrochloride powder, sparingly soluble in water, soluble in solutions of alkali hydroxides and carbonates, slightly soluble in ethanol (96%), practically insoluble in chloroform and in ether.

MINOLIRA™ for oral administration contain two types of minocycline hydrochloride beads equivalent to 105 mg (26.25 mg of minocycline as immediate release beads and 78.75 mg of minocycline as extended release beads), and 135 mg (33.75 mg of minocycline as immediate release and 101.25 mg of minocycline as extended release beads. In addition, the 105 mg and 135 mg tablets contain the following inactive ingredients: microcrystalline cellulose NF, polyethylene glycol 400 NF, ethyl cellulose NF, hypromellose USP, triethyl citrate NF, silicified microcrystalline cellulose NF, sodium stearyl fumarate NF, talc USP, isopropyl alcohol USP and purified water USP. Both 105 mg and 135 mg tablets also contain Opadry clear which contains hydroxyl propyl cellulose NF and hypromellose USP.

The proposed indication is the same as for the listed drug, SOLODYN, “indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.” Proposed dosage at approximately 1 mg/kg is the same as for the listed drug, SOLODYN.

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of topical and systemic drugs are available for the treatment of acne vulgaris. Approved therapies for acne vulgaris include oral and topical antibiotics and antimicrobials (e.g. erythromycin, clindamycin, benzoyl peroxide) systemic hormonal
Clinical Review
Patricia C. Brown, M.D.
NDA 209269
Minolira™ (minocycline hydrochloride) extended-release tablets

therapies (e.g. ethinyl estradiol/norgestimate) and topical retinoids (e.g. tretinoin, tazarotene). The oral formulation of isotretinoin is also available for severe, recalcitrant, nodulo-cystic acne.

Table 1: Currently Available Treatments for Acne

<table>
<thead>
<tr>
<th>Categories</th>
<th>Drug Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical</strong></td>
<td></td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Multiple products</td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>Multiple products</td>
</tr>
<tr>
<td>Sulfa products</td>
<td>Sulfacetamide, Sulfacetamide/Sulfur</td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>Cream</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Clindamycin, Erythromycin</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Tretinoin, Adapalene, Tazarotene</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Erythromycin, Tetracycline, Doxycycline, Minocycline</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Isotretinoin</td>
</tr>
<tr>
<td>Hormonal therapies</td>
<td>Various oral contraceptives</td>
</tr>
</tbody>
</table>

Table 2: Oral Acne Products

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Formulations</th>
<th>Applicant/Owner</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline HCl</td>
<td>SOLODYN</td>
<td>Extended release tablets 55mg, 65 mg, 105 mg, 115 mg</td>
<td>Medicis</td>
<td>Only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.</td>
</tr>
<tr>
<td>Doxycycline hyclate</td>
<td>DORYX MPC</td>
<td>Delayed release tablets, 60 &amp; 120mg</td>
<td>Mayne pharma</td>
<td>In severe acne may be useful adjunctive therapy</td>
</tr>
<tr>
<td></td>
<td>Doxycycline hyclate</td>
<td>Delayed release tablets, 75, 100, 150, 200mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline Monohydrate</td>
<td>Monodox</td>
<td>Capsule; 50 mg, 75 mg, 100mg</td>
<td>AquaPharms</td>
<td>In severe acne may be useful adjunctive therapy</td>
</tr>
<tr>
<td>Tetracycline Hydrochloride</td>
<td>Tetracycline hydrochloride</td>
<td>Capsule; 250 mg, 500 mg</td>
<td>Heritage Pharms Inc</td>
<td>In severe acne may be useful adjunctive therapy</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>ABSORICA</td>
<td>Capsules; 10, 20, 25, 30, 35, 40 mg</td>
<td>Ranabxy</td>
<td>Severe recalcitrant nodular acne in patients 12 years of</td>
</tr>
</tbody>
</table>
Clinical Review
Patricia C. Brown, M.D.
NDA 209269
Minolira™ (minocycline hydrochloride) extended-release tablets

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Formulations</th>
<th>Applicant/Owner</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotretinoin</td>
<td>AMNESTEEM</td>
<td>Capsules; 10, 20, 40 mg</td>
<td>Mylan Pharms Inc.</td>
<td>Severe recalcitrant nodular acne (not studied in patients less than 12 years of age)</td>
</tr>
<tr>
<td></td>
<td>generic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CLARAVIS</td>
<td>Capsules; 10, 20, 30, 40 mg</td>
<td>Teva Pharms USA</td>
<td>Severe recalcitrant nodular acne (not studied in patients less than 12 years of age)</td>
</tr>
<tr>
<td></td>
<td>generic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MYORISAN</td>
<td>Capsules; 10, 20, 30, 40 mg</td>
<td>Douglas Pharm Dr Reddy’s Labs, Ltd</td>
<td>Severe recalcitrant nodular acne (not studied in patients less than 12 years of age)</td>
</tr>
<tr>
<td></td>
<td>generic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ZENATANE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drospirenone 3 mg/ethinyl estradiol .02 mg</td>
<td>Yaz</td>
<td>Tablets</td>
<td>Bayer Healthcare</td>
<td>Moderate acne for women at least 14 years old only if patient desires an oral contraceptive for birth control</td>
</tr>
<tr>
<td>Norgestimate 0.180, 0.215, 0.250 mg/ethinyl estradiol .035 mg</td>
<td>Ortho-cyclen</td>
<td>Tablets</td>
<td>Janssen Pharms</td>
<td>moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche</td>
</tr>
<tr>
<td>Norgestimate 0.250 mg/ethinyl estradiol .035 mg</td>
<td>Ortho Tri-cyclen</td>
<td>Tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Compiled by reviewer from websites “Drugs at FDA,” and “DAILYMED” accessed March 22, 2017.

2.3 Availability of Proposed Active Ingredient in the United States

Minocycline Hydrochloride has been marketed in the United States since FDA approval in 1971 as MINOCIN®, oral capsules.

Minocycline is a second generation, semi-synthetic derivative of tetracycline. It is indicated to treat a variety of infections caused by susceptible microorganisms (both
gram negative and gram positive), as adjuvant therapy for severe acne vulgaris (e.g. the tradename drug MINOCIN® and the generic drug DYNACIN®), and to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older (tradename SOLODYN®). Minocycline hydrochloride is also available as ARESTIN® Microspheres, a product indicated as an adjunct to scaling and root planning procedures for reduction of pocket depth in patients with adult periodontitis.

Minocycline hydrochloride is marketed by applicants in multiple strengths as oral capsules (immediate release) and extended release tablets. An extended release capsule form in various strengths was approved 7/11/2012 but was discontinued. Minocycline hydrochloride is also marketed as a sterile powder for injection 100 mg/vial. Generic formulations include oral tablets and capsules (both immediate release) and extended release tablets in a variety of strengths. Minocycline hydrochloride is also available in microsphere form as a subgingival sustained-release product.

2.4 Important Safety Issues with Consideration to Related Drugs

Minocycline is a member of the tetracycline class drugs (tetracycline, doxycycline, minocycline).

Labeling for minocycline includes the following:

1. Teratogenic Effects: Minocycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman.

2. Pseudomembranous colitis

3. Hepatotoxicity: Post-marketing cases of serious liver injury, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal) have been reported with minocycline use in treatment of acne.

4. The anti-anabolic action of the tetracyclines may cause an increase in BUN.

5. Central nervous system side effects including light-headedness, dizziness, or vertigo

6. Autoimmune syndromes: The long-term use of minocycline in the treatment of acne has been associated with drug-induced lupus-like syndrome, autoimmune hepatitis and vasculitis.

8. Photosensitivity

9. Serious skin/hypersensitivity reaction: Cases of anaphylaxis, serious skin reactions (e.g. Stevens Johnson syndrome), erythema multiforme, and drug rash
with eosinophilia and systemic symptoms (DRESS) syndrome have been reported postmarketing with minocycline use in patients with acne.

10. Tissue hyperpigmentation

From approved labeling for SOLODYN® (October 2013) adverse events seen in clinical trials at a rate greater than placebo (in at least 1% of clinical trial subjects) include fatigue, dizziness, pruritus, malaise, somnolence, urticaria, tinnitus, and arthralgia.

Labeling for minocycline includes the following from Contraindications from approved labeling for SOLODYN® (October 2013): “This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.”

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Under IND 120026 the applicant, Dr. Reddy’s Laboratories, Inc., has completed two pivotal relative BA/BE trials for MINOLIRA (minocycline HCl) extended-release tablets 135 mg in comparison to SOLODYN (80 mg + 55 mg, taken at the same time) under fasting and fed conditions. This is submitted pursuant to Section 505(b)(2) of the Federal Food Drug and Cosmetic Act and in accordance with Title 21 of Code of Federal Regulations.

The current application was received July 8, 2016 and is for a new formulation. According to section II/C/I/b of the Guidance for Industry, “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,” the effectiveness of an alternative formulation may be extrapolated from the efficacy data for another product on the basis of evidence of bioequivalence.

Presubmission Regulatory Activity:
Pre-IND
Written responses were submitted December 13, 2013 to questions submitted in a November 8, 2013 briefing package.

In the submitted questions, the applicant stated that DFD-10 (MINOLIRA) is being developed to be bioequivalent to SOLODYN and differs from SOLODYN in the following formulation aspects:

- MINOLIRA has different formulation design and composition compared to SOLODYN
- MINOLIRA differs in terms of product presentation with proposed strengths of 105 mg (52.5-52.5 mg), 135 mg (67.5-67.5 mg) Each tablet has a single score line, facilitating splitting of tablets into two equal halves. The figures within the parentheses represent the two split portions of each tablet.
The proposed strengths of MINOLIRA are intended to cover a patient population with a wider range of body weights for delivering the recommended dose of about 1 mg/kg similar to that of listed drug (LD).

The applicant stated that they intended to submit a 505(b)(2) NDA using SOLODYN as the listed drug (LD) for MINOLIRA.
IND
To open the IND, on June 4, 2015, the Agency received protocols for two relative BA/BE trials; DFD-10-CD-007 (fasting trial) and DFD-10-CD-008 (fed trial). These were to be open-label, randomized, 2-way, crossover (2 period, 2-sequence) comparative bioavailability trials under fasting and fed conditions of DFD-10 (MINOLIRA) (minocycline HCl) extended release 135 mg tablets versus the listed drug SOLODYN (80 mg + 55 mg).

An advice letter was sent July 20, 2015 that included CMC, pre-clinical, and clinical comments. Highlights include the following:

CMC:
Several specified impurity limits were noted to exceed levels recommended by ICH guidance for industry Q3A Impurities in New Drug Substances and the USP monograph for minocycline hydrochloride (e.g., impurity at \( \text{[redacted]} \)). The FDA requested that the sponsor re-evaluate these limits based on manufacturing and stability data and justify any limits that exceed ICH Q3A guidelines.

The FDA stated that further CMC data (e.g., content uniformity, stability) may be required to support future clinical studies relying on split tablets since this information has not been provided under the current IND.

Pharmacology/Toxicology:
The proposed specifications for a number of impurities in the drug substance were noted to be higher than the qualification threshold described in the ICH Q3A guidance document. These impurities are \( \text{[redacted]} \). The FDA requested that the sponsor provide scientific rationales with supporting toxicology information (e.g., a computational toxicology assessment described in the ICH guidance for industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk) to justify the proposed higher limits for these impurities.

Clinical:
To avoid contraceptive failure, the FDA requested that the sponsor advise female subjects who are using low dose oral contraceptives to use a second form of contraceptive during treatment with minocycline (SOLODYN\textsuperscript{\textregistered} labeling; Drug Interactions).
The FDA requested that, for females of childbearing potential, pregnancy testing be obtained at the final visit.

The FDA advised that: because tetracyclines have been shown to depress plasma prothrombin activity, subjects who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (SOLODYN® labeling: Section 7.1).

**Pre-NDA:**
Pre-NDA comments in response to applicant questions (received 4/20/2016 in a briefing package) were faxed to the sponsor May 20, 2016. Highlights include the following:

The use of a combination of 80 mg and 55 mg SOLODYN Extended Release Tablets as the reference for the comparative bioavailability studies appeared reasonable.

The impurity profiles of the sponsor’s drug product and SOLODYN are very similar. No additional nonclinical studies are needed to qualify the impurities in the sponsor’s drug product.

The applicant asked if the Agency concurs that the data from the pivotal comparative bioavailability studies are adequate to establish a clinical bridge to SOLODYN and no additional clinical studies are required to support a 505(b) (2) NDA submission. The Agency responded that provided that the data demonstrated bioequivalence, the applicant’s proposal appears reasonable; however, the final decision will be made at the time of NDA review.

The Agency stated in response to an applicant question, that under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply at this time to the applicant’s application, the applicant is exempt from these requirements.

2.6 Other Relevant Background Information

The applicant’s tablet formulation of minocycline hydrochloride is not currently marketed in foreign countries at this time. There is no additional foreign regulatory information.

3 Ethics and Good Clinical Practices
Clinical Review  
Patricia C. Brown, M.D.  
NDA 209269  
Minolira™ (minocycline hydrochloride) extended-release tablets

3.1 Submission Quality and Integrity

The overall organization of the submission and the ease of finding information were adequate.

3.2 Compliance with Good Clinical Practices

All clinical studies submitted in this New Drug Application were conducted in compliance with good clinical practice, including review and approval by an independent ethics committee, in accordance with 21 CFR Part 56 for Institutional Review Boards and 21 CFR Part 50 for informed consent.

Dr. Reddy’s Laboratories, limited, has conducted five pilot clinical pharmacology (comparative bioavailability) studies with prototype formulations of DFD-10 (MINOLIRA) and one with the final formulation of MINOLIRA. DRL has also conducted two pivotal studies (Studies DFD-10-CD-007 and DFD-10-CD-008) with the final formulation of MINOLIRA (Batch ET15030) in support of the 505(b)(2) NDA application.

These studies were all conducted in accordance with Good Clinical Practice (ICH-GCP E6 guidance) and per the local regulations after obtaining approval from Ethics Committees.

OSI Audit:
The Office of Study Integrity and Surveillance (OSIS), Division of New Drug Bioequivalence Evaluation (DNDBE) was consulted for biopharmaceutical inspections for clinical and analytical sites for trials DFD-10-CD-007 and DFD-10-CD-008 in order to verify the quality and integrity of study data in support of NDA 209269 submission. The clinical portion of both trials was conducted at Celeron, 2420 West Baseline Road, Tempe, Arizona 85283, USA. The analytical portion of both trials was conducted at

For the analytical site, DNDBE recommended accepting data without an on-site inspection. The rationale for this decision was as follows:

“Although the last inspection was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.”
3.3 Financial Disclosures

The applicant submitted form FDA 3454 for the 8 clinical trials DFD-10CD-001 through DFD-10-CD-008, certifying that they, the sponsor of the submitted trials, had not entered into any financial arrangements with the clinical investigators. A list of the clinical investigators for the 8 clinical trials was provided.

From Clinical Investigator Financial Disclosure Review Template:

<table>
<thead>
<tr>
<th>Was a list of clinical investigators provided:</th>
<th>Yes ☑</th>
<th>No ☐ (Request list from applicant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of investigators identified:</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Number of investigators who are sponsor employees (including both full-time and part-time employees):</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Application Technical Lead’s Assessment, by Yichun Sun, PhD, Branch V, Division of New Drug Products, II, dated March 10, 2017.

**Drug Product:**
Please see chemistry review by Hong Cai, Ph. D., dated Feb 28, 2017.

MINOLIRA™ (DFD-10) is formulated as minocycline hydrochloride extended-release tablets for oral administration. MINOLIRA are available in two strengths: 105mg and 135mg. Each 105 mg tablet contains 105 mg minocycline, equivalent to 113.4 mg of minocycline hydrochloride. Each 135 mg tablet contains 135 mg minocycline, equivalent to 145.8 mg of minocycline hydrochloride. The tablet is functionally scored, white to off-white rectangular shape with brown or golden colored speckles.

MINOLIRA tablets are manufactured by [redacted] with a mixture of 75% extended release (ER) pellets and 25% of the immediate release (IR) pellets.

The composition of minocycline hydrochloride extended release capsules is shown in the following table:
<table>
<thead>
<tr>
<th>Components</th>
<th>Function</th>
<th>Quality standard</th>
<th>% w/w</th>
<th>Amount per unit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minocycline hydrochloride $^*$</td>
<td>Drug Substance</td>
<td>USP</td>
<td>12.67</td>
<td>113.369</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td></td>
<td></td>
<td></td>
<td>105 mg 135 mg</td>
</tr>
<tr>
<td>Oparin clear</td>
<td></td>
<td></td>
<td></td>
<td>0 (0) (0)</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypropellose</td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td></td>
<td></td>
<td></td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sodium stearyl fumarate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isopropyl alcohol+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified water+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

USP - United States Pharmacopeia, NF - National Formulary, q.s.- quantity sufficient, IH - In-house
$^*$ Adjust the quantity of minocycline hydrochloride USP (if calculated assay value on anhydrous basis is less than 100% basis potency calculation).
$113.4 \text{ mg} \ of \ minocycline \ hydrochloride \ is \ equivalent \ to \ minocycline \ 105 \ mg$
$145.760 \text{ mg} \ of \ minocycline \ hydrochloride \ is \ equivalent \ to \ minocycline \ 135 \ mg$
+ Does not appear in the final product except in traces.

Source: Applicant’s NDA, Quality Overall Summary, Description Table and Composition of the Drug Product, Table 2.3.P.2-1, pp 1-2.
Excipients: "MINOLIRA extended release tablets (DFD-10) contain commonly used excipients for oral drugs. All excipients are either USP or NF grade except Opadry clear [a][b]. Opadry clear [a][b] contains two components: hydroxypropyl cellulose [b][c] and Hypromellose and both are compendial grade (USP or NF). The levels of the excipients in DFD-10 are within the quantitation limits of the currently marketed drugs based in FDA IIIG."

Impurities: The impurities observed in MINOLIRA (minocycline HCl) extended-release tablets are same as that of drug substance. They are [a][d] and are both degradation impurities. The CMC reviewer states that minocycline has a long history as the active ingredient human drugs. The above impurities are also controlled in the drug substances with their characterizations. The CMC reviewer’s conclusion regarding impurities is "Adequate."

Container closure system: "The containers are the white colored, open mouth plastic containers made of high density polyethylene (HDPE) with three configurations: 60cc (10 counts of 105mg and 135mg), 100cc for 30 counts of 105mg and 120cc for 30 counts of 135mg. The closures are the child resistant plastic caps with [b][d] liners (33mm & 38 mm)."

"The container and closure systems are adequate for their intended purpose from the drug product perspective."

Stability: "Based on the drug product assessment, an expiration dating period of 24 months for the product stored under 20° to 25° C (68° to 77° F) with excursion permitted between 15°C – 30°C (59°F-86°F) [see USP Controlled Room Temperature] and protect from light and moisture is granted to MINOLIRA extended-release tablets, 105mg and 135mg."

From Executive Summary of Quality Assessment: Facilities: "All the facilities are deemed acceptable in their identified functions and responsibilities to support approval of NDA 209269. The facility review of the NDA has been conducted by Consumer Safety Officer, Donald Lech."

Quality Microbiology: "The NDA is recommended for approval from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Peter Guerrieri."

Biopharmaceutics: "From the Biopharmaceutics perspective, NDA 209269 for minocycline HCl extended release tablets, 105 mg and 135 mg is recommended for approval. The review on the biopharmaceutics of the drug product of the NDA has been conducted by Dr. Hansong Chen." According to Dr. Chen’s review, provided
bioequivalence is demonstrated for the 135 mg strength product the Biowaiver is granted for the strength 105 mg…”

**OPQ Recommendations and Conclusion on Approvability:**
The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product.

The facility review team from the Office of Process and Facility (OPF) has issued an “Approval” recommendation for the facilities involved in this application.

However, the issues on labels/labeling are not completely resolved at this time. Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6) until the aforementioned issues are satisfactorily resolved

**A. Labeling Deficiencies:**

**A. Package Insert**

a) Highlight Section
- The established name should be revised to: “(minocycline hydrochloride) extended-release tablets”
- Dosage Forms and Strengths should be revised to: “Extended-release tablets: 105 mg and 135 mg of minocycline, functionally scored.”

b) Full Prescribing Information

#3: Dosage Forms and Strengths
- Need to add additional tablet descriptive characteristics of functionally scored, with brown or gold color speckles and also the salt equivalency statement as follows:

- MINOLIRA extended-release tablets are white to off-white, functionally scored, rectangular tablets with brown or gold color speckles and a single score line on both surfaces. MINOLIRA are available in the following two strengths.
  - 105 mg extended release tablets: ‘M1’ debossed on one surface, where ‘M’ and ‘1’ are on either side of the score line. Each tablet contains 105 mg minocycline, equivalent to 113.4 mg of minocycline hydrochloride.
  - 135 mg extended release tablets: ‘M3’ is debossed on one surface, where ‘M’ and ‘3’ are on either side of the score line. Each tablet contains 135 mg minocycline, equivalent to 145.8 mg of minocycline hydrochloride.
#11: Description

- Add the established name and dosage form to this section. The established name and the dosage form should be presented along with the proprietary name as follows:
  “MINOLIRA (minocycline hydrochloride) extended-release tablets”

- Add the salt equivalency statement and revise the extended and immediate release characteristic descriptions as follows:
  MINOLIRA (minocycline hydrochloride) extended-release tablets for oral administration contain 105 mg or 135 mg of minocycline, equivalent to 113.4 mg or 145.8 mg of minocycline hydrochloride, respectively. MINOLIRA extended-release tablets, 105 mg and 135 mg, contain 25% of minocycline as immediate release beads and 75% of minocycline as extended release beads.

- Consider listing the inactive ingredients in alphabetical order (see USP Chapter <1091>).

#16: How Supplied/Storage and Handling

- Revise the strengths and dosage forms to:
  MINOLIRA is supplied as functionally scored extended-release tablets containing minocycline hydrochloride equivalent to 105 mg or 135 mg of minocycline.

- The 105 mg extended release tablets are white to off-white, rectangular with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with ‘M1’ on one surface. On the face with debossing, ‘M’ and ‘1’ are on either side of the score line.

- The 135 mg extended release tablets are white to off-white, rectangular with brown or gold color speckles. The tablets have a single score line on both surfaces and are debossed with ‘M3’ on one surface. On the face with debossing, ‘M’ and ‘3’ are on either side of the score line.

- Add the following statement to the Storage Condition:
  Protect from light and moisture.

- Provide the Manufacturer/distributor name.
Clinical Review
Patricia C. Brown, M.D.
NDA 209269
Minolira™ (minocycline hydrochloride) extended-release tablets

B. Container Label Deficiencies:
- Present the product title as: “MINOLIRA™ (minocycline hydrochloride) extended-release tablets”.
- Revise “Rx” to “Rx only”.
- Add the salt equivalency statements:
  For 105 mg strength:
  Revise from (b) [4]
  “Each tablet contains 105 mg of minocycline (26.25 mg as immediate release beads and 78.75 mg as extended release beads), equivalent to 113.4 mg of minocycline hydrochloride.”

  For 135 mg strength:
  Revise from (b) [4]
  tablet contains 135 mg of minocycline (33.75 mg as immediate release beads and 101.25 mg as extended release beads), equivalent to 145.8 mg of minocycline hydrochloride.”
- Add the following storage conditions: Protect from light and moisture.

4.2 Clinical Microbiology
No new information regarding clinical microbiology was submitted in this 505(b)(2) application.

4.3 Preclinical Pharmacology/Toxicology

The sponsor intends to develop MINOLIRA (minocycline HCl) extended release oral tablets, 135 mg and 105 mg, for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older, through a 505(b)(2) regulatory pathway, using SOLODYN® (minocycline HCl) Extended Release Tablets as the listed drug.

No nonclinical study reports were submitted to the NDA except the impurity assessment.

Pharmacology/Toxicology Discussion of Nonclinical Findings
Minocycline's toxicity profile is consistent with the class effects of tetracyclines. In
embryofetal developmental studies conducted in rats and rabbits, minocycline induced skeletal malformations in fetuses. In a peri- and post-natal developmental study in rats, gross external anomalies were noted in F1 pups, including reduced body size, improperly rotated forelimbs, and reduced size of extremities. In fertility studies in rats, minocycline adversely affected spermatogenesis, including reduced sperm count and increased number of morphologically abnormal sperm cells. No genotoxic potential was noted for minocycline in a complete battery of genotoxicity assays. In a 2-year oral carcinogenicity study in rats, minocycline HCl was associated with follicular cell tumors of the thyroid gland in both genders. In another 2-year oral carcinogenicity study in mice, exposure to minocycline HCl did not result in a significantly increased incidence of neoplasms.

A number of impurities have been identified in the drug substance and the sponsor provided computational toxicology information, impurity profile comparative analysis and scientific rationales to support the proposed specifications for these impurities. The provided data and rationales are acceptable and no additional nonclinical studies are recommended.

**Pharmacology/Toxicology Recommendations:**
This NDA is approvable from a pharmacology/toxicology perspective. No postmarketing requirement is recommended for this NDA.

**Labeling recommendations:**
It is recommended that the underlined wording be inserted into and the strikeout wording be deleted from the sponsor proposed MINOLIRA label reproduced below.

8.1 Pregnancy
Risk Summary:

In animal reproduction studies, minocycline induced skeletal malformations in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at systemic exposure of approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients administered MINOLIRA [see Data].
Data:

Animal Data
Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus. [see Warnings and Precautions (5.1)].

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients administered MINOLIRA). Reduced mean fetal body weight was observed when minocycline was administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients administered MINOLIRA).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients administered MINOLIRA). No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

8.3 Female and Males of Reproductive Potential

Limited human studies suggest that minocycline may
Clinical Review
Patricia C. Brown, M.D.
NDA 209269
Minolira™ (minocycline hydrochloride) extended-release tablets

have a deleterious effect on spermatogenesis.

Infertility

In a fertility study in rats, minocycline adversely affected spermatogenesis when orally administered to male rats at doses resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients administered [see Nonclinical Toxicology (13.1)].

12.1 Mechanism of Action

The mechanism of action of MINOLIRA for the treatment of acne is unknown.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a carcinogenicity study in which minocycline HCl was orally administered to male and female rats once daily for up to 104 weeks at dosages up to

Reference ID: 4080447
200 mg/kg/day, minocycline hydrochloride was associated in both genders with follicular cell tumors of the thyroid gland, including increased incidences of adenomas, carcinomas and the combined incidence of adenomas and carcinomas in males, and adenomas and the combined incidence of adenomas and carcinomas in females. In a carcinogenicity study in which minocycline HCl was orally administered to male and female mice once daily for up to 104 weeks at dosages up to 150 mg/kg/day, exposure to minocycline hydrochloride did not result in a significantly increased incidence of neoplasms in either males or females.

Minocycline was not mutagenic in vitro in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic in vitro using human peripheral blood lymphocytes or in vivo in a mouse micronucleus test.

Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (which resulted in up to approximately 40 times the level of systemic exposure to minocycline observed in patients administered MINOLIRA). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients administered MINOLIRA) adversely affected spermatogenesis. Effects observed at 300 mg/kg/day included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

### 4.4 Clinical Pharmacology

Please see review by Yanhui Lu, Ph.D., Division of Clinical Pharmacology 3, dated March 9, 2017.
4.4.1 Mechanism of Action

The mechanism of action of minocycline hydrochloride for the treatment of acne is unknown.

4.4.2 Pharmacodynamics

The pharmacodynamics of minocycline hydrochloride for the treatment of acne are unknown.

4.4.3 Pharmacokinetics

To support this NDA, the Applicant has completed 2 pivotal relative BA/BE trials for the highest proposed strength, 135 mg, and submitted a biowaiver request for lower strengths.

The 2 pivotal relative BA/BE trials were:
- Trial DFD-10-CD-007 conducted under fasting conditions
- Trial DFD-10-CD-008 conducted under fed conditions

The results of the 2 pivotal trials showed that the 90% confidence interval (CI) of the geometric mean ratios of Cmax, AUC0-t, and AUC0-inf were within the no effect boundary of 80% to 125% under both fasting and fed conditions.

Trial 007:
This was a single-center, open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fasting conditions. Healthy male or female adults (18-55 years of age, inclusive) who were continuous non-smokers and had body mass index (BMI) ≥ 18.5 and ≤ 30.0 kg/m² and weight > 50 kg were enrolled.

The objectives under fasting conditions were to:
1) Assess comparative bioavailability of MINOLIRA (minocycline HCl) extended-release Tablets 135 mg (Dr. Reddy’s Laboratories Limited, India) versus SOLODYN® (minocycline HCl) Extended Release Tablets 80 mg + 55 mg (co-administered) (Medicis, The Dermatology Company, USA), following a single oral dose of 135 mg under fasting conditions in healthy human subjects.
2) Evaluate and compare the safety and tolerability profiles of each investigational product.
Trial 007:
This was a single-center, open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fed conditions. Healthy male or female adults (18-55 years of age, inclusive) who were continuous non-smokers and had body mass index (BMI) $\geq 18.5$ and $\leq 30.0$ kg/m$^2$ and weight > 50 kg were enrolled.

The objectives under fasting conditions were to:
1) Assess comparative bioavailability of MINOLIRA (minocycline HCl) extended-release Tablets 135 mg (Dr. Reddy’s Laboratories Limited, India) versus SOLODYN® (minocycline HCl) Extended Release Tablets 80 mg + 55 mg (co-administered) (Medicis, The Dermatology Company, USA), following a single oral dose of 135 mg under fed conditions in healthy human subjects.
2) Evaluate and compare the safety and tolerability profiles of each investigational product.

Trial 008:
This was a single-center, open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fed conditions. Healthy male or female adults (18-55 years of age, inclusive) who were continuous non-smokers and had body mass index (BMI) $\geq 18.5$ and $\leq 30.0$ kg/m$^2$ and weight > 50 kg were enrolled.

The objectives under fasting conditions were to:
1) Assess comparative bioavailability of MINOLIRA (minocycline HCl) extended-release Tablets 135 mg (Dr. Reddy’s Laboratories Limited, India) versus SOLODYN® (minocycline HCl) Extended Release Tablets 80 mg + 55 mg (co-administered) (Medicis, The Dermatology Company, USA), following a single oral dose of 135 mg under fed conditions in healthy human subjects.
2) Evaluate and compare the safety and tolerability profiles of each investigational product.

Table 4: PK parameters (mean ± SD) Trial 007

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DFD-10 (MINOLIRA) 135 mg (N=77)</th>
<th>Solodyn 135 mg (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>700.35 ± 261.25</td>
<td>656.76 ± 229.91</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng*h/mL)</td>
<td>10873.5 ± 3717.09</td>
<td>11013.6 ± 3475.67</td>
</tr>
<tr>
<td>$AUC_{0-inf}$ (ng*h/mL)</td>
<td>11410.4 ± 3891.05</td>
<td>11569 ± 3688.53</td>
</tr>
<tr>
<td>T $\frac{1}{2}$ (h)</td>
<td>15.6 ± 2.46</td>
<td>15.6 ± 2.62</td>
</tr>
<tr>
<td>T max (h)*</td>
<td>2.0 (1.0, 4.5)</td>
<td>4.0 (1.5, 6.0)</td>
</tr>
</tbody>
</table>

A single dose of DFD-10 (MINOLIRA) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) was administered in each of 2 study periods with a 7-day washout period between the two doses. *Tmax is presented as median (range).

Source: Applicant’s NDA, Table 11.1, Clinical Study Report DFD-10-CD-007, p. 42.

Table 5: PK parameters (mean ± SD) Trial 008

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DFD-10 (MINOLIRA) 135 mg (N=36)</th>
<th>Solodyn 135 mg (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>707.40 ± 189.82</td>
<td>749.60 ± 208.10</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng*h/mL)</td>
<td>11999.6 ± 2966.98</td>
<td>12851.2 ± 2821.86</td>
</tr>
<tr>
<td>$AUC_{0-inf}$ (ng*h/mL)</td>
<td>12724.4 ± 3341.2</td>
<td>13690.5 ± 3540.3</td>
</tr>
<tr>
<td>T $\frac{1}{2}$ (h)</td>
<td>17.1 ± 3.03</td>
<td>17.6 ± 4.42</td>
</tr>
<tr>
<td>T max (h)*</td>
<td>3.5 (1.5, 6.0)</td>
<td>5.0 (2.0, 6.0)</td>
</tr>
</tbody>
</table>

A single dose of DFD-10 (MINOLIRA) 135 mg or SOLODYN 135 mg (1 × SOLODYN 80 mg tablet + 1 × SOLODYN 55 mg tablet [co-administered]) was administered in each of 2 study periods with a 7-day washout period between the two doses. *Tmax is presented as median (range).

Source: Applicant’s NDA, Table 11.1, Clinical Study Report DFD-10-CD-008, p. 42.
Clinical Review
Patricia C. Brown, M.D.
NDA 209269
Minolira™ (minocycline hydrochloride) extended-release tablets

Relative BA Assessments Trials 007 and 008:

Table 6: Summary of Relative BA Results Trials 007 and 008

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fasting Conditions</th>
<th>Fed Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Trial DFD-10-CD-007)</td>
<td>(Trial DFD-10-CD-008)</td>
<td></td>
</tr>
<tr>
<td>(N=77)</td>
<td>(N=36)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>105.92 99.67 – 112.56</td>
<td>94.68 89.62 – 100.03</td>
</tr>
<tr>
<td>AUC0-t (ng*h/mL)</td>
<td>97.76 92.32 – 103.52</td>
<td>92.84 89.97 – 95.80</td>
</tr>
<tr>
<td>AUC0-inf (ng*h/mL)</td>
<td>97.76 92.45 – 103.38</td>
<td>92.69 89.71 – 95.78</td>
</tr>
</tbody>
</table>

Test = MINOLIRA tablets 135 mg
Reference = SOLODYN tablets 135 mg administered as a combination of SOLODYN ER tablets, 80 mg and 55 mg

Source: Clinical Pharmacology Review of NDA 209269 by Yanhui Lu, PhD, Table 1, p. 3.

The clinical pharmacology reviewer notes that under fed conditions (trial 008), the upper limits of the 90% CI for AUC0-t and AUC0-inf were less than 100%. They were 95.80% and 95.78%, respectively and this suggests that the exposure of minocycline following administration of MINOLIRA 135 mg ER tablet was slightly less than that of the approved SOLODYN 135 mg tablets (1 × 80 mg tablet and 1 × 55 mg tablet co-administered). The clinical pharmacology reviewer states that although this small magnitude of difference in drug exposure would be unlikely to result in lack of efficacy, the use of MINOLIRA as a listed drug for future 505(b)(2) NDA applications should be carefully considered due to the risk of bio-creep.

Clinical Pharmacology Labeling Recommendations:

The underlined text indicates insertion recommended by the clinical pharmacology reviewer and the strikethrough text indicates recommended deletion.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

MINOLIRA Tablets 135 mg is bioequivalent to SOLODYN, 135 mg (80 mg + 55 mg).

The pharmacokinetics of minocycline following oral administration of a single dose of MINOLIRA (135 mg) was investigated in 77 healthy male and female adult subjects under fasting conditions. The pharmacokinetic parameters of minocycline under fasting conditions are presented in Table 3.
Clinical Review  
Patricia C. Brown, M.D.  
NDA 209269  
Minolira™ (minocycline hydrochloride) extended-release tablets

### Table 3: Pharmacokinetic Parameters of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fasting Conditions (N = 77)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>700 ± 261</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)*</td>
<td>2.0 (1.0–4.0) hrs</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.hr/mL)</td>
<td>10874 ± 3717</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>15.6 ± 2.46</td>
</tr>
</tbody>
</table>

*Median (Min-Max)

In a separate trial, a single dose of MINOLIRA (135 mg) was administered orally with a high-fat, high-calorie meal that included dairy products to 36 healthy male and female adult subjects. The estimated calorie content of the meal was 848 Kcal, consisting of 145 Kcal from protein, 250 Kcal from carbohydrates, and 453 Kcal from fat. The pharmacokinetic parameters of minocycline under fed conditions are presented in Table 4.

### Table 4: Pharmacokinetic Parameters of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fed Conditions (N = 36)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>707 ± 190</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)*</td>
<td>3.5 (1.5–6.0) hrs</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (ng.hr/mL)</td>
<td>12000 ± 2967</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>17.1 ± 3.03</td>
</tr>
</tbody>
</table>

*Median (Min-Max)

**Clinical Pharmacology Recommendation:**
The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 finds NDA 209269 acceptable provided labeling comments are adequately addressed by the Applicant.
5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Type of trial</th>
<th>Trial Design</th>
<th>Subject population</th>
<th>Sites</th>
<th># of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFD-10-CD-006</td>
<td>Pilot relative BA/BE, fasting</td>
<td>Open-label, randomized, 3-treatment, 3 period crossover</td>
<td>Asian Males, age range 18 to 45 years, inclusive</td>
<td>(1) Ahmedabad, India</td>
<td>18 dosed, 18 BE assessed, 17 assessed for effect of applesauce</td>
</tr>
<tr>
<td>DFD-10-CD-007</td>
<td>Relative BA/BE fasting</td>
<td>Open-label, randomized, 2-treatment, 2-sequence, crossover</td>
<td>Males and females, age range 18 to 55 years, inclusive</td>
<td>(1) Tempe, Arizona</td>
<td>79 dosed, 77 BE assessed-fasting</td>
</tr>
<tr>
<td>DFD-10-CD-008</td>
<td>Relative BA/BE fed</td>
<td>Open-label, randomized, 2-treatment, 2-sequence, crossover</td>
<td>Males and females, age range 18 to 55 years, inclusive</td>
<td>(1) Tempe, Arizona</td>
<td>36 dosed 36 BE assessed-fed</td>
</tr>
</tbody>
</table>

Source: Applicant’s NDA submission compiled from clinical study reports, DFD-10-CD 006, 007 and 008.

5.2 Review Strategy

Five pilot comparative bioavailability studies (DFD-10-CD-001 through DFD-10-CD-005) with prototype formulations of DFD-10 (MINOLIRA) were conducted to evaluate and compare the single dose oral bioavailability MINOLIRA with SOLODYN under fasting or fed conditions.

One pilot study (DFD-10-CD-006) with the final formulation/registration batch was conducted to evaluate and compare the single dose oral bioavailability of MINOLIRA with SOLODYN under fasting conditions. The study population consisted of 18 male Asian (Indian) subjects.

The applicant has also conducted two pivotal studies (Trials DFD-10-CD-007 and DFD-10-CD-008) with the final formulation of MINOLIRA (Batch ET15030) in support of the 505(b)(2) NDA application. These two trials were reviewed in detail for safety. The study
population for these two trials, based in the US, consisted of males and females, age range 18 to 55 years, inclusive.

5.3 Discussion of Individual Studies/Clinical Trials

BA/BE Trials: Review of Trials 007 and 008:
The two pivotal trials performed as part of the development program were of similar design. They were 2-sequence, crossover, open-label, randomized 2-treatment trials.

Please see clinical pharmacology review by Yanhui Lu, Ph.D., dated March 9, 2017, for further details.

Results:

Demographics:

Trial 007:
Of the 79 subjects who were dosed in the trial, 77 subjects (14 females and 63 males) with a mean age of 39.2 years (range = 19 to 55 years) were included in the relative bioavailability assessment. The subjects included in the assessment consisted of 67 Whites; 8 subjects were Black/ African American; 1 subject was Black or African American, American Indian, or Alaska Native (mixed race); and 1 subject was White, Black, or African American (mixed race). With respect to ethnicity, 55 subjects were Hispanic or Latino and 22 were non-Hispanic.

Table 7: Demographic Summary (Trial 007)

<table>
<thead>
<tr>
<th>Trait</th>
<th>Treatment Sequence</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AB</td>
<td>BA</td>
<td>Overall</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>10 (26%)</td>
<td>4 (10%)</td>
<td>14 (18%)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>28 (74%)</td>
<td>35 (90%)</td>
<td>63 (82%)</td>
</tr>
<tr>
<td>Race</td>
<td>Black or African American</td>
<td>4 (11%)</td>
<td>4 (10%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td></td>
<td>Black or African American, American Indian/Alaska Native</td>
<td>1 (2.6%)</td>
<td>0</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>32 (84%)</td>
<td>35 (90%)</td>
<td>67 (87%)</td>
</tr>
<tr>
<td></td>
<td>White, Black or African American</td>
<td>1 (2.6%)</td>
<td>0</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic or Latino</td>
<td>27 (71%)</td>
<td>28 (72%)</td>
<td>55 (71%)</td>
</tr>
<tr>
<td></td>
<td>Not Hispanic or Latino</td>
<td>11 (29%)</td>
<td>11 (28%)</td>
<td>22 (29%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>N</td>
<td>38</td>
<td>39</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>40.2 ± 9.76</td>
<td>38.3 ± 10.17</td>
<td>39.2 ± 9.95</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>42.0</td>
<td>39.0</td>
<td>42.0</td>
</tr>
</tbody>
</table>
Demographic features of the populations studied generally appear balanced across treatment sequence groups. It is noted however, that female subjects constituted 26% of the treatment sequence AB group versus 10% of the treatment sequence BA group.

Trial 008:
All subjects who entered the trial were dosed and completed the relative bioavailability assessment (6 females and 30 males). The mean age was 38.9 (range 18 – 54 years). The subjects completing the trial consisted of 33 White and 3 Black/African American subjects. With respect to ethnicity, 28 subjects were Hispanic or Latino and 8 were non-Hispanic.

<table>
<thead>
<tr>
<th>Trait</th>
<th>Treatment Sequence</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AB</td>
<td>BA</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (11%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (89%)</td>
<td>14 (78%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (6%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>White</td>
<td>17 (94%)</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>15 (83%)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>3 (17%)</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

Reference ID: 4080447
Demographic features of the populations studied generally appear balanced across treatment sequence groups. It is noted however, that non-Hispanic Latino subjects constituted 17% of the treatment sequence AB group versus 28% of the treatment sequence BA group.

Subject Disposition: Trial 007

Table 9: Summary of Subject Disposition (Trial 007)

<table>
<thead>
<tr>
<th>Category</th>
<th>AB</th>
<th>BA</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosed</td>
<td>39 (100%)</td>
<td>40 (100%)</td>
<td>79 (100%)</td>
</tr>
<tr>
<td>Completed Trial</td>
<td>37 (95%)</td>
<td>39 (98%)</td>
<td>76 (96%)</td>
</tr>
<tr>
<td>Dropped from Trial</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Personal Reason</td>
<td>1 (3%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Treatment A: A single oral dose of 135 mg MINOLIRA (minocycline HCl) (1 x 135 mg Extended Release Tablet) on Day 1 following an overnight fast
Treatment B: A single oral dose of 135 mg SOLODYN® (1 x 80 mg Extended Release Tablet + 1 x 55 mg Extended Release Tablet [coadministered]) on Day 1 following an overnight fast
Source: Applicant’s NDA, Table 10.1, Clinical Study Report DFD-10-CD-007, p. 37.
Clinical Review  
Patricia C. Brown, M.D.  
NDA 209269  
Minolira™ (minocycline hydrochloride) extended-release tablets

Treatment Sequence AB:  
_Dropped from trial:_  
Lost to Follow-Up:  
Subject #  (42-year-old White female healthy volunteer of Hispanic ethnicity)  
Failed to complete end-of trial phone call, attempts to reach subject were unsuccessful.

Personal Reason:  
Subject #  (53-year-old American Indian or Alaska Native female healthy volunteer). Subject decided to withdraw from the study (after dosing) on Day 1 of Period 1 due to personal reasons.

Treatment Sequence BA:  
_Dropped from trial:_  
Lost to Follow-Up:  
Subject # (46-year-old White male healthy volunteer of Hispanic ethnicity)  
Subject failed to return to the clinic on Day -1 of Period 2. Attempts to reach the subject were unsuccessful.

For trial 007, subjects not completing the trial were generally balanced across treatment sequences.

Subject Disposition: Trial 008

**Table 10: Summary of Subject Disposition (Trial 008)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Sequence</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AB</td>
<td>BA</td>
</tr>
<tr>
<td>Dosed</td>
<td>18 (100%)</td>
<td>18 (100%)</td>
</tr>
<tr>
<td>Completed Trial</td>
<td>18 (95%)</td>
<td>18 (96%)</td>
</tr>
<tr>
<td>Dropped from Trial</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment A: A single oral dose of 135 mg MINOLIRA (minocycline HCl) (1 x 135 mg Extended Release Tablet) on Day 1 under fed conditions  
Treatment B: A single oral dose of 135 mg SOLODYN® (1 x 80 mg Extended Release Tablet + 1 x 55 mg Extended Release Tablet [coadministered]) on Day 1 under fed conditions  
Source: Applicant’s NDA, Table 10.1, Clinical Study Report DFD-10-CD-008, p. 37.

6 Review of Efficacy

No efficacy studies were conducted with this NDA. Because this is a 505(b)2 application, this NDA relies on the Agency’s findings of effectiveness for the listed drug
SOLODYNN®. The scientific justification for this reliance is provided by data from two bioequivalence trials performed in humans, trials 007 and 008.

7 Review of Safety

Safety Summary
Because this is a 505(b)2 application, this NDA relies on the Agency’s findings of safety for the listed drug SOLODYNN®. The scientific justification for this reliance is provided by data from two relative BA/BE trials 007 and 008. The safety of minocycline hydrochloride extended release tablets, 135 mg, for the indication of “treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older” was established with the approval (May 8, 2006) of NDA 50-808, SOLODYNN® (minocycline HCl) Extended Release Tablets, 135 mg.

The applicant submitted additional safety data from the two pharmacokinetic trials performed to evaluate bioequivalence, 007 and 008.

There were no deaths, serious adverse events or significant adverse events. Attribution of adverse events to specific treatment whether MINOLIRA or SOLODYNN is rendered imprecise due to the cross-over design of trials 007 and 008. For subjects exposed to MINOLIRA, the most common TEAEs in descending order of frequency were: pruritus 6/55 (11%), headache 6/55 (11%), and arthralgia 3/55 (5%).

For the reference drug SOLODYNN, labeled adverse reactions include pruritus, headache, and arthralgia.

All adverse events for subjects exposed to MINOLIRA were of mild severity except for two cases of headache and one case each of arthralgia, pain in extremity, dizziness and anxiety which were classified as moderate in severity.

Evaluation of laboratory findings and vital signs did not reveal clinically significant safety signals.

7.1 Methods

Safety data, including adverse events and laboratory testing, from the two pharmacokinetic trials, 007 and 008, was evaluated.
7.1.1 Studies/Clinical Trials Used to Evaluate Safety

<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Type of trial</th>
<th>Trial Design</th>
<th>Subject population</th>
<th>Sites</th>
<th># of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFD-10-CD-006</td>
<td>Pilot relative BA/BE, fasting</td>
<td>Open-label, randomized, 3-treatment, 3 period crossover</td>
<td>Asian Males, age range 18 to 45 years, inclusive</td>
<td>(1) Ahmedabad, India</td>
<td>18 dosed, 18 BE assessed, 17 assessed for effect of applesauce</td>
</tr>
<tr>
<td>DFD-10-CD-007</td>
<td>Relative BA/BE fasting</td>
<td>Open-label, randomized, 2-treatment, 2-sequence, crossover</td>
<td>Males and females, age range 18 to 55 years, inclusive</td>
<td>(1) Tempe, Arizona</td>
<td>79 dosed, 77 BE assessed-fasting</td>
</tr>
<tr>
<td>DFD-10-CD-008</td>
<td>Relative BA/BE fed</td>
<td>Open-label, randomized, 2-treatment, 2-sequence, crossover</td>
<td>Males and females, age range 18 to 55 years, inclusive</td>
<td>(1) Tempe, Arizona</td>
<td>36 dosed 36 BE assessed-fed</td>
</tr>
</tbody>
</table>

Source: Applicant’s NDA submission compiled from clinical study reports, DFD-10-CD 006, 007 and 008.

7.1.2 Categorization of Adverse Events

For trials 007 and 008, adverse events were coded using the MedDRA dictionary (version 18.1) for preferred terms, and system organ class. The adverse event categorization and preferred terms used in trials 007 and 008 appear satisfactory.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

For trials 007 and 008 in the clinical development program, the applicant pooled adverse event data.

TEAEs were defined as AEs that occurred on or after the date and time of study drug administration, or those that first occurred pre-dose but worsened in frequency or severity after study drug administration.

MedDRA® dictionary Version 18.1 was used to classify all TEAEs reported during the studies by System-Organ-Class (SOC) and Preferred Term (PT).

Each subject could contribute only once to each of the incidence rates for a specific TEAE following a given treatment, regardless of the number of occurrences; the highest severity or highest causality was presented, as appropriate.
7.2 Adequacy of Safety Assessments

Safety was monitored through physical examination, vital sign measurements, orthostatic vital sign measurements, 12-lead electrocardiograms (ECGs), AEs, and clinical laboratory tests. Summary statistics for the laboratory safety tests, 12-lead ECGs and vital signs were computed and provided, as deemed clinically appropriate.

The safety assessments noted above were adequate for the type of studies performed; single-center, 2-sequence, crossover, open-label, randomized 2-treatment trials.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the three clinical pharmacology studies conducted with the final DFD-10 formulation (MINOLIRA) and SOLODYN, a total of 133 healthy human subjects were exposed to between one and three 135 mg single doses of minocycline hydrochloride MINOLIRA or SOLODYN or both) with intervals of at least one week between consecutive doses.

In specific, 132 subjects received one or two doses of MINOLIRA (115 subjects received one dose of DFD-10 and 17 subjects received two doses of MINOLIRA). In the same studies, 132 subjects received a 135 mg dose of minocycline hydrochloride constituted by co-administration of SOLODYN 80 mg and SOLODYN 55 mg tablets. (Note: Since the 135 mg dose strength of is no longer marketed by Medicis, a combination of one 80 mg SOLODYN and one 55 mg SOLODYN taken together served as the reference treatment in all clinical pharmacology studies.)

<table>
<thead>
<tr>
<th>Trial #</th>
<th>DFD-10 (mg)</th>
<th>SOLODYN (80 + 55 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No doses</td>
<td>1 single dose</td>
</tr>
<tr>
<td>006</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>007</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>008</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td>Total # of subj.</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>% of total</td>
<td>0.75</td>
<td>86.47</td>
</tr>
</tbody>
</table>

Source: Applicant’s NDA, Table 2.7.4.9-1, 2.7.4 Summary of Clinical Safety, Appendix, p 33.
# Table 12: Demographics of Safety Population (All Subj. Dosed: Trials 0006, 007, 008)

<table>
<thead>
<tr>
<th>Trait</th>
<th>006</th>
<th>007</th>
<th>008</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>64</td>
<td>30</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>-</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>American Indian or Alaska</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American,</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>-</td>
<td>68</td>
<td>33</td>
</tr>
<tr>
<td>White, Black or African</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (Indian)</td>
<td>18</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td>56</td>
<td>28</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>18</td>
<td>23</td>
<td>8</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>79</td>
<td>36</td>
</tr>
<tr>
<td>Mean + SD</td>
<td>32.89 + 6.07</td>
<td>39.5 + 9.97</td>
<td>38.9 + 11.07</td>
</tr>
<tr>
<td>Median</td>
<td>34.50</td>
<td>42.0</td>
<td>40.5</td>
</tr>
<tr>
<td>Minimum - Maximum</td>
<td>19 - 44</td>
<td>20 – 54</td>
<td>18 - 55</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>79</td>
<td>36</td>
</tr>
<tr>
<td>Mean + SD</td>
<td>58.37 + 6.08</td>
<td>75.79 + 10.963</td>
<td>75.14 + 11.973</td>
</tr>
<tr>
<td>Median</td>
<td>57.75</td>
<td>73.9</td>
<td>74.2</td>
</tr>
<tr>
<td>Minimum - Maximum</td>
<td>51.30 – 71.00</td>
<td>58.5 – 106.6</td>
<td>51.9 -99.6</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>79</td>
<td>36</td>
</tr>
<tr>
<td>Mean + SD</td>
<td>164.58 + 4.49</td>
<td>170.1 + 10.34</td>
<td>169.9 + 10.88</td>
</tr>
<tr>
<td>Median</td>
<td>165.25</td>
<td>169</td>
<td>171</td>
</tr>
<tr>
<td>Minimum - Maximum</td>
<td>157 - 174</td>
<td>151 – 201</td>
<td>147 - 191</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>8</td>
<td>79</td>
<td>36</td>
</tr>
<tr>
<td>Mean + SD</td>
<td>21.55 + 2.14</td>
<td>26.138 + 2.3847</td>
<td>25.991 + 2.9682</td>
</tr>
<tr>
<td>Median</td>
<td>21.02</td>
<td>26.33</td>
<td>27.22</td>
</tr>
</tbody>
</table>

Source: Applicant’s NDA, Adapted from Table 2.7.4.9-3, 2.7.4 Summary of Clinical Safety, Appendix, pp 35 – 36 and Clinical Study Report DFD-10-CD-006, Appendix 16.2.4.
Table 13: Race and Ethnicity Compared with US Population (Trials 007 & 008)

<table>
<thead>
<tr>
<th>Trait</th>
<th>007</th>
<th>008</th>
<th>US Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>8 (10%)</td>
<td>3 (8%)</td>
<td>13.8%</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1 (1%)</td>
<td>-</td>
<td>1.7 %</td>
</tr>
<tr>
<td>Black or African American,</td>
<td>1 (1%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>68 (86%)</td>
<td>33 (92%)</td>
<td>76.2%</td>
</tr>
<tr>
<td>White, Black or African American</td>
<td>1 (1%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>-</td>
<td>-</td>
<td>6 %</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>56 (71%)</td>
<td>28 (78%)</td>
<td>17.1 %</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>23 (29%)</td>
<td>8 (22%)</td>
<td>82.9%</td>
</tr>
</tbody>
</table>

U. S. Census Bureau, 2013 American Community Survey, Table DP05 - ACS Demographic and Housing Estimates, 2013 American Community Survey 1-Year Estimates.

Source: Applicant’s NDA, Adapted from Table 2.7.4.9-3, 2.7.4 Summary of Clinical Safety, Appendix, pp 35 – 36

The subject population consisted of male and female subjects, ages to be included 18 to 55 years (inclusive), healthy, non-smoking.

As compared with the U.S. population, the demographics of the populations dosed in studies 007 and 008 show a moderate over representation of Caucasians and an under representation of Black /African Americans and Asians. In these two trials Hispanic or Latino ethnicity was over represented. The majority of subjects were male 82% (M:F 94/21) with a mean age of 39.33 (range 18 to 55 years). In this reviewer’s opinion, demographics were broadly representative of the U.S. population. Over or under representations see are not expected to materially affect the results of the pivotal relative BA/BE trials.

7.2.2 Explorations for Dose Response

Dose response for adverse events was not explored in the 2 dose pharmacokinetic trials, 007 and 008.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing (regarding adverse events) was conducted for this application.
7.2.4 Routine Clinical Testing

Routine clinical testing performed was appropriate for the 2 dose pharmacokinetic trials, 007 and 008.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic, clearance, and interaction workup were not performed as part of this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The safety of minocycline hydrochloride extended release tablets, 135 mg, for the indication of “treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older” was established with the approval (May 8, 2006) of NDA 50-808, SOLODYN® (minocycline HCl) Extended Release Tablets, 135 mg. The pharmacokinetic trials, 007 and 008, included in this submission were not designed to evaluate adverse events for labeling purposes.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in trials 006, 007 or 008.

7.3.2 Nonfatal Serious Adverse Events

No Serious Adverse Events were reported in trials 006, 007, or 008.

7.3.3 Dropouts and/or Discontinuations

There were no subject discontinuations due to adverse events in trials 006, 007, or 008.

7.3.4 Significant Adverse Events

No clinically significant adverse events were reported for trials 006, 007 or 008.

7.3.5 Submission Specific Primary Safety Concerns

This submission did not reveal clinically significant safety concerns. The majority of adverse events reported were of mild severity and were generally consistent with those
found in approved labeling for the listed drug (NDA 50-808) SOLODYNN® (minocycline HCl) Extended Release Tablets.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

**Trial 006:**
In this 3 period trial, each enrolled subject received a single 135 mg dose of minocycline hydrochloride tablet(s) in each study period with a wash-out of at least 7 days separating consecutive doses. Therefore, in total, the subjects (with the exception of subject no. 10) received 3 single doses of minocycline hydrochloride extended release tablets in the course of the study.

Table 14: TEAE’s Trial DFD-10-CD-006

<table>
<thead>
<tr>
<th>Subject #, Period #</th>
<th>Adverse Event</th>
<th>Investigational Product</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>09(1)</td>
<td>Nausea</td>
<td>R: SOLODYNN Ext Rel Tab 80 mg and 55mg co-administered</td>
<td>Mild</td>
</tr>
<tr>
<td>08(3)</td>
<td>Nausea</td>
<td>T_A: MINOLIRA ext rel tablets 135 mg with applesauce</td>
<td>Mild</td>
</tr>
</tbody>
</table>

**Pivotal Trial 007 - Fasting:**
This was an open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fasting conditions.

Subjects were randomized to receive either MINOLIRA (Treatment A: Test) or SOLODYNN® (Treatment B: Reference) in 2 study periods in the following sequences: AB or BA. In each period, a pre-dose blood sample was collected from all subjects prior to the scheduled dosing time. Subjects then received a single 135 mg oral dose of minocycline HCl as Extended Release Tablets (either MINOLIRA (minocycline HCl) extended-release tablets 135 mg or co-administration of SOLODYNN® 80 mg and SOLODYNN® 55 mg Extended Release Tablets), followed by blood sampling up to 72 hours post-dose for the determination of minocycline PK. The washout period was 7 days between the doses of minocycline HCl.

In trial 007, 79 subjects were dosed at least once and 16 (20%) of subjects had a total of 41 treatment-emergent adverse events. Of the TEAEs, 35 were mild in intensity and 6 were moderate.
### Table 15: TEAE Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) and Those of Moderate Severity Noted: Trial 007

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Number of adverse events</td>
<td>29 (100%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Crying</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>0</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Fall</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (10%) moderate x 1</td>
<td>2 (17%) Moderate</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (3%) moderate</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (3%) moderate</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (14%) Moderate x 2</td>
<td>3 (25%) Moderate</td>
</tr>
<tr>
<td>Paresthesis</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (3%) moderate</td>
<td>0</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (3%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (21%) Moderate</td>
<td>2 (17%) Moderate</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

**Treatment A** = A single oral dose of 135 mg MINOLIRA (minocycline HCl) (1 x 135 mg extended-release tablet) on Day 1 following an overnight fast

**Treatment B** = A single oral dose of 135 mg SOLODYN® (1 x 80 mg Extended Release Tablet + 1 x 55 mg Extended Release Tablet [co-administered]) on Day 1 following an overnight fast

Source: Applicant’s NDA, Adapted from Table 14.3.1.2 and Appendix 16.2.7.2, Clinical Study Report DFD-10-CD-007.
### Table 16: TEAE Frequency by Treatment – Number of Subjects Reporting Events (% of Subjects Dosed): Trial 007

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects dosed</td>
<td>78 (100%)</td>
<td>78 (100%)</td>
<td>79 (100%)</td>
</tr>
<tr>
<td>Number of subjects with TEAEs</td>
<td>13 (17%)</td>
<td>7 (9%)</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Crying</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Fall</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (5%)</td>
<td>3 (4%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Acne</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Treatment A = A single oral dose of 135 mg MINOLIRA (minocycline HCl) (1 x 135 mg Extended Release Tablet) on Day 1 following an overnight fast
Treatment B = A single oral dose of 135 mg SOLODYN® (1 x 80 mg Extended Release Tablet + 1 x 55 mg Extended Release Tablet [co-administered]) on Day 1 following an overnight fast
Source: Applicant’s NDA, Adapted from Table 12-3, Clinical Study Report DFD-10-CD-007.

(Each subject could contribute only once to each of the incidence rates for a specific TEAE following a given treatment, regardless of the number of occurrences; the highest severity or highest causality was presented, as appropriate.)

Headache was the most common AE, reported a total of 7 times by 6 (8%) subjects, with 4 subjects following MINOLIRA (minocycline HCl) and 3 subjects following SOLODYN®
For the reference drug SOLODYN,® labeled adverse reactions include headache, dizziness, blurred vision, arthralgia, and pruritus.

**Pivotal Trial 008 - Fed:**
This was an open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fed conditions.

Subjects were randomized to receive either MINOLIRA (Treatment A: Test) or SOLODYN® (Treatment B: Reference) in two study periods in the following sequences: AB or BA. In each period, a pre-dose blood sample was collected from all subjects at least 1 hour prior to the scheduled dosing time. Subjects then received a single 135 mg oral dose of minocycline HCl as Extended Release Tablets [either MINOLIRA (minocycline HCl) extended-release tablets 135 mg or co-administration of SOLODYN® 80 mg and SOLODYN® 55 mg Extended Release Tablets], exactly 30 minutes after the start of a standard high-fat and high calorie breakfast on Day 1. The dosing was followed by blood sampling up to 72 hours post-dose for the determination of minocycline PK. The washout period was 7 days between the 2 doses of minocycline HCl.

In trial 008, 36 subjects were dosed at least once and 10 (28%) of subjects had a total of 14 treatment-emergent adverse events. Of the TEAEs, 13 were mild in intensity and 1 was moderate.

### Table 17: TEAE Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) and One of Moderate Severity Noted: Trial 008

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Number of adverse events</td>
<td>5 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>0</td>
<td>2 (22%)</td>
</tr>
<tr>
<td></td>
<td>moderate x 1</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (20%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (40%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Crying</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1 (20%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0</td>
<td>1(11%)</td>
</tr>
</tbody>
</table>

Treatment A: A single oral dose of 135 mg MINOLIRA (minocycline HCl)(1 x 135 mg extended-release Tablet) on Day 1 under fed conditions
Treatment B: A single oral dose of 135 mg SOLODYN® (1 x 80 mg Extended Release Tablet + 1 x 55 mg Extended Release Tablet [coadministered]) on Day 1 under fed conditions
Table 18: TEAE Frequency by Treatment – Number of Subjects Reporting Events (% of Subjects Dosed): Trial 008

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Number of subjects dosed</td>
<td>36 (100%)</td>
<td>36 (100%)</td>
</tr>
<tr>
<td>Number of subjects with TEAEs</td>
<td>4 (11%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>0</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Crying</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Treatment A: A single oral dose of 135 mg MINOLIRA (minocycline HCl) (1 x 135 mg extended-release tablet) on Day 1 under fed conditions
Treatment B: A single oral dose of 135 mg SOLODYN® (1 x 80 mg Extended Release Tablet + 1 x 55 mg Extended Release Tablet [coadministered]) on Day 1 under fed conditions

Headache was the most common AE, reported a total of 7 times by 4 (11%) subjects, with 2 subjects following MINOLIRA and 2 subjects following SOLODYN®.

For the reference drug SOLODYN®, labeled adverse reactions include headache, dizziness, blurred vision, arthralgia, and pruritus.

**Combined Pivotal Trials 007 & 008:**
A total of 55 TEAEs were reported by 27 (23.48%) of the 115 subjects enrolled in the fasting and fed pivotal comparative bioavailability trials (007 and 008). A total of 34 TEAEs were reported in 17 subjects (14.91%) who received MINOLIRA and 21 TEAEs in 13 subjects (11.40%) who received SOLODYN®.
The most common TEAEs reported in the two trials, in descending order of frequency, were headache (11/55; 20%), pruritus (8/55; 14.55%) joint pain or arthralgia (5/55; 9.09%) and dizziness (3/55; 5.45%). Two incidents each (3.64%) of elevated serum triglyceride levels, nausea, nasal congestion and erythema (redness of skin) were reported in the trials. Except for elevated serum triglyceride levels (both incidents reported after administration of SOLODYN®) and pruritus (6 out of 8 incidents reported after MINOLIRA), the distribution of adverse events was fairly equitable between the two treatments.

For SOLODYN®, the most common TEAEs in descending order of frequency were: headache (5/55; 9%), pruritus (2/55; 4%), and arthralgia (2/55; 4%), and blood triglycerides increased (2/55; 4%).

For MINOLIRA, the most common TEAEs in descending order of frequency were: pruritus (6/55; 11%), headache (6/55; 11%), and arthralgia (3/55; 5%).

For the reference drug SOLODYN,® labeled adverse reactions include headache, dizziness, blurred vision, arthralgia, and pruritus.

For both trials 007 and 008, all adverse events are described as having resolved without sequelae.

Because these were crossover studies with each subject receiving both MINOLIRA and SOLODYN,® attribution of adverse events to one or the other treatment is imprecise. Adverse events were assigned based on proximity in time of the administration of treatment to the event.

7.4.2 Laboratory Findings

Routine hematology, serum biochemistry and urinalysis were repeated for all subjects on the day before dosing (Baseline) and at 72 hours post-dose (End of Period) in each study period.

For trial 007, no laboratory adverse events were reported.

For trial 008, 2 laboratory adverse events were reported. Subject exhibited increased blood triglycerides (reference range 37 – 288 mg/dL) at the Day 4 assessment following SOLODYN®, with a value of 1657 mg/dL (5.8 x ULN). Upon recheck 9 days later, the value had returned to acceptable limits (365 mg/dL). The Principal Investigator considered this AE unrelated to study drug.

Subject exhibited increased blood triglycerides at check-in for Period 2 (8 days following SOLODYN®), with a value of 503 mg/dL (1.7 x ULN). Of note, the subject’s
triglycerides were elevated at all study time points leading up to this, including screening, with values ranging from 291 to 338 mg/dL. Upon recheck at the scheduled Day 4 assessment (following MINOLIRA (minocycline HCl), the value had decreased to 374 mg/dL and the AE was considered resolved. The Principal Investigator considered this AE unrelated to study drug.

**Trial 007:**
Mean serum chemistry, hematology, and urinalysis parameters were within reference range at the Day 4 assessment and no notable treatment-related changes from baseline were observed.

**Shifts in Individual Subject Values:**
There was a shift noted in basophil percentage from normal at baseline to elevated post-dose for a total of 9 subjects on Day 4, with 8 subjects following MINOLIRA and 3 subjects following SOLODYN®. Of note, no similar shift for absolute basophils was observed.

There was a shift noted in monocyte percentage from normal at baseline to elevated postdose for a total of 9 subjects on Day 4, with 4 subjects following MINOLIRA and 5 subjects following SOLODYN®. Of these subjects, 2 following SOLODYN® exhibited a similar shift for absolute monocyte count on Day 4.

**Trial 008:**
Mean serum chemistry, hematology, and urinalysis parameters were within reference range at the Day 4 assessment; with the exception that mean direct bilirubin minimally exceeded reference range (0 – 0.2 mg/dL) at the Day 4 assessment following SOLODYN®, with a value of 0.21 mg/dL.

**Shifts in Individual Subject Values:**
There was a shift noted in basophil percentage from normal at baseline to elevated post-dose for a total of 8 subjects on Day 4, with 2 subjects following MINOLIRA and 6 subjects following SOLODYN®. Of note, no similar shift for absolute basophils was observed.

**For both trials 007 and 008:**
Results from pregnancy tests, drug screens, cotinine (a biomarker for exposure to tobacco smoke) screen and serology tests were negative or non-reactive for all subjects over the course of the trials.
Clinical Review  
Patricia C. Brown, M.D.  
NDA 209269  
Minolira™ (minocycline hydrochloride) extended-release tablets

7.4.3 Vital Signs

Vital signs parameters (body temperature, heart rate, systolic and diastolic blood pressure and respiratory rate) were measured and evaluated for clinical significance if out of defined normal range at Screening, before administration of investigational product and at 1, 2, 6, 12, 24, 36, 48 and 72 hours post-dose (at check-out) from each period.

**Trial 007:**  
There were no vital sign adverse events in this trial.  
Mean blood pressure, heart rate, respiratory rate, and body temperature results remained within normal limits at assessed post-dose time points. No clinically significant changes from pre-dose were observed for vital sign parameters with respect to study treatment. Regarding orthostatic vital sign changes, significant postural drops in blood pressure were not observed in trial subjects when evaluated at 4 hours post-dose. Individual shifts of vital signs to abnormal values were sporadic and usually corrected upon repeat measurement.

**Trial 008:**  
There were no vital sign adverse events in this trial.  
Mean blood pressure, heart rate, respiratory rate, and body temperature results remained within normal limits at assessed post-dose time points. No clinically significant changes from pre-dose were observed for vital sign parameters with respect to study treatment. Regarding orthostatic vital sign changes, significant postural drops in blood pressure were not observed in trial subjects when evaluated at 4 hours post-dose. Individual shifts of vital signs to abnormal values were sporadic and usually corrected upon repeat measurement.

7.4.4 Electrocardiograms (ECGs)

All subjects underwent physical examinations and 12-lead electrocardiography at screening. A 12-lead ECG was again performed within 24 hours prior to the scheduled administration of Investigational Product at and 72 hours post-dose (or earlier in case of premature termination) for subjects in each of the two study periods.

**Trial 007:**  
There were no ECG adverse events in this trial.
Mean ECG parameters (heart rate, PR, QRS, QT, and QTcB intervals) were within normal limits at the Day 4 post-dose assessment. No clinically significant changes were observed from pre-dose.

Shifts in Individual Subject Values:
There were 3 female subjects (# – 452 msec, # – 452 msec, # – 456 msec) with isolated post-dose QTcB intervals > 450 msec on Day 4 (or early termination visit), all following MINOLIRA. The maximum QTcB interval of 456 msec was exhibited 13 days following dosing (subject 71). All remaining post-dose QTcB intervals were ≤ 450 msec.

**Trial 008:**
There were no ECG adverse events in this trial.

Mean ECG parameters (heart rate, PR, QRS, QT, and QTcB intervals) were within normal limits at the Day 4 post-dose assessment. No clinically significant changes were observed from pre-dose.

Shifts in Individual Subject Values:
There were 2 male subjects (# – 451 msec, # – 454 msec) with post-dose QTcB intervals > 450 msec on Day 4, 1 following each of the two treatments. The maximum QTcB interval of 454 msec was exhibited by subject 16 following SOLODYN®. All remaining post-dose QTcB intervals were ≤ 450 msec.

7.4.5 Special Safety Studies/Clinical Trials

The applicant did not perform special safety studies as part of the clinical development program.

7.4.6 Immunogenicity

This is not applicable since the drug is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events is not evaluable in the bioequivalence trials 007 and 008 due to limited number of subjects and limited dosing.

7.5.2 Time Dependency for Adverse Events

Most subjects experienced adverse events within hours or days after product ingestion.
7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not evaluable in the bioequivalence trials 007 and 008 due to limited number of subjects.

7.5.4 Drug-Disease Interactions

No formal analyses were performed for drug-disease interactions with this drug product.

7.5.5 Drug-Drug Interactions

Labeling proposed by the applicant is the same as that for the listed drug SOLODYN® (minocycline HCl) Extended Release Tablets.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Since this is a 505(b)2 application, labeling for human carcinogenicity is the same as that for the listed drug, Solodyne®.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant women were excluded from trials 007 and 008 and instances of pregnancy during these studies were not reported.

Labeling proposed by the applicant

For section 8.1 Pregnancy (USE IN SPECIFIC POPULATIONS) the applicant submitted revised labeling in accord with the Pregnancy and Lactation Labeling Rule (PLLRR). PLLRR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and creation of a new subsection for information with regard to females and males of reproductive potential. Under this rule, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

The submitted labeling has been evaluated by DPMH (Division of Pediatric and Maternal Health). The DPMH Review by Carrie Ceresa, Pharm D., MPH, was
7.6.3 Pediatrics and Assessment of Effects on Growth

Labeling submitted by the applicant has been evaluated by DPMH. The Pediatric Labeling Review by Jacqueline A. Spaulding, MD, was completed April 3, 2017. As stated by the pediatric consultant: “Recommended labeling for the pediatric population is based on labeling discussions between DDDP and DPMH and is provided per 21 CFR 201.57(c)(9)(iv). Various comments were also provided for the division’s consideration to align MINOLIRA labeling with that of the currently approved SOLDYN label, where applicable.”

Pediatric Review Committee:
This application was not presented to the Pediatric Review Committee because it did not trigger PREA.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria applied to the current application, the applicant was exempted from these requirements.

Regarding Bioequivalence Studies:
Bioequivalence studies are not required in the 12 to 16 year old population because:
A) The Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (March 2003) states under “trial population” that: “We recommend that, unless otherwise indicated by a specific guidance, subjects recruited for in-vivo BE studies be 18 years of age or older and capable of giving informed consent.”

B) ICH E11 Clinical investigation of medicinal products in the pediatric population (December 2000) states under Pharmacokinetics: “Relative bioavailability comparisons of pediatric formulations with the adult oral formulation typically should be done in adults.” (In the case with MINOLIRA™ and SOLODYN® the pediatric and adult formulations are the same).
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant has proposed labeling that is the same as that for SOLODYN®.

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

7.7 Additional Submissions / Safety Issues

- Included in the current submission is the report of a search of worldwide medical literature to identify articles published between January 1, 1970 and April 29, 2016. The intent of each search was to identify published safety information that might not yet be reflected in current FDA-approved labeling for minocycline hydrochloride extended release. Each search was performed by PAREXEL and the output was reviewed by a Drug Safety Physician at PAREXEL and a clinician from Dr. Reddy’s Laboratories.

The following databases were searched:
  - MEDLINE (1946 to current): Produced by the United States (US) National Library of Medicine as a major source for biomedical literature. Includes citations and abstracts from over 4,800 journals published in the US and 70 other countries.
  - Biosis Previews (1926 - current)
  - EMBASE Alert (2016)
  - EMBASE (1947 - current)
  - International Pharmaceutical Abstracts (1970 - current)
  - SciSearch(R) Cited Ref Sci (1990 - current)

According to the applicant, ultimately, 10 publications were identified as describing new safety information. The publications discussed the use of minocycline for indications of lumbar radicular neuropathic pain; epidermal growth factor receptor inhibitor (EGFRi) induced rash, vitiligo and acne vulgaris. Few publications discussed the most effective dose or the dose dependent safety profile of minocycline. Use of triple therapy consisting of minocycline was emphasized to be a significant treatment option for the indication of moderate to severe acne vulgaris. As stated by the applicant, a common finding across publications was that 1 mg/kg dose of minocycline is both efficacious and safe; no additional benefit is noticed with a higher dose.

The applicant states that a total of 411 patients reported ≥ 1 Treatment-Emergent Adverse Event(s) from among the 964 patients who received one or more doses of oral minocycline formulation in the course of 7 of the 9 studies where the relevant safety information was available in their respective publication for this calculation. Information for subject discontinuation is available for 7 of the 9 studies. In these 7 studies there
Clinical Review
Patricia C. Brown, M.D.
NDA 209269
Minolira™ (minocycline hydrochloride) extended-release tablets

were a total of 47 patients who discontinued due to adverse effects from among the 1061 patients receiving minocycline as study treatment. Among adverse events leading to discontinuation were pruritus, urticarial rash, aggravated/exacerbated acne, and fatigue. No deaths or other SAEs were found from the information available in the publications.

According to the applicant, analysis of the safety information emerging from the above mentioned clinical studies revealed no new or unexpected side effects.

➢ The applicant submitted a 120 day safety update, supporting document 10, received January 17, 2017.

The applicant states that searches of the worldwide medical literature were conducted to identify articles published between April 30, 2016 and November 10, 2016. The intent of each search was to identify published safety information that might not yet be reflected in current Food and Drug Administration (FDA)-approved labeling for minocycline hydrochloride extended release (ER) tablets (SOLODYN® United States Prescribing Information [USPI]). Each search was performed by PAREXEL and the output was reviewed by a Drug Safety Physician at PAREXEL and a clinician from Dr. Reddy’s Laboratories. The following databases were searched:

- MEDLINE (1946 to current): Produced by the United States (US) National Library of Medicine as a major source for biomedical literature. Includes citations and abstracts from over 4,800 journals published in the US and 70 other countries.
- Biosis Previews (1926 - current)
- EMBASE Alert (2016)
- EMBASE (1947 - current)
- International Pharmaceutical Abstracts (1970 - current)
- SciSearch(R) Cited Ref Sci (1990 - current)

The search identified a total of 97 publications covering clinical information and 59 publications covering nonclinical information. All titles and abstracts were reviewed for those that might contain information relevant to the clinical or nonclinical safety of minocycline hydrochloride. Ultimately, four articles with information on clinical safety and two articles describing the nonclinical safety of minocycline hydrochloride were identified.

Articles regarding clinical safety:

This case report highlights a severe presentation of DRESS in a 13-year-old female patient that resulted in autoimmune sequelae including type 1 diabetes mellitus. The patient required a liver transplantation and was given therapy with immunosuppressants
including tacrolimus, mycophenolate mofetil, and prednisone. In addition to deregulated T-regulatory cells, viral reactivation could play a role in post-DRESS autoimmunity.

The current United States Prescribing Information (USPI) of minocycline ER tablets includes DRESS with autoimmune sequelae.


This is a case report of a patient with a pigmented vulvar lesion who was referred to a dermatologist by her gynecologist to determine a follow-up strategy for this lesion and consider a complete resection to rule out melanoma. Minocycline binds to plasma proteins and has a propensity for depositing into soft tissues rich with collagen. In this case, a type I hyperpigmentation (most common minocycline hyperpigmentation, appearing as blue-black/grey pigment staining in areas of acne scarring or inflammation as seen by the patient) was present in her vulvar lesion caused by the chronic inflammation associated with her vaginal atrophy, resulting in progressive minocycline deposition in the dermis as seen on histology.

According to the current USPI of minocycline ER tablets, tetracycline-class antibiotics are known to cause hyperpigmentation. “Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other tissue pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as over sites of scars or injury.”


This report concerned three patients treated with tetracycline-class antibiotics (two treated with minocycline and one treated with doxycycline) who developed nonimmune-mediated thyroid dysfunction that was severe and/or persistent. Tetracycline antibiotic-induced thyroid dysfunction may be more common, serious, and persistent than previously realized and should be considered in the differential diagnosis for pediatric cases of antibody-negative thyroid dysfunction. Thyroiditis from minocycline in these cases appears to be a non-autoimmune chemical thyroiditis resulting in cytotoxic damage sufficient to cause marked release of thyroid hormone and, in some cases, subsequent persistent hypothyroidism. Minocycline and doxycycline can cause a nonimmune chemical thyroiditis leading to severe hyperthyroidism.

The current USPI of minocycline ER tablets lists abnormal thyroid function as an adverse reaction.

This report presents multimodal, noninvasive imaging of severe minocycline-related ocular hyperpigmentation, providing the first posterior segment images utilizing swept-source optical coherence tomography (SS-OCT) and SS-OCT angiography. With these images the authors postulate on the pathophysiologic mechanism of drug-induced posterior pigmentation. The patient’s vision was limited due to Fuchs’ endothelial dystrophy and previous penetrating keratoplasty in the right eye. This patient did report mild symptoms of metamorphopsia (a type of distorted vision in which a grid of straight lines appears wavy and parts of the grid may appear blank), likely due to the large pigmented epithelial detachments (PEDs), but most patients remain visually asymptomatic. The finding suggests that the oxidized drug forms PEDs and concentrates in the macula due to its high melanin content.

According to the current USPI of minocycline ER tablets, tetracycline-class antibiotics are known to cause hyperpigmentation. “Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, and alveolar bone), sclera, and heart valves.”

**Conclusion:**
At this time, the applicant’s review of the published literature during the reporting period (from April 30, 2016 until November 10, 2016) did not reveal safety information sufficient to change the statement of contraindications, warnings, precautions, and adverse reactions in the current labeling of FDA-approved minocycline.

**8 Postmarket Experience**

The applicant’s product, MINOLIRA™ (minocycline hydrochloride) extended-release tablets, is not marketed in any country at this time.
9 Appendices

9.1 Literature Review/References

Literature references are cited in the body of the review.

9.2 Labeling Recommendations

Labeling submitted by the applicant was reviewed. Significant changes to the applicant-proposed labeling are shown below:

Full Prescribing Information

5 Warnings and Precautions

FDA proposed (as of April 5, 2017):

Reviewer comment:
Section 5 was reorganized to include new sections 5.2 Tooth Discoloration and 5.3 Inhibition of Bone Growth; however, no new information is included. Please also see Division of Pediatric and Maternal Health (DPMH) Review by Carrie Ceresa, Pharm D., MPH, dated February 15, 2017.

5.1 Teratogenic Effects

Avoid MINOLIRA use during pregnancy. MINOLIRA, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman. MINOLIRA, like other tetracycline-class drugs, may cause permanent discoloration of the teeth and inhibit bone growth when administered during pregnancy. Based on animal data, tetracyclines cross the placenta, are found in fetal tissues, and can cause skeletal malformation and retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy. If MINOLIRA is used during pregnancy, advise the patient of the potential risk to the fetus and discontinue treatment [see Use in Specific Populations (8.1)].
5.2 Tooth Discoloration

The use of tetracycline class drugs during tooth development (second and third trimesters of pregnancy, infancy, and childhood up 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 tetracycline but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use of tetracycline drugs is not recommended during tooth development.

The safety and effectiveness of MINOLIRA have not been established in pediatric patients less than 12 years of age.

5.3 Inhibition of Bone Growth

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. The safety and effectiveness of MINOLIRA have not been established in patients less than 12 years of age [see Use in Specific Populations (8.1,8.4)].

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy [see Use in Specific Populations (8.1)].

Reviewer comment:

“A decrease in fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours.”

For the proposed subsection 5.3, (quoted sentence above) Inhibition of Bone Growth, the Division of Dermatology and Dental Products (DDDP) intends to keep the Applicant’s language regarding a study conducted in the early 1960’s that evaluated the effect of tetracycline on the developing skeleton in the premature infant by measuring fibula growth rates. DDDP would like to retain this information since it is present in SOLODYNE labeling, has not been superseded by more current information and may be more useful than a general statement.
FDA Proposed (as of April 5, 2017):

Reviewer comment:
Section 5.8 is updated to include current terminology for increased intracranial pressure, “intracranial hypertension (IH).” This historically has been known as pseudotumor cerebri.

5.8 Intracranial Hypertension

Intracranial hypertension has been associated with the use of tetracycline-class drugs including MINOLIRA. Clinical manifestations of intracranial hypertension 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 a greater risk for developing intracranial hypertension. Concomitant use of isotretinoin and tetracycline should be avoided because isotretinoin, a systemic retinoid, is also known to cause intracranial hypertension.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

FDA proposed (as of April 5, 2017):

Section 8.1 is revised to conform to PLLR labeling. Please also see the Pediatric Labeling Review by Jacqueline A. Spaulding, MD, dated April 3, 2017.

Risk Summary

MINOLIRA, like tetracycline class drugs, may cause permanent discoloration of teeth and reversible inhibition of bone development when administered during pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]. Post-marketing cases of minocycline use in pregnant women report congenital anomalies such as limb reductions. The limited data are not sufficient to inform a drug-associated risk for birth defects or miscarriage. In animal reproduction studies, minocycline induced skeletal malformations in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at systemic exposure of approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients administered MINOLIRA [see Data]. If a patient becomes pregnant while taking this drug, advise the patient of the risk to the fetus and discontinue treatment.

Reference ID: 4080447
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data
The use of tetracycline during tooth development (second and third trimesters of pregnancy) may cause permanent discoloration of deciduous teeth. This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses.

Animal Data
Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus [see Warnings and Precautions (5.1)].

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits during the period of organogenesis at doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3-times and 2-times, respectively, the systemic exposure to minocycline observed in patients administered MINOLIRA). Reduced mean fetal body weight was observed when minocycline was administered to pregnant rats during the period of organogenesis at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients administered MINOLIRA).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation, at doses of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients administered MINOLIRA). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

8.2 Lactation
Risk Summary
Tetracycline-class drugs including minocycline are present in breast milk. It is not known whether minocycline has an effect on the breastfed infant or on milk production. Because of the potential for serious adverse effects on bone and tooth development in breastfed infants from the tetracycline-class drugs, advise a woman that breastfeeding is not recommended with MINOLIRA therapy [see Warnings and Precautions (5.1)].

8.3 Females and Males of Reproductive Potential

Contraception
MINOLIRA may reduce the effectiveness of low-dose oral contraceptives. Patients of reproductive potential should not rely on low-dose oral contraceptives as an effective contraceptive method, and should use an additional method of contraception during treatment with MINOLIRA [see Drug Interactions (7.5)].

Infertility
Avoid using MINOLIRA in males who are attempting to conceive a child. Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis. In a fertility study in rats, minocycline adversely affected spermatogenesis when orally administered to male rats at doses resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients administered MINOLIRA [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

The safety and effectiveness of MINOLIRA have been established in pediatric patients 12 years of age and older for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris [see Pharmacokinetics (12.3) and Clinical Studies (14)]. Tooth discoloration and inhibition of bone growth have been observed in pediatric patients [see Warnings and Precaution (5.2, 5.3)]. The safety and effectiveness of MINOLIRA have not been established in pediatric patients less than 12 years of age.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

Applicant proposed (July 8, 2016):

MINOLIRA Tablets, 135 mg is bioequivalent to SOLODYN, 135 mg (80 mg + 55 mg).
The pharmacokinetics of minocycline following oral administration of MINOLIRA was investigated in 36 healthy male and female adult subjects under fasting conditions. The pharmacokinetic parameters of minocycline are presented in Table 3.

Table 3: Pharmacokinetic Parameters of Minocycline Following Administration of MINOLIRA under Fasting Conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>700 ± 261</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>2.01 (1.0 – 4.5 hrs)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.hr/mL)</td>
<td>15.6 ± 2.46</td>
</tr>
</tbody>
</table>

In a separate trial, MINOLIRA was administered with a high-fat, high-calorie meal that included dairy products to 36 healthy male and female adult subjects. The pharmacokinetic parameters of minocycline are presented in Table 4.

Table 4: Pharmacokinetic Parameters of Minocycline Following Administration of MINOLIRA under Fed Conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>707 ± 190</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>3.5 (1.5 – 6.0)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.hr/mL)</td>
<td>17.1 ± 3.03</td>
</tr>
</tbody>
</table>

Minocycline is lipid soluble and distributes into the skin and sebum.

FDA proposed (as of April 5, 2017):

The pharmacokinetics of minocycline following oral administration of a single dose of MINOLIRA (135 mg) was investigated in 77 healthy male and female adult subjects under fasting conditions. The pharmacokinetic parameters of minocycline under fasting conditions are presented in Table 3.

Table 3: Pharmacokinetic Parameters of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fasting Conditions (N=77)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>Mean ± SD 700 ± 261</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (hr)</td>
<td>Mean ± SD 2.0(1.0 – 4.5)</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.hr/mL)</td>
<td>Mean ± SD 10874 ± 3717</td>
</tr>
<tr>
<td>$T_{1/2}$ (hr)</td>
<td>Mean ± SD 15.6 ± 2.46</td>
</tr>
</tbody>
</table>

*Median (Min-Max)

In a separate trial, a single dose of MINOLIRA (135 mg) was administered orally with a high-fat, high-calorie meal that included dairy products to 36 healthy male and female adult
subjects. The estimated calorie content of the meal was 848 Kcal, consisting of 145 Kcal from protein, 250 Kcal from carbohydrates, and 453 Kcal from fat. The pharmacokinetic parameters of minocycline under fed conditions are presented in Table 4.

<table>
<thead>
<tr>
<th>Table 4 : Pharmacokinetic Parameters of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fed Conditions (N = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
</tr>
<tr>
<td>Mean ± SD</td>
</tr>
</tbody>
</table>

*Median (Min-Max)

Minocycline is lipid soluble and distributes into the skin and sebum.

17 PATIENT COUNSELING INFORMATION

FDA proposed (as of April 5, 2017):

Section 17 is updated to conform to current labeling practice per the Guidance for Industry: Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products –Content and Format.

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instruction for Use).

Advise patients of the following:

**Teratogenic effects**
- Advise patients to avoid use of MINOLIRA during pregnancy.
- Advise patients that MINOLIRA use during pregnancy may cause inhibition of fetal bone growth.
- Advise patients that MINOLIRA use during pregnancy may cause discoloration of deciduous teeth.

**Tooth Discoloration**
Advise caregivers of pediatric patients that MINOLIRA use may cause permanent discoloration of deciduous and permanent teeth.

**Lactation**
• Advise a woman that breast feeding is not recommended during MINOLIRA therapy.

Contraception
• Advise patients of reproductive potential that MINOLIRA may reduce the effectiveness of low-dose oral contraceptives. Advise patients of reproductive potential not to rely on low-dose oral contraceptives as an effective contraceptive method and to use an additional method of contraception during treatment with MINOLIRA.

Infertility
• Advise males of reproductive potential that MINOLIRA may impair fertility.

Tissue Hyperpigmentation
• Inform patients that MINOLIRA can cause discoloration of skin, scars, teeth or gums.

Pseudomembranous Colitis
• Advise patients that pseudomembranous colitis can occur with minocycline therapy, including MINOLIRA. Advise patients to seek medical attention if they develop watery or bloody stools.

Hepatotoxicity
• Inform patients about the possibility of hepatotoxicity. Advise patients to seek medical advice if they experience symptoms or signs of hepatotoxicity, including loss of appetite, tiredness, diarrhea, jaundice, increased bleeding tendencies, confusion, and sleepiness.

Central Nervous System Effects
• Inform patients that central nervous system adverse reactions including dizziness or vertigo have been reported with minocycline therapy. Caution patients about driving vehicles or using hazardous machinery if they experience such symptoms while on MINOLIRA.

Intracranial Hypertension
• Inform patients that intracranial hypertension can occur with minocycline therapy. Advise patients to seek medical attention if they develop unusual headache, visual symptoms, such as blurred vision, diplopia, and vision loss.

Autoimmune Syndromes
• Inform patients that autoimmune syndromes, including drug-induced lupus-like syndrome, autoimmune hepatitis, vasculitis and serum sickness have been observed with tetracycline-class drugs, including minocycline. Symptoms may be manifested by arthralgia, fever, rash and malaise.
• Advise patients who experience such symptoms to stop the drug immediately and seek medical help.

Photosensitivity
• Inform patients that photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including minocycline.
• Advise patients to minimize or avoid exposure to natural or artificial UV light (tanning beds or UVA/B treatment) while using MINOLIRA.
• Discuss other sun protection measures, if patients need to be outdoors while using MINOLIRA.
• Advise patients to discontinue treatment at the first evidence of sunburn.

Important Administration Instructions
• Inform patients to take MINOLIRA as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the current treatment course and increase the likelihood that bacteria will develop resistance and will not be treatable by other antibacterial drugs in the future.
• Advise patients to swallow MINOLIRA whole and not to chew, or crush the tablets.
• Advise patients to split MINOLIRA tablet across the score line if required depending on patient’s body weight.

At the time of closure of this review, labeling negotiation was ongoing. For final approved labeling please see approval letter.

Patient Package Insert
The Patient Package Insert (PPI) and the Instructions for Use (IFU) were evaluated by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug promotion (OPDP), review dated March 29, 2017. The PPI follows the question and answer Med Guide format and is reflective of information in the Physician Insert. The IFU reflects efforts to reduce redundancy to make patient information more consistent and concise, and to include the information necessary for patients to safely take their medication.

9.3 Advisory Committee Meeting
No Advisory Committee was convened in response to this application
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA C BROWN
04/05/2017

GORDANA DIGLISIC
04/05/2017