CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209269Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 6, 2017
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	209269
Applicant	Dr. Reddy's Laboratories Limited
Date of Submission	Letter date: July 8, 2016 CDER stamp date: July 8, 2016
PDUFA Goal Date	May 8, 2017
Proprietary Name / Established (USAN) names	MINOLIRA (minocycline hydrochloride)
Dosage forms / Strength	Extended Release Tablets / 105 mg and 135 mg Functionally scored
Proposed Indication(s)	Only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patient 12 years of age and older
Recommended:	*Approval*

1. Introduction

MINOLIRA (minocycline hydrochloride) Extended Release Tablets, is an oral drug product for which the applicant seeks approval under Section 505 (b) (2) of the Federal Food Drug and Cosmetic Act for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. This application is for a new formulation of minocycline hydrochloride, an extended release tablets with single score line on each tablet in array of strengths (105 and 135 mg). The proposed dosing regimen is approximately 1 mg/kg once daily for 12 weeks. The listed drug is SOLODYN® (minocycline HCl) Extended Release Tablets (45*, 55, 65, 80, 90*, 105, 115, and 135* mg; * no longer distributed or sold by Medicis). SOLODYN® was approved on May 8, 2006 for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. The recommended dosage of SOLODYN® is approximately 1 mg/kg once daily for 12 weeks.

The active ingredient, minocycline hydrochloride, is a tetracycline-class drug, which is currently marketed in the U.S. in various dosage forms (Immediate Release Capsule; Extended Release Tablets; Microspheres; Injectable). Minocycline hydrochloride is approved for the treatment of a number of infections (due to susceptible strains including *Mycoplasma, Chlamydia,* gram-negative and gram-positive microorganisms), for adjuvant therapy for severe acne vulgaris, for treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris, and as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. In the U.S. it has been marketed since 1971.

This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

MINOLIRA (minocycline hydrochloride) Extended Release Tablets was developed under IND 120026 initially submitted on June 4, 2015.

During their development program, the applicant interacted with the Agency at the Pre-IND Meeting and requested Pre-NDA Meeting.

On June 4, 2015, the applicant submitted a protocol for two comparative bioavailability trials; DFD-10CD-007(Fasting) and DFD-10-CD-008(Fed). 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 (minocycline HCl) extended release 135 mg tablets versus 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:

- Several specified impurity limits 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 (b) (4)). Re-evaluate these limits based on manufacturing and stability data and justify any limits that exceed ICH Q3A guidelines.
  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.
- The proposed specifications for a number of impurities in the drug substance are higher than the qualification threshold described in the ICH Q3A guidance document. These impurities are (b) (4) 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

The applicant requested a Pre-NDA Meeting; however, after receiving the Premeeting Communication, the applicant cancelled the meeting (scheduled for May 23, 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 appears reasonable.

- Regarding impurities, [redacted] the applicant performed a computational toxicology assessment of the 7 impurities in drug substance [redacted] The assessment was performed in accordance with the ICH Guidance for Industry "M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" using *in-silica* software programs. Based on the structural analysis, the applicant concluded that these three impurities do not pose any concern for mutagenicity for the following reasons:
  a) Impurities [redacted] are listed in USP Official Monograph of Minocycline Hydrochloride Extended Release Tablets and impurity at [redacted] is a close structural derivative of [redacted].
  b) All these three impurities, are structurally related very closely to either the parent drug minocycline, other non-mutagenic minocycline impurities or tetracycline class of approved drugs
  c) The impurity profile of [redacted] (Type II DMF # [redacted]) and [redacted] (Type II DMF # [redacted]) minocycline hydrochloride manufactured by [redacted] is comparable, based on which supplier has adopted the same impurity limits for [redacted] minocycline hydrochloride. The supplier has also indicated that minocycline hydrochloride with this impurity profile supplied by [redacted] has been in human use in the US pharmaceutical market since 1990's and the Type II DMF # [redacted] is currently referenced in several drug applications approved by USFDA.
  d) The impurity profile in [redacted] and SOLODYN [redacted] are comparable which indicates that presence of similar impurity profile including [redacted] in marketed product of minocycline hydrochloride.
  The Agency commented that no additional nonclinical studies are needed to qualify the impurities in the proposed drug product since the impurity profiles of the proposed drug product and SOLODYN are very similar.

In this new submission, the applicant seeks approval of their application under section 505(b)(2) of the Federal Food Drug and Cosmetic Act. The listed drug is SOLODYN® (minocycline HCl) Extended Released Tablets. Their clinical bridge consists of two pivotal comparative bioavailability trials (DFD-10CD-007 and DFD-10-CD-008), discussed in section 5 of this review. These trials were conducted in a population representative of the United States population and included both male and female subjects. Through the clinical bridge, the applicant is relying on the Agency's finding of safety and efficacy for SOLODYN® (minocycline HCl) Extended Release Tablets, NDA 50808, to satisfy systemic safety and efficacy data needs in this application (specifically nonclinical genetic toxicology, carcinogenicity, and reproductive and developmental toxicology, and clinical safety and efficacy data).

3. CMC

Drug Substance

The active ingredient in MINOLIRA (minocycline hydrochloride) Extended Release Tablets is minocycline hydrochloride. Minocycline hydrochloride, a semi synthetic derivative of tetracycline, is designated chemically as [4S- (4α,4aα,5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a- tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide mono hydrochloride. Minocycline hydrochloride is (b) (4) It is soluble in solutions of alkali hydroxides and carbonates; sparingly soluble in water; slightly soluble in ethanol (96%); practically insoluble in chloroform and in ether. Detailed CMC information on minocycline hydrochloride is referred to DMFs # (b) (4). DMFs # (b) (4) have been reviewed and found adequate for the approval of this NDA (review by Dr. Benjamin D. Stevens dated 01/19/17)

Drug Product

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. In addition, 105 mg and 135 mg tablets contain the following inactive ingredients: microcrystalline cellulose NF, polyethylene glycol 400 NF, ethyl cellulose (b) (4) NF, hypromellose (b) (4) 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 (b) (4) which contains hydroxyl propyl cellulose NF and hypromellose (b) (4) USP.

The tablets are functionally scored, rectangular shaped, white to off-white color with brown or golden colored speckles. MINOLIRA tablets contain a single score line on both surfaces. The 105 mg tablets are debossed with ‘M1’ on one surface, where ‘M’ and ‘1’ are on either side of the score line. The 135 mg tablets are debossed with ‘M3’on one surface, where ‘M’ and ‘3’ are on either side of the score line.

Specifications
Specification for MINOLIRA tablets is adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. Stability data from the stability samples packaged in the proposed commercial container closure systems support an expiration dating period of 24 months when stored at the 20 to 25°C (68 to 77°F), excursions permitted between 15°C and 30°C (59 - 86°F). The drug product should be protected from light and moisture.

Container Closure System

The tablets are packaged in high density polyethylene (HDPE) bottles with child- resistant closures (CRC). The bottles containing 30 tablets are used for marketing and the 10 tablets packaging configuration is used for physician samples. Each HDPE bottle also contains 1 g of silica gel canister and a (b) (4) coiler.

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.

A claim for categorical exclusion from the environmental assessment has been submitted by the NDA applicant and the request is granted.

The drug product is recommended for *Approval* from the drug product perspective (review by Dr. Hong Cai, Ph.D. dated 02/28/17).

The facility review team from the Office of Process and Facility (OPF) has issued an "*Approval*" recommendation for the facilities involved in this application (review by Consumer Safety Officer, Donald Lech dated 03/07/17)

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 (review by Yichun Sun, Ph.D.; Application Technical Lead, Branch V Division of New Drug Products II dated 03/10/2017)

4. Nonclinical Pharmacology/Toxicology

The applicant did not submit any nonclinical studies conducted with MINOLIRA Extended Release Tablets.

The applicant is relying on the Agency's previous finding of safety for SOLODYN® (minocycline HCl) Extended Release Tablets to supply the genetic toxicology, carcinogenicity, and reproductive and developmental toxicology safety data needs in their MINOLIRA application. Information from the SOLODYN® package insert on these topics has been incorporated into MINOLIRA labeling (Sections 8.1 Pregnancy and 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility). Of note, the carcinogenic potential of minocycline HCl is being evaluated in mice and rats as a post-marketing commitment under NDA 50808 (SOLODYN®). The results from the carcinogenicity studies conducted with minocycline HCl should be incorporated into the MINOLIRA labeling.

(b) (4)

(b) (4)

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 applicant 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 considered acceptable and no additional nonclinical studies are recommended." (Review by Jianyong Wang Ph.D.)

There are no outstanding pharmacology-toxicology issues.
The pharmacology-toxicology reviewer, Jianyong Wang Ph.D., recommended *Approval* of this application (review dated 03/14/17).

5. Clinical Pharmacology/Biopharmaceutics

The applicant pursued a 505(b) (2) pathway for MINOLIRA Extended Release Tablets and identified SOLODYN® Extended Release Tablets as the listed drug product.
To support this application, the applicant submitted data from two Bioavailability (BA) / Bioequivalence (BE) trials:

- Trial DFD-10-CD-007 conducted under **fasting** conditions (an open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover studyin healthy male or female adults)
  - The primary objective was to assess the comparative bioavailability of the test formulation, DFD-10 (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.

- Trial DFD-10-CD-008 conducted under **fed** conditions (an open-label, randomized, 2-period, 2-sequence, 2-treatment, crossover study in healthy male or female adults)
  - The primary objective was to assess the comparative bioavailability of the test formulation, DFD-10 (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.

The studies were conducted in the population representative of U.S. population. For trial DFD-10-CD-007, the mean age of the subjects was 39.2 years (range 19 to 55 years). The mean weight was 76.0 kg (range 58.5 to 106.6 kg). There were more males than females (82% versus 18%). For trial DFD-10-CD-008, the mean age of the subjects was 38.9 years (range 18 to 54 years). The mean weight was 75.14 kg (range 51.9 to 99.6 kg). There were more males than females (83% versus 17%).

Both the pivotal trials used the highest strength of MINOLIRA (135 mg). The studies compared systemic exposure (C_{max} and AUC) of minocycline following a single dose of MINOLIRA 135 mg Extended Release Tablets to that following a single dose of SOLODYN (minocycline HCl) 135 mg Extended Release Tablets (administered as a combination of SOLODYN ER tablets, 80 mg and 55 mg). The results of the 2 pivotal trials showed that that the 90% confidence interval (CI) of the geometric mean ratios of C_{max}, AUC_{0-t}, and AUC_{0-inf} were within the no effect boundary of 80% to 125% under both fasting and fed conditions. Summary of the results are shown in Table 1:

Table 1: Summary of relative BA results under fasting and fed conditions for the test (MINOLIRA tablets 135 mg) and reference (SOLODYN tablets 135 mg administered as a combination of SOLODYN ER tablets, 80 mg and 55 mg).

	Fasting Conditions (Trial DFD-10-CD-007) (N=77)		**Fed Conditions** (Trial DFD-10-CD-008) (N=36)	
Parameters	**Test/Reference Ratio**	**90% CI**	**Test/Reference Ratio**	**90% CI**
C_{max} (ng/mL)	105.92	99.67 - 112.56	94.68	89.62 - 100.03
AUC_{0-t} (ng*h/mL)	97.76	92.32 - 103.52	92.84	89.97 - 95.80
AUC_{0-inf} (ng*h/mL)	97.76	92.45 - 103.38	92.69	89.71 - 95.78

Source: Clinical Pharmacology Review by Yanhui Lu, Ph.D. dated 03/10/17

Therefore, the results indicated that MINOLIRA 135 mg Extended Release Tablets were bioequivalent to SOLODYN 135 mg Extended Release Tablets (80 mg and 55 mg co-administered) under fasting and fed conditions.

Biowaiver of lower strengths

The applicant submitted a waiver request of in vivo BA testing for the lower strengths of 52.5 mg (a half of the 105 mg tablet), 67.5 mg (a half of the 135 mg tablet), and 105 mg. This was reviewed by the Dr. Hansong Chen (Biopharmaceutics reviewer). Dr. Cheng concluded that

the biowaiver request was acceptable to support approval of lower strengths (review dated 03/02/17)

The Clinical Pharmacology team Yanhui Lu, Ph.D. and Chinmay Shukla, Ph.D. recommended *Approval* from a clinical pharmacology perspective provided the labeling comments are adequately addressed by the applicant. (Clinical Pharmacology review by Yanhui Lu, Ph.D. dated 03/10/17).

The Clinical Pharmacology team made the following labeling recommendations: (deletions are noted as ~~strikethrough~~ and additions are noted as double underlines)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

(b) (4)

The pharmacokinetics of minocycline following oral administration of a single dose of MINOLIRA (135 mg) was investigated in (b) (4) 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 (b) (4) of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fasting Conditions (N = 77)

	C_{max} (ng/mL) (b) (4)	T_{max} (hr)* (b) (4)	$AUC_{0-\infty t}$ (ng.hr/mL) (b) (4)	$T_{1/2}$ (hr) (b) (4)
(b) (4) Mean ± SD	700 ± 261	2.0 (b) (4) (1.0 (b) (4) – 4.5 (b) (4))	(b) (4) 10874 ± (b) (4) 3717	15.6 ± 2.46

*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 (b) (4) of Minocycline Following Administration of a Single Dose of MINOLIRA (135 mg) under Fed Conditions (N = 36)				
	C_{max} (ng/mL) (b) (4)	T_{max} (hr)* (b) (4)	$AUC_{0-\infty t}$ (ng.hr/mL) (b) (4)	$T_{1/2}$ (hr) (b) (4)
(b) (4) Mean ± SD	707 ± 190	3.5 (1.5 (b) (4) – 6.0 (b) (4))	(b) (4) 12000 ± (b) (4) 2967	17.1 ± 3.03

*Median (Min-Max)

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

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The applicant did not conduct clinical trials to determine the efficacy of their product. Instead, the applicant has established a biobridge [consists of two pivotal comparative bioavailability trials (DFD-10CD-007 and DFD-10-CD-008)] between their product, MINOLIRA, and the listed drug SOLODYN®, in order to rely upon the Agency's finding of safety and effectiveness for SOLODYN®.

Information from the SOLODYN® package insert has been incorporated into MINOLIRA labeling (Section 14 CLINICAL STUDIES).

8. Safety

The applicant did not conduct clinical trials to determine the safety of their product. Instead, the applicant has established a biobridge between their product, MINOLIRA, and the listed drug SOLODYN®, in order to rely upon the Agency's finding of safety for the listed product. The clinical bridge consists of two pivotal comparative bioavailability trials (DFD-10CD-007 and DFD-10-CD-008). The applicant submitted additional safety data from these two pharmacokinetic trials. There were no deaths or serious adverse events (AE). Attribution of adverse events to specific treatment whether MINOLIRA or SOLODYN® is rendered

imprecise by the cross-over design of trials DFD-10CD-007 and DFD-10-CD-008. The most common AEs 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%). All adverse events are described as having resolved without sequelae. These adverse events are currently included in labeling for the listed drug SOLODYN®. 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, electrocardiograms and vital signs did not reveal clinically significant safety signals.

The reader is referred to the clinical review (dated April 5, 2017) by Dr. Patricia Brown for full discussion.

Information from the SOLODYN® package insert including Sections 4 CONTRAINDICATIONS; 5 WARNINGS AND PRECAUTIONS; 6 ADVERSE REACTIONS has been incorporated into MINOLIRA labeling.

No postmarketing commitments or requirements to address safety concerns are warranted.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. Minocycline hydrochloride is not a new molecular entity.

10. Pediatrics

The proposed indication, as for the listed drug SOLODYN®, is for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. The proposed dosing regimen, like for the listed drug, is approximately 1 mg/kg once daily for 12 weeks.

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 to this application, the applicant is exempt from these requirements.

11. Other Relevant Regulatory Issues

- The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommended accepting data without an on-site inspection for the analytical and clinical sites for the two pivotal trials (Memorandum by Dr. Shila S. Nkah dated 10/05/16).

- Division of Medication Error Prevention and Analysis (DMEPA) found the tradename MINOLIRA would not misbrand the proposed product, and acknowledged it is conditionally acceptable (Proprietary Name Review by Madhuri R Patel, dated 10/14/16)

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR).
Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.

Significant changes incorporated into revised draft labeling, following labeling review, include:

- Revision to **Section 8.1**; **8.2** ; **8.3** and **8.4** (see Pharmacology –Toxicology recommendation regarding labeling; and review by Division of Pediatric and Maternal Health)
- Revision to the applicant's proposed **12.3 Pharmacokinetics Section**
  (Clinical Pharmacology recommendation regarding labeling: see section 5 of this review)
- Revision to Section **5 WARRNINGS AND PRECOUTIONS** 5.7 Pseudotumor Cerebri (based on current terminology) to:

  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.

- Revision to Section **5 WARRNINGS AND PRECOUTIONS** (re-organization, no new information; refer to Pediatric Labeling review by Dr. Jacqueline A Spaulding dated April 3, 2017; Division of Pediatric and Maternal Health, Office of Drug Evaluation IV)

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 human 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)]*.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval*

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 209269, MINOLIRA (minocycline HCl) Extended Release Tablets pending agreement of the applicant with the recommended labeling revisions.

Risk Benefit Assessment

- I find that the applicant has constructed an adequate clinical bridge to the listed drug, SOLODYN® Extended Released Tablets, which allows the application to rely on the FDA findings of safety and efficacy for the listed drug. The risk-benefit ratio for this product is appropriate for the indication of the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

- Postmarketing risk management beyond professional labeling, prescription status, and routine pharmacovigilance is not needed.

Recommendation for other Postmarketing Requirements and Commitments

- None

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/s/

GORDANA DIGLISIC
04/06/2017