CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209269Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	8 May 2017
From	Jill A. Lindstrom, MD
Subject	Division Director Summary Review
NDA #	209269
Applicant Name	Dr. Reddy's Laboratories, Limited
Date of Submission	8 July 2016
PDUFA Goal Date	8 May 2017
Proprietary Name	MINOLIRA
Established (USAN) Name	Minocycline hydrochloride
Dosage Form	Tablet, extended release
Strength	105mg, 135mg
Proposed Indication(s)	Treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Patricia Brown, MD
Statistical Review	NA
Pharmacology Toxicology Review	Jianyong Wang, PhD
CMC Review/OBP Review	Benjamin Stevens, PhD; Hong Cai, PhD; Peter Guerrieri, PhD; Donald Lech, PhD; Hansong Chen, PhD; Granton Adams; Yichun Sun, PhD;
Microbiology Review	NA
Clinical Pharmacology Review	Yanhui Lu, PhD
DPMH	Carrie Ceresa, PharmD, MPH; Jacqueline Spalding, MD
ADL	Nancy Xu, MD
CDTL Review	Gordana Diglisic, MD
OSE/DMEPA	Madhuri R. Patel, PharmD
OPDP	Silvia Wanis, PharmD, CPH
PLT	Rowell Medina, PharmD, BCPS
Regulatory Project Manager	Belainesh Robnett, MS

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

MINOLIRA (minocycline hydrochloride) extended release tablet, 105mg and 135mg, is an oral drug product for which the applicant seeks approval under Section 505 (b)(2) of the Federal Food Drug and Cosmetic Act (FFDCA) for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. The applicant identified SOLODYN (minocycline HCl) extended release tablet as the listed drug, FDA's finding of safety and effectiveness for which the application will rely. This memo summarizes the findings of the multidisciplinary review team, and provides the rationale for my decision.

2. Background

Acne is a chronic inflammatory disease of the pilosebaceous follicles of the skin that primarily occurs the face, chest, and back of adolescents and adults. The primary lesions of acne consist of closed and open comedones and inflammatory papules, pustules and nodules; scars and post-inflammatory hyper- and hypopigmentation may also occur. The pathophysiology of acne is thought to involve follicular hyperkeratinization, microbial colonization by *Propionibacterium acnes*, sebum production and inflammation. The pharmaceutical therapeutic armamentarium for acne includes topical drugs (salicylic acid, benzoyl peroxide, antibiotics [clindamycin, erythromycin], retinoids, azelaic acid, dapsone, and combinations of these), systemic antibiotics, combined oral contraceptives, and isotretinoin.

Minocycline, a synthetic antibiotic in the tetracycline class, was initially approved for marketing in 1971. Marketed dosage forms include capsule, extended release capsule, tablet, extended release tablet, suspension, injectable, and extended release powder. Strengths range from 1mg to 135mg, depending on the dosage form. Labeled indications for these products include a variety infections, severe acne (adjunctive therapy), inflammatory lesions of non-nodular moderate to severe acne, and reduction of pocket depth (adjunctive to scaling and root planing procedures).

SOLODYN (minocycline HCl) Extended Release Tablets, identified by the applicant as the listed drug for their application, is marketed in 55, 65, 80, 105 and 115mg strengths to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

This application relied on the Agency's finding of safety and effectiveness for SOLODYN to establish the safety and effectiveness for their product. The applicant provided scientific justification for this reliance by demonstrating the bioequivalence of their product to the listed drug under fasting and fed conditions in two comparative bioavailability studies. Because the safety and effectiveness of systemically-administered products are a function of the systemic

exposure, demonstration of bioequivalence supports the clinical bridge between the two products (SOLODYN, the listed drug, and MINOLIRA, the new drug).

The application is not appropriate for an Abbreviated New Drug Application under section 505(J) of the FFDCA as the formulation (extended release tablets that are functionally scored) and requisite labeling differ from that of the listed drug (extended release tablets that are not scored).

3. CMC/Device

The drug substance, minocycline hydrochloride, (b) (4) with an empiric formula of $C_{23}H_{27}N_3O_7$, HCl, and a molecular weight of 493.95. The drug product, MINOLIRA extended release tablet, contains 25% immediate-release and 75% extended release beads containing minocycline, and is white to off-white, functionally scored, rectangular tablets with brown or gold color speckles and a single score line on both surfaces. The 105mg strength tablet has an "M" and a "1" debossed on one surface on either side of the score, and the 135mg strength tablet has an "M" and a "3" debossed on one surface on either side of the score. The composition of the drug product is described in the following table:

Ingredient	Function	%w/w	Quantity per unit (mg)	
			105mg	135mg
Minocycline hydrochloride	Active ingredient	12.67	113.369	145.760
Microcrystalline cellulose (b) (4)	(b) (4)			
Opadry Clear (b) (4)				
Polyethylene glycol 400				
Ethyl cellulose				
Hypromellose (b) (4)				
Triethyl citrate				
Silicified microcrystalline cellulose				
Microcrystalline cellulose (b) (4)				
Sodium stearyl fumarate				
Talc				
Isopropyl alcohol				
Purified water				
Total weight				

Source: Adapted from CMC Review, NDA 208286, page 42.

All of the excipients are compendial.

The drug product will be supplied as 30 tablets packaged with a 1gm silica gel canister and (b) (4) coil in a white wide-mouth round high density polyethylene bottle closed with a 38mm child-resistant plastic cap; a 10-tablet physician sample configuration will also be supplied. Stability supports an expiry of 24 months.

The drug substance is manufactured in (b) (4), and the drug product in (b) (4). All the manufacturing and testing sites of the NDA were deemed acceptable in their identified functions and responsibilities to support NDA 209269.

The CMC lead reviewer, Dr. Yichun Sun, concluded that the applicant provided sufficient information to assure the identity, strength, purity and quality of the drug product, and did not recommend any postmarketing commitments.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing and testing sites were deemed acceptable. Stability testing supports an expiry of 24 months. There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The applicant did not conduct any new nonclinical studies, but is relying on the Agency's finding of safety for SOLODYN to address nonclinical informational needs. To support such reliance, the applicant demonstrated bioequivalence to SOLODYN (see section 5 of this review).

As described in SOLODYN labeling, minocycline was assessed for carcinogenicity potential in rats and mice; follicular cell tumors of the thyroid gland were observed in rats of both genders, but no impact on tumor incidence was observed in mice. Minocycline was not mutagenic in either of two in vitro assays and was not clastogenic in either an in vitro or an in vivo assay. Minocycline impaired male fertility in rats, and induced skeletal malformations in rats and rabbits. These findings are included in MINOLIRA labeling.

The pharmacology/toxicology reviewer, Dr. Jianyong Wang, recommended *Approval* of this application from a pharmacology/toxicology perspective; he did not identify the need for any nonclinical postmarketing commitments or requirements.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

MINOLIRA (minocycline hydrochloride) extended release tablet is intended to be taken by mouth once daily for the treatment of the inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

To establish a clinical bridge, the applicant conducted two randomized, single-dose, crossover studies to assess the comparative bioavailability (BA) of their product and Solodyn under fed and fasting conditions, respectively. The studies compared MINOLIRA 135 mg strength tablet to SOLODYN tablets, administered as a combination of SOLODYN tablets, 80mg and 55 mg.

Under fed and fasting conditions, the relative bioavailability of MINOLIRA compared to SOLODYN, measured as the 90% confidence interval of the ratio of the geometric mean of C_{max} and AUC, was within the no effect boundary of 80% to 125% of that for SOLODYN. This provides for the clinical bridge to the Agency's finding of safety and efficacy for SOLODYN. The results of the comparison are summarized in the following table:

	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: Office of Clinical Pharmacology Review, Yanhui Lu, PhD; archived 3/10/17; p.3

The Clinical Pharmacology reviewer, Dr. Yanhui Lu, found the application acceptable and did not recommend any postmarketing commitments or requirements.

The applicant requested a waiver for in vivo bioavailability testing of the lower strength tablet. Dr. Hansong Chen, the Biopharmaceutics reviewer, found the biowaiver request was acceptable to support approval of the lower strength.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant proposed reliance on the FDA finding of efficacy for SOLODYN to establish the efficacy of MINOLIRA. To support such reliance, the applicant constructed a clinical bridge between SOLODYN and MINOLIRA by demonstrating that under fed and fasting conditions, the relative bioavailability of MINOLIRA compared to SOLODYN, measured as the 90% confidence interval of the ratio of the geometric mean of C_{max} and AUC, was within the no effect boundary of 80% to 120% of that for SOLODYN. The applicant did not conduct

any clinical efficacy studies with MINOLIRA. Therefore the clinical studies section of labeling will include information from the SOLODYN labeling, along with a statement that the applicant relied on information from studies conducted with minocycline hydrochloride.

The reader is referred to the clinical review by Dr. Patricia Brown. I concur with Dr. Brown that the clinical bridge allows reliance on the FDA finding of efficacy for SOLODYN.

8. Safety

The applicant proposed reliance on the FDA finding of safety for SOLODYN to establish the safety of MINOLIRA. To support such reliance, the applicant constructed a clinical bridge between SOLODYN and MINOLIRA by demonstrating that under fed and fasting conditions, the relative bioavailability of MINOLIRA compared to SOLODYN, measured as the 90% confidence interval of the ratio of the geometric mean of C_{max} and AUC, was within the no effect boundary of 80% to 120% of that for SOLODYN. The applicant did not conduct any clinical safety studies with MINOLIRA. Therefore the labeling will include information from the SOLODYN labeling, along with a statement that the applicant relied on information from studies conducted with minocycline hydrochloride.

The clinical pharmacology studies conducted with MINOLIRA did not reveal novel safety issues. The reader is referred to the clinical review by Dr. Patricia Brown for a discussion of the safety database.

9. Advisory Committee Meeting

No advisory committee meeting was held, as the application did not present novel issues which merited advisory committee input.

10. Pediatrics

The product will be indicated for use in patients 12 years of age and older. Product labeling will contain warnings about the risk for tooth discoloration and inhibition of bone growth in pediatric patients.

Because the application does not seek approval for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration, the requirement under the Pediatric Research Equity Act to include an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless waived, deferred, or inapplicable, does not apply.

11. Other Relevant Regulatory Issues

The applicant provided documentation of their notification of Medicis, the listed drug NDA holder, of their intent to file a 505(b)(2) application. Medicis sued the applicant following

receipt of the notification, but subsequently provided consent to an immediate effective date of approval on March 17, 2017.

There are no other unresolved relevant regulatory issues.

12. Labeling

All components of labeling were reviewed.

The proposed proprietary name, MINOLIRA, was found acceptable from a safety and misbranding perspective.

The carton and container labels were acceptable

The package insert conforms to the Physicians Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

Information in the WARNINGS AND PRECAUTIONS section was reorganized without addition of new safety information. Specifically, information relevant to pediatric and adult patients was removed from 5.1, Teratogenic Effects, and placed into two new subsections: 5.2, Tooth Discoloration, and 5.3, Inhibition of Bone Growth.

Information regarding methoxyflurane was removed from DRUG INTERACTIONS subsection 7.3. Methoxyflurane was removed from the US market for safety reasons, and inclusion of information about a drug interaction with a product no longer marketed in the US is irrelevant for the US population. Inclusion of such information may also be misleading as it does not convey the full breadth of safety risks presented by methoxyflurane.

Patient labeling (a patient package insert) is appropriate to inform patients about risks associated with minocycline use.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval
I concur with the recommendations of the multi-disciplinary review team regarding NDA 209269 MINOLIRA (minocycline hycrochloride) extended release tablet, 105mg and 135mg.

Risk-benefit assessment: The applicant relied on the FDA finding of safety and effectiveness for Solodyn. The efficacy of the product justifies the known risks of minocycline hydrochloride, which are described in labeling.

Postmarketing Risk Evaluation and Management Strategies: Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Postmarketing requirements (PMR) and commitments (PMC): None

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/s/

JILL A LINDSTROM
05/08/2017