CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201922Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 9th, 2012
From	Susan J. Walker, M.D., F.A.A.D
Subject	Division Director Summary Review
NDA/Supplement #	NDA 20-1922
Applicant Name	Ranbaxy Laboratories Limited
Date of Submission	February 4th, 2011
PDUFA Goal Date	July 14th, 2012
Proprietary Name / Established (USAN) Name	Ximino/minocycline hydrochloride
Dosage Forms / Strength	Extended-Release Capsules
Proposed Indication(s)	inflammatory lesions of non-nodular moderate to severe acne vulgaris
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review	Gordana Diglisic, M.D.
Medical Officer Review	Patricia Brown, M.D., G. Diglisic, M.D. (TL)
Clinical Pharmacology Review	Chinmay Shukla, Ph.D., Doanh Tran, Ph.D. (TL)
CMC Review	Y. Sun, Ph.D., M. Rhee, Ph.D, T. Ochletree, Ph.D.
ONDQA Biopharmaceutics	John Duan, Ph.D., Patrick Marroum, Ph.D.
Pharmacology Toxicology Review	Renquin Duan, Ph.D., Barbara Hill, Ph.D.
SEALD	J. Delasko, R.N.

OND-Office of New Drugs
CMC- Chemistry, Manufacturing and Controls
ONDQA- Office of New Drug Quality Assessment
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This application provides for the approval, via a 505(b) (2) regulatory pathway, of an oral extended-release minocycline hydrochloride capsule proposed in multiple strengths and intended for the treatment of inflammatory lesions of acne vulgaris. The application includes biopharmaceutics trials comparing the plasma concentrations of the listed drug, Solodyn, an extended-release tablet and the new drug product Ximino, an extended-release capsule.

2. Background

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.

The multi-disciplinary review team recommends approval of this application, and there are no outstanding issues. I concur with the recommendations of the team for approval.

3. CMC/Device

The drug substance, minocycline hydrochloride, is a second-generation semi-synthetic derivative of tetracycline. It is a yellow crystalline powder. The specifications for the drug substance are in line with the USP monograph for the API and include all the critical attributes that may affect the manufacturing and quality of the drug product.

During the review process, ONDQA reviewers engaged in multiple internal and external discussions regarding the application. Dr. Rhee states that the information submitted is sufficient to meet the statutory requirements for the *identity*, *strength*, and *purity* of the drug product and Dr Ocheltree concurs with the recommendation for approval.

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

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were not submitted with this application, as the applicant is relying upon the Agency's findings of safety or Solodyn (minocycline HCL) tablets through generation of a clinical bridge (comparative clinical pharmacokinetic study) to support a 505(b) (2) submission.

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

5. Clinical Pharmacology/Biopharmaceutics

The bioequivalence and dissolution studies have been extensively reviewed by the Clinical Pharmacology reviewer and the Biopharmaceutics reviewer, Dr. Shukla and Dr. Duan, and their findings follow:

The sponsor has submitted results of 2 pivotal bioavailability (BA)/ bioequivalence (BE) trials comparing the plasma concentrations obtained following administration of minocycline HCl 135 mg extended-release capsules with plasma levels obtained following administration of the listed drug, Solodyn® (minocycline) HCl 135 mg extended-release tablets under fasted (Trial# 3739) and fed (Trial# 3740) conditions in healthy adult subjects. These studies were conducted in a population representative of the United States population and included both male and female subjects. For the lower strengths, (45mg, 67.5mg, 90mg, and 112.5 mg), the Sponsor submitted a biowaiver request based on dissolution profile comparisons with the highest strength, 135 mg. Food effects were assessed on the 135mg dose (Trial #3740) and dose proportionality was evaluated between the 45mg and 135mg extended release capsules (Trial #3739).

The biopharm team concludes that the results of these trials indicate that minocycline HCL, 135mg extended-release capsules are bioequivalent to Solodyn 135mg extended-release tablets under fed and fasted conditions. The results of the biowaiver request were reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer) who concluded that the biowaiver request was acceptable and recommended approval of lower strengths provided the bioequivalence trials with the highest dose (135 mg) were deemed acceptable.

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

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

Clinical safety and efficacy trials were not necessary for this 505(b) (2) application proposing a new dosage form, an extended-release capsule. Bioavailability/bioequivalence trials were sufficient.

8. Safety

The applicant has established a bridge between their product, Ximino, and the listed drug in order to rely upon the Agency's previous findings. The 120 day safety update did not identify and new safety signals.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

A partial waiver will be granted for pediatric patients 0-12 years. Because this is a 505(b) (2) application that relies on the Agency's previous findings of safety and effectiveness, and the applicant has established that such reliance is scientifically appropriate, no additional pediatric trials are necessary.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name – Concur with Ximino
- Physician labeling - Physician labeling has been agreed upon with the applicant.
- Carton and immediate container labels - Final agreements have been reached

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – The product will be approved.
- Risk Benefit Assessment – Minocycline hydrochloride has been marketed under multiple trade names with multiple strengths and in multiple dosage forms since 1971. This product does not present any new or novel concerns.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies - None
- Recommendation for other Postmarketing Requirements and Commitments - None

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/s/

SUSAN J WALKER
07/10/2012