

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201922Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	Jun 26 , 2012
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	201922
Applicant	Ranbaxy Laboratories Limited
Date of Submission	Letter date: February 1, 2011 CDER stamp date: February 4, 2011
PDUFA Goal Date	December 4, 2011; extended to March 4, 2012 (by major Amendment), and to July 14, 2012 (b) (4)
Proprietary Name / Established (USAN) names	Ximino (minocycline hydrochloride)
Dosage forms / Strength	Extended Release Capsules / 45mg; 67.5mg; 90mg; 112.5mg and 135mg
Proposed Indication(s)	Only inflammatory lesions of non-nodular moderate to severe acne vulgaris
Recommended:	<i>Approval</i>

1. Introduction

Ximino (minocycline hydrochloride) Extended-Release Capsules, 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 dosage form of minocycline hydrochloride, an extended release capsule in array of strengths (45, 67.5, 90, 112.5, 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). 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

The current application, received February 4, 2011, is a submission after a Refuse to File action, taken by the Agency on July 16, 2010.

Ximino (minocycline hydrochloride) Extended-Release Capsules was developed under IND 107472 initially submitted on December 9, 2009. The applicant submitted a protocol for two Bioavailability (BA)/ Bioequivalence (BE) trials, 1974/09 (Fasting) and 1975/09 (Fed). Trial 1974/09 was initiated on December 1, 2009 and trial 1975/09 was initiated on December 10, 2009, before the IND was received by the Agency. Both trials included only male subjects and were conducted in a population of South Asians. The population studied was not the population representative of the United States population nor was representative of the population for whom the applicant was seeking approval. The Agency requested that the applicant address those issues (Advice/Information Request Letter dated January 14, 2010). However, the applicant completed both trials before they received the advice/information request letter from the Agency.

On May 10, 2010 the applicant submitted an NDA under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for (minocycline hydrochloride) Extended Release Capsules, 135 mg., and identified SOLODYN[®] Extended Released Tablets as the listed drug. The applicant did not address the Agency comments to the IND prior to the NDA submission and did not request a Pre-NDA meeting.

After a preliminary review, the Division found that the application was not sufficiently complete to permit a substantive review. The Division refused to file the application under 21 CFR 314.101(d). Deficiencies included the following (RTF Letter dated July 16, 2010):

Your bioequivalence studies do not contain adequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets, or the subset of patients weighing less than 200 pounds (91 kg).

You conducted your bioequivalence studies 1974/09 and 1975/09 in an ethnically homogeneous population of South Asians. This population is not representative of the United States population. Furthermore, your bioequivalence studies included only male subjects. However, you are seeking approval for an indication that affects both male and female patients.

You provided information to support only the 135mg dose, which would not provide the appropriate dose for patients weighing less than 200 pounds (91 kg).

A Type A meeting with the applicant was held on August 31, 2010. The purpose of the meeting was to discuss the deficiencies provided in the Refuse to File Letter. The applicant was advised:

“Since drug bioavailability is formulation dependent and different populations may respond differently to your formulation and the listed drug formulation, demonstrating bioequivalence (BE) of your formulation to the listed drug in an ethnically homogenous population of South Asian males can not be extrapolated as demonstrating BE in an ethnically diverse population of both males and females. We advise you to conduct new BE studies under fasting and fed conditions with their to-be-marketed 135 mg formulation. The new pivotal BE studies should be conducted in a population representative of the United States population and should include similar proportions of males and females.” (Meeting Minutes dated 09/03/10)

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 Bioavailability (BA)/ Bioequivalence (BE) trials (trial #3739 and #3740), 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 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.

Drug Product

The following strengths: 45 mg, 67.5 mg, 90 mg, 112.5 mg, and 135 mg of drug product, Ximino (minocycline hydrochloride) Extended-Release Capsule, have been proposed for marketing. The capsules are prepared by

(b) (4)

(b) (4)

The composition of the extended release capsules is described in the following table:

Ingredients	Quantity mg/Capsule					
	45 mg	67.5 mg	90 mg	112.5 mg	135 mg	% w/w
(b) (4)						
Minocycline HCl USP equivalent to Minocycline ¹	(b) (4)					
(b) (4)						
(b) (4)						
Hypromellose						
(b) (4)						
Lactose Monohydrate ²						
(b) (4)						
(b) (4)						
(b) (4)						
Magnesium Stearate						
Colloidal Silicon Dioxide						
Total (Core Tablet)						
Film Coating	(b) (4)					
Opadry (Clear) ⁴	(b) (4)					
(b) (4)	(b) (4)					
Total (Coated Tablet)	153.000	229.500	306.000	382.500	459.000	(b) (4)
Empty Gelatin Capsule Shell	1	1	1	1	1	-

¹ (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Source: adapted from CMC Review of NDA 20-1922, Yichun Sun, Ph.D., modified by clinical reviewer, P. Brown, M.D., from Table on p. 42.

Control of Drug Product:

Specifications

The applicant proposed a drug product specification for unknown impurities of (b) (4), which is higher than the specification for the listed drug product (NMT (b) (4)), and could not be supported by nonclinical toxicology data. Additionally, the limit set for (b) (4) at (b) (4) is higher than for the listed drug product (b) (4).

An Information Request Letter was sent on Jun 21, 2011. The applicant agreed to tighten the specification limit for any unknown impurity from NMT (b) (4) to NMT (b) (4) and the specification limit for (b) (4) from NMT (b) (4) to NMT (b) (4) in the amendment dated July 5, 2011. However, no meaningful expiration dating period could be recommended because of the high levels of unknown impurity, which are higher than the acceptance criterion (b) (4), in the stability samples. The deficiency was communicated with the applicant via a T-Con dated August 3, 2011.

During the teleconference conducted on August 3, 2011, the applicant stated that they had developed a new HPLC method for quantitation of impurities in the drug product. They clarified that the new HPLC method allows for identification of additional impurities (newly found in the drug substance) that previously could not be well resolved using the previous HPLC method. The applicant stated that the unknown impurity observed in the drug product is attributed to one of the four newly specified known related impurities, (b) (4), in the drug substance. An information request was sent to the sponsor on August 4, 2011 requesting additional information about the new HPLC method and a revision of the impurity specifications based on the data generated with the new HPLC method. An amendment in response to the IR was received on August 10, 2011. The applicant updated drug product specification for all strengths of the extended release capsules with inclusion of revised limits for (b) (4) and any unknown impurity (b) (4) and for microbial limit test (USP <1111>). Per the primary chemistry reviewer, the proposed acceptance criteria are acceptable.

Four new impurities, (b) (4), (b) (4), (b) (4) and (b) (4), were identified in the drug substance (according to the amendment dated July 5, 2011). Per CMC reviewer: "Two of the newly identified impurities (b) (4) co-elute with the minocycline peak in the HPLC method used for identification and assay (strength). The retention time is not specific to minocycline hydrochloride and the values of the assay are overestimated because of the co-elution." The chromatograms of the revised HPLC method used for quantitation of impurities in the stability samples are different from those provided in the revised HPLC method validation report in terms of baseline. The CMC reviewer states that the accuracy and precision of the revised HPLC method for impurities are questionable due to baseline changes

and, therefore, “the accuracy of the data obtained using the revised HPLC method for impurities cannot be ascertained. . . . The (b) (4) impurity, which was unknown in the original HPLC method, is re-categorized as related substance/degradant and will be monitored in the drug product specification with a limit of NMT (b) (4) at release and NMT (b) (4) during stability. The limits for all the other process related impurities in the drug product specification are in line with the drug substance specification limits for the respective impurities.” The applicant proposed to monitor all the known impurities of the drug substance as well as degradants in the drug product.

On August 30, 2011, the applicant provided revised impurity specifications based on the new HPLC method:

Impurity	Specification (% w/w)	
	Regulatory (release)	Self life
(b) (4)		

From a Pharmacology/Toxicology perspective, the proposed impurity specifications are acceptable. (Pharmacology/toxicology review by Requin Duan Ph.D. dated 10/04/11)

The primary CMC reviewer, Yichun Sun, Ph.D., concluded that “although the acceptance criteria set in the drug product specification are adequate, the drug product specification is not adequate to assure the identity, purity, strength and quality of the drug product because of the issues of the HPLC methods used for assay and purity”.

Dr. Sun recommended “*Not-Approval*” for this application. The recommendation is based on the following reasons:

1. The application has not provided adequate information to assure the identity, strength, and purity of the drug product.
2. This conclusion was based on the evaluation of the analytical methods described in the application for the *identity*, “assay” for the *strength*, and “assay” for the *purity* with regard to the related substances.
3. The Office of Compliance has not issued an overall recommendation of “Acceptable” for the facilities involved in manufacturing and testing the drug products described in this application.
4. Label/labeling issues have not been satisfactorily resolved. (Waiting for the container/carton labels to be fixed by the applicant)

(Yichun Sun, Ph.D. Review Chemist, DNDQA II; ONDQA; dated 09/28/11)

Analytical methods:

Re-evaluation of the analytical methods (HPLC method for the *identity* test, HPLC method of the assay for the *strength* test, and HPLC method of related substances for the *purity* test) were done by Moo Jhong Rhee, Ph.D., Branch Chief, Division of New Drug Quality Assessment II (DNDQA II):

1. HPLC method for the *identity* test:

Two of the newly identified impurities (b) (4) co-elute with the minocycline peak in the HPLC method used for identification and assay. These are to be controlled within (b) (4) and (b) (4) respectively. In Dr. Rhee's opinion, "Ideally, the impurity peaks should be sufficiently separated from the drug substance peak as discussed by Dr. Sun; however, the contribution of these two impurities to the drug substance peak is negligible and do not compromise the ability to identify the drug substance in the drug product when compared to the reference standard." He notes that a second test utilizing an UV spectroscopic method is used to further assure the identity of the drug substance. Additionally, "complementary assurance of the "*identity*" comes from the fact that, during the whole manufacturing process, the drug substance is checked for the *identity* as one of the routine incoming raw material controls before it is added to the formulation."

2. HPLC method of the assay for the *strength* test

Dr. Rhee states that "...from the practical perspective where the strength of a dosage form is allowed for varying +/- 10% of the label claim, it is questionable if the error in the assay arising from the two co-eluting impurities (maximum of (b) (4) together) could potentially compromise the strength of the drug product. "

3. HPLC method of related substances for the *purity* test

Dr. Rhee comments that: "...The nature of the humps observed in the chromatographs for the stability samples is not clear at this time. However, as long as the impurities can be quantitated in a reasonably accurate manner by the computer associated with the HPLC system, the risk to the quality of the drug product are negligible as long as the calculated levels are within the approved acceptance criteria." Dr. Rhee recommends, to assure that the method is appropriate, that the method be evaluated by the Office of Testing and Research, Division of Pharmaceutical Analysis (DPA).

Branch Chief DNDQA II/ONDQA Conclusion and Recommendation (Memorandum by Moo-Jhong Rhee, Ph.D., dated September 28, 2011)

"... although the information submitted in the application may not be as ideal as the primary reviewer, Dr. Sun, had expected, the information as submitted is sufficient enough to meet the statutory requirements for the *identity*, *strength*, and *purity* of the drug product."

Evaluation by Director, DNDQA II, ONDQA

(Memorandum by Terrance Ocheltree, Ph.D., R.Ph., dated September 30, 2011)

“... While the methods and method validations for Identity, Assay, and Purity (impurities) are not ideal, as identified and discussed by Dr. Sun, the risk that these will negatively impact the overall quality of the product or patient safety is minimal. I further concur with Dr. Rhee’s recommendation to submit the methods to DPA via the ONDQA Method Validation Program for further evaluation.

Therefore, I concur that the ONDQA recommendation for this application is a Complete Response based on the following two pending issues:

- Lack of an “Acceptable” recommendation from the Office of Compliance
- Unresolved label/labeling issues.”

Manufacturers:

On December 9, 2011, the Office of Compliance gave an overall “Acceptable” recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product. (Memorandum by Yichun Sun, Ph.D. Review Chemist, ONDQA; Premarketing Assessment Division II; ONDQA dated 01/31/12).

Container Closure System

All the components used in the container closure system comply with the FDA 21 CFR regulations. The blister pack is child-resistant.

On January 18, 2012, the applicant submitted an amendment providing the finalized mock up container and carton labels. All the labels have the required information.

The CMC reviewer, Yichun Sun, Ph.D., recommended *Approval* of this application (Memorandum by Yichun Sun, Ph.D. Review Chemist, ONDQA; Premarketing Assessment Division II; ONDQA dated 01/31/12)

4. Nonclinical Pharmacology/Toxicology

The applicant did not submit any nonclinical studies conducted with Ximino Extended-Release Capsules.

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 Ximono application. Information from the SOLODYN[®] package insert on these topics has been incorporated into Ximio 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 Ximino labeling when become available.

There are no outstanding pharmacology-toxicology issues.
The pharmacology-toxicology reviewer, Requin Duan Ph.D., recommended *Approval* of this application (review dated 10/04/11).

5. Clinical Pharmacology/Biopharmaceutics

The applicant pursued a 505(b) (2) pathway for Ximino Extended-Release Capsules and identified SOLODYN[®] Extended Release Tablets as the listed drug product.

To support this application, the applicant submitted data from two Bioavailability (BA) and Bioequivalence (BE) trials:

- trial # 3739, entitled “*A Three-Way Crossover, Open-Label, Balanced, Randomized, Single-Dose, Fasting, Bioequivalence and Dose Proportionality Study of Minocycline HCl 45 mg ER Capsules, Minocycline HCl 135 mg ER Capsules, and Solodyn[®] 135 mg ER Tablets in Normal, Healthy, Non-Smoking Male and Female Subjects*” and
- trial # 3740, entitled “*A Three-Way Crossover, Open-Label, Balanced, Randomized, Single-Dose, Bioequivalence and Food-Effect Study of Minocycline HCl 135 mg ER Capsules and Solodyn[®] 135 mg ER Tablets in Normal, Healthy, Non-Smoking Male and Female Subject*”.

These trials were conducted in a population representative of the United States population and included forty-two subjects enrolled in each of the two trials.

The objectives of the above trials were to:

1. Demonstrate BE between Ximino 135 mg ER Capsules and SOLODYN[®] 135 mg ER Tablets under fasting and fed conditions
2. Assess the dose proportionality of Ximino 45 mg and 135 mg ER Capsules under fasting conditions
3. Assess the effect of food on Ximino 135 mg ER Capsules

Base on the results from BA/BE trials, Ximino 135 mg ER Capsules are bioequivalent to SOLODYN[®] 135 mg ER Tablets under fasted and fed conditions (Table 1 and 2):

Table 1: Relative bioavailability analysis for minocycline under fasted conditions of Test: 1 minocycline HCl 135 mg ER capsule versus Reference: 1 SOLODYN[®] 135 mg ER tablet

Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn 135 mg ER Tablet		
AUC _{0-t} (ng*hr/mL)	13663.60 (30.27)	13681.66 (31.80)	92.94 % to 108.30%	100.32%
AUC _{0-inf} (ng*hr/mL)	13873.69 (30.05)	13861.77 (31.51)	93.32% to 108.30%	100.53%
C _{max} (ng/mL)	749.54 (37.11)	780.10 (38.85)	88.84% to 105.32%	96.73%

Source: Clinical Pharmacology Review by Chinmay Shukla, Ph.D. dated 10/04/11

Table 2: Relative bioavailability analysis for minocycline under fed conditions of Test: 1 minocycline HCl 135 mg ER capsule versus Reference: 1 SOLODYN[®] 135 mg ER tablet

Parameter	Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Minocycline 135 mg ER Capsule	Solodyn 135 mg ER Tablet		
AUC _{0-t} (ng*hr/mL)	13546.24 (21.91)	13229.22 (23.49)	93.89 % to 108.89%	101.11%
AUC _{0-inf} (ng*hr/mL)	13850.54 (21.91)	13513.70 (23.40)	93.93% to 108.92%	101.15%
C _{max} (ng/mL)	824.57 (24.12)	770.97 (25.75)	98.05% to 114.28%	105.85%

Source: Clinical Pharmacology Review by Chinmay Shukla, Ph.D. dated 10/04/11

Biowaiver of lower strengths

Since the two BA/BE trials were conducted only with the highest proposed strength (135mg), the applicant submitted a biowaiver request for lower strengths (45, 67.5, 90 and 112.5 mg) based on dissolution profile comparisons with the highest strength (135 mg).

This was reviewed by Dr. John Z. Duan (Biopharmaceutics reviewer). Dr. Duan concluded that the biowaiver request was acceptable and recommended approval of lower strengths provided the BE trials with the highest dose (135 mg) are deemed acceptable (Dr. John Z. Duan in DARRTS dated 08/31/2011)

Dose-proportionality of the 45 mg and 135 mg ER Capsules was evaluated as part of BE trial # 3739. The results of dose proportionality evaluation indicated that AUC and C_{max} of minocycline increased in a dose proportional manner following oral administration of 45 mg and 135 mg ER capsules.

The effect of food on minocycline HCl 135 mg ER capsule was evaluated as part of trial # 3740. The clinical pharmacology reviewer concluded: “The results indicated that comparing minocycline HCl 135 mg ER capsule under fed versus fasted conditions showed that the 90%

confidence interval (CI) of the ratio of geometric means of AUC_{0-t} and $AUC_{0-\infty}$ were between 80 - 125 %. However, the 90% CI of the ratio of the geometric mean of C_{max} was 118.22 - 137.61 % which was outside the no effect range of 80 -125%. This increase in C_{max} with food is unlikely to result in any safety issues because based on the original approval of Solodyn[®] with only 3 strengths, the actual dose with the approved Solodyn[®] ranged from 1.48 to 0.76 mg/kg while the proposed dose for minocycline ER capsule (5 different strengths) will range from 1.21 to 0.82 mg/kg. The 28% increase in C_{max} due to food would still be within the range determined to be safe and effective in the original Solodyn[®] approval. Hence, no dose adjustment with food will be required.”

The clinical review team concurs with this assessment.

The Clinical Pharmacology reviewer 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 Chinmay Shukla, Ph.D. dated 10/04/11).

The Clinical Pharmacology team made the following labeling recommendations:
(the **bold and underlined** text indicates insertion recommended by the reviewer and the strikethrough text indicates recommended deletion)

7.5 Low Dose Oral Contraceptives

In a multi-center study to evaluate the effect of minocycline hydrochloride **(administered as another extended release formulation which is bioequivalent to TRADE NAME)** on low dose oral contraceptives, hormone levels over one menstrual cycle with and without minocycline hydrochloride 1 mg/kg once-daily were measured. Based on the results of this trial, minocycline-related changes in estradiol, progestinic hormone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, can not be ruled out. To avoid contraceptive failure, female patients are advised to use a second form of contraceptive during treatment with minocycline.

12.3 Pharmacokinetics

(b) (4) ~~-TRADE NAME-is~~ not bioequivalent to (b) (4) release minocycline products. (b) (4)

Following administration of a single dose TRADE NAME (135 mg) to healthy male and female adult subjects, the mean (SD) AUC(0-∞) and Cmax were 12.87

(4.04) mcg x hr/mL and 0.68 (0.25) mcg/mL, respectively, under fasting conditions.

When a single dose TRADE NAME (135 mg) was administered with a high fat meal to the same subjects in the same study in a crossover design, the mean (SD) AUC(0-∞) and Cmax were 14.16 (3.10) mcg x hr/mL and 0.85 (0.20) mcg/mL, respectively.

A single-dose, (b) (4) crossover study demonstrated that TRADE NAME (b) (4) (45 mg and 135 mg) exhibited dose-proportional pharmacokinetics.

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 Bioavailability (BA)/ Bioequivalence (BE) trials (trial #3739 and #3740)] between their product, Ximino, 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 Ximio 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, Ximino, 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 Bioavailability (BA)/ Bioequivalence (BE) trials (trial #3739 and #3740). The applicant submitted additional safety data from these two pharmacokinetic trials. There were no deaths or serious adverse events. Attribution of adverse events to specific treatment whether Ximino or SOLODYN[®] is rendered imprecise by the cross-over design of trials 3739 and 3740. The most common adverse events reported in subjects exposed to Ximino (all doses, fed, and fasting) were headache 8/84 (9.5%) and elevated AST 3/84 (3.6%) and ALT 2/84 (2.3%). These adverse events are currently included

in labeling for the listed drug SOLODYN[®]. All adverse events were of mild severity except for one case each of vomiting, back pain, and nail infection, which were classified as moderate in severity. Evaluation of laboratory findings and vital signs did not reveal clinically significant safety signals.

The 120-day safety update was reviewed, and did not identify new safety signals. The reader is referred to the clinical review (dated June 26, 2012) by Dr. Patricia Brown and the review by Jessica Weintraub, Pharm D., Safety Evaluator; Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance I (DPV I) dated January 18, 2012 for full discussion.

Information from the SOLODYN[®] package insert including Sections 4 CONTRAINDICATIONS; 5 WARNINGS AND PRECAUTIONS; 6 ADVERSE REACTIONS has been incorporated into Ximio 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, like 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 applicant seeks approval for use in adolescents aged 12 to 17 years (and adults), and waiver for ages below 12 years because the product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested (0-12). The justification for partial waiver follows:

0-7 yr. old:

As per listed drug labeling, section

8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use

Use of tetracycline-class antibiotics below the age of 8 is not recommended due to the potential for tooth discoloration

5 WARNINGS AND PRECAUTIONS 5.1 Teratogenic Effects

B. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF 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 drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT).

8-11 yr. old:

The majority of patients with acne vulgaris are in their middle and late teenage years. The onset of acne is associated with an increase in serum levels of DHEAS and sebum production. The onset of sebum production can herald the onset of menarche by up to a year. Menarcheal data from the Third National Health and Nutrition Survey indicate that the median age at menarche for US girls is 12.43 years (Chumlea C, et al. "Age at Menarche and Racial Comparisons in US Girls." Pediatrics 2003;111:110-113.) Thus the majority of US girls having acne would be expected to be age 12 and older.

12-16 yr. old:

Listed drug (SOLODYN[®]) is approved for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. Bioequivalence with the listed drug has been established.

The application was presented to the Pediatric Review Committee (PeRC) on September 7, 2011. The committee concurred with the Division's recommendation:

- to grant a partial waiver for pediatric patients aged 0-12 years, and
- because this is a 505(2)(b) application that relies for approval on Agency's finding of safety and effectiveness for a listed drug, SOLODYN[®], and the applicant has established that such reliance is scientifically appropriate (by comparative bioavailability data), no additional pediatric trials are required.

11. Other Relevant Regulatory Issues

- OSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted. (Review by Dr. Charles Bonapace dated 09/02/11; Office of Scientific Investigations)
- By letter dated February 25, 2009, CDER invoked the Agency's Application Integrity Policy (AIP) on the applicant's facility in Paonta Sahib, India. On January 26, 2012, the District Court for the District of Maryland entered a consent decree of permanent

injunction (decree) and imposes AIP-like requirements on the applicant's applications containing data or other information developed or generated at its facility in Dewas, India.

(b) (4), (b) (5)



- DDMAC found the tradename Ximino to be non-promotional. Division of Medication Error Prevention and Analysis (DMEPA) found the tradename Ximino not vulnerable to name confusion that could lead to medication errors, and acknowledged it as acceptable (Proprietary Name Review by Lissa C. Owens, PharmD dated 10/26/11)

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. 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 the applicant's proposed **12.3 Pharmacokinetics Section** (Clinical Pharmacology recommendation regarding labeling: see section 5 of this review)

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Approval*

- I concur with the recommendations of the multi-disciplinary review team for approval of NDA 201922, Ximino (minocycline HCl) Extended-Release Capsules pending agreement of the applicant with the recommended labeling revisions.

Risk Benefit Assessment

- I find that the applicant constructed an adequate clinical bridge to the listed drug, SOLODYN[®] Extended Released Tablets, for the purposes for which the application relies on the FDA finding 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
06/26/2012