CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201922
Priority or Standard	Standard
Submit Date(s)	February 1, 2011
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PDUFA Goal Date	July 14, 2012
Division / Office	DDDP/ODEIII
Reviewer Name(s)	Patricia C. Brown, MD
Review Completion Date	June 26, 2012
Established Name	Minocycline hydrochloride
(Proposed) Trade Name	Ximino
Therapeutic Class	Acne agent
Applicant	Ranbaxy Laboratories Limited
Formulation(s)	Extended Release Capsules
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

APPEARS THIS WAY ON ORIGINAL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Review of the pharmacokinetic studies, 3739 and 3740, has demonstrated that Ximino (minocycline hydrochloride) 135 mg Extended Release Capsules are bioequivalent to the listed drug Solodyn® (minocycline HCl) 135 mg Extended Release Tablets. The applicant's biowaiver request for lower strengths (45, 67.5, 90, 112.5 mg) is acceptable. Based on these findings, this reviewer recommends approval of Ximino (minocycline hydrochloride) Extended Release Capsules 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, Ranbaxy, is submitting for approval, a new dosage form, an extended release capsule in array of strengths (45, 67.5, 90, 112.5, and 135 mg). As a note of comparison, the listed drug Solodyn® is also available in an array of strengths (45, 55, 65, 80, 90, 105, 115, and 135 mg). The availability of a capsule formulation may provide an alternative to those who might find the extended release tablets less acceptable due to taste or to ease of swallowing.

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 HCl) Extended Release Tablets. The scientific justification for this reliance is provided by data from two bioequivalence trials performed in humans, trials 3739 and 3740.

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

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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, Ranbaxy Laboratories Limited, has submitted a 505(b)2 application for Ximino (minocycline hydrochloride) Extended Release Capsules 45 mg/ 67.5 mg/ 90mg/ 112.5 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 dosage form (extended release capsules). 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 dosage form from extended tablets to extended release capsules. The ANDA process requires pharmaceutical equivalence; same active ingredient(s), dosage form, and route of administration as the listed drug.

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 bioequivalence studies 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 Ximino extended release capsules, 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 Ximino Extended Release Capsules 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.

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Minocycline hydrochloride, USP is a yellow crystalline powder, sparingly soluble in water, soluble in solutions of alkali hydroxides and carbonates, slightly soluble in alcohol, practically insoluble in chloroform and in ether.

Ximino (minocycline hydrochloride) Extended Release Capsules for oral administration contain minocycline hydrochloride, USP equivalent to 45 mg, 67.5 mg, 90 mg, 112.5 mg, or 135 mg of minocycline. The 45 mg, 67.5 mg, 90 mg, 112.5 mg, and 135 mg capsules contain the following inactive ingredients: colloidal silicon dioxide, D&C Yellow #10 (in 45 mg strength), FD&C Blue #1, FD&C Yellow #6 (in 45 mg, 67.5 mg, and 135 mg strength), gelatin, hypromellose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and titanium dioxide.

The 45 mg, 67.5 mg, 90 mg, 112.5 mg, and 135 mg capsules also contain Opadry Clear which contains hypromellose, polyethylene glycol 400, polyethylene glycol 6000, and talc.

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

Currently there are multiple products available to treat acne, both topical and systemic:

Table 1: Currently Available Treatments for Acne

Categories	Drug Products
Topical	
Salicylic acid	Multiple products
Benzoyl peroxide	Multiple products
Sulfa products	Sulfacetamide, Sulfacetamide/Sulfur
Azelaic acid	Cream, gel
Antibiotics	Clindamycin, Erythromycin
Retinoids	Tretinoin, Adapalene, Tazarotene
Systemic	
Antibiotics	Erythromycin, Tetracycline, Doxycycline, Minocycline
Retinoids	Isotretinoin
Hormonal therapies	Various oral contraceptives

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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. It is also marketed as a sterile powder for injection 100 mg/vial. Generic formulations include oral tablets and capsules (both immediate release). Generic formulations also include 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 (excerpted) from Warnings and Precautions from approved labeling for Solodyn® (July 2011):

1) Teratogenic Effects: Minocycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman. 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). Enamel hypoplasia has also been reported.
2) Pseudomembraneous 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) Pseudotumor cerebri (benign intracranial hypertension) in adults and adolescents has been associated with the use of tetracyclines and minocycline.

7) 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® (July 2011) adverse events seen in clinical trials at a rate greater than placebo include fatigue, dizziness, pruritus, malaise, somnolence, urticaria, tinnitus, and arthralgia.

Labeling for minocycline includes the following from Contraindications from approved labeling for Solodyn® (July 2011): "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

The current application, received February 4, 2011, is a submission after a Refuse to File action, taken by the Agency on July 16, 2010. The current application is for a new dosage form for minocycline hydrochloride and the applicant is filing a 505(b)(2) application under which pivotal pharmacokinetic studies are performed. As cited by the applicant, 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:
Under IND 107,472 the applicant, Ranbaxy Lab. Ltd submitted (12/9/2009) a protocol for two bioequivalence trials, 1974/09 (Fasting Trial) and 1975 (Fed Trial). These studies were to be randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover, bioequivalence studies of minocycline hydrochloride extended release capsules 135 mg from Ranbaxy Laboratories Ltd. and Solodyn® (minocycline HCL) Extended Release Tablets 135 mg from Medicis under fasting conditions (1974) or under fed conditions (1975).

An advice letter was sent January 14, 2010 that included clinical and clinical pharmacology comments.

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Clinical:
1. Thyroid function tests and an ANA should be added to the baseline labs. Patients with abnormalities of either TFT's or ANA should be excluded from participation in the study.
2. Male volunteers who are actively trying to father a child should also be excluded from participation in the study.

[Pertinent exclusion criteria were added to the clinical pharmacology trials (3739 and 3740) in the current application, NDA 201922]

Clinical Pharmacology:
Comments included the following:
"The pivotal PK study will be conducted in India. Explain how the results of the proposed study will reflect the safety and efficacy in the ethnically diverse population in USA."

On May 10, 2010 the applicant submitted an NDA under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (minocycline hydrochloride) Extended Release Capsules, 135 mg.

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 (from RTF letter 7/16/2010):

> 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 meeting was held August 31, 2010 to discuss comments provided in the Refuse to File letter dated July 14, 2010. The principal area of discussion at this meeting revolved around the applicant's belief that they had conducted BE studies sufficient to support the 135 mg strength, filed pursuant to Section 505(b)(2) of the Federal Food, Drug, and

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Cosmetic Act and relying on the agency's findings for a previously approved drug (Solodyn®) to make the application sufficiently complete to permit a substantive review.

The Agency did not agree. The applicant had completed both studies before receiving the advice/information request letter from the Agency on 1/14/2010. The applicant did not address the Agency's comments to the IND prior to the NDA submission.

From Meeting minutes dated August 31, 2010:

> 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 your 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.

2.6 Other Relevant Background Information

The applicant's capsule 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

3.1 Submission Quality and Integrity

The overall organization of the submission and the ease of finding information were adequate. However, the information provided in the original submission of February 4, 2011 was inadequate. A number of information requests were made in 2011, March 22, April 8, May 27, June 13, June 21, July 19, August 4, and September 1 by the CMC, biopharmaceutical, non-clinical, and clinical reviewers for data, information, clarifications, and to provide comments.

The information request of September 1, 2011 requested all safety information available to data regarding the new drug since a 120 day safety update had not been provided with the submission. The applicant's response to the September 9 request consisted of

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an unsolicited major amendment which necessitated extending the NDA goal date by three months to provide time for a full review of the submission.

Application Integrity Policy (AIP):

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

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

3.2 Compliance with Good Clinical Practices

According to the clinical trial reports, the two studies in the clinical development program were conducted in compliance with Good Clinical Practice (GCP) standards. Treatment of human subjects in the two studies met the requirements of 21 CFR Parts

50 and 56. Clinical investigations and informed consent were reviewed and approved by an Institutional Review Board prior to trial initiation. Informed consent was obtained.

Regarding the treatment of human subjects, the applicant also states that they also met the requirements of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the Declaration of Helsinki, the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (August 1998), and Division 5 of the Canadian Food and Drug Regulations.

For Trial 3739, the applicant states that due to errors in Subject Information and Consent Form (Version 1.1), a Subject Information and Consent Form Update was generated, approved by the IRB, and provided to subjects. This update involved the agreement by the subject that they would not donate blood until 45 days after the last blood draw of Period III rather than, as previously described, Period II of Trial 3739.

OSI Audit:
The Office of Scientific Investigations (OSI), Division of Bioequivalence and GLP Compliance (DBGC) was consulted for biopharmaceutical inspections for clinical (b) (4) for Trial 3739 and 3740. The clinical (b) (4) was conducted at Lambda Therapeutic Research, Inc., Toronto, Ontario, Canada. The rationale for this international inspection was that: "There is a lack of domestic data that solely supports approval."

An audit of the clinical (b) (4) of studies 3739 and 3740 was conducted by OSI, DBGC. Based on the audit findings, DBGC recommended that the clinical (b) (4) data generated at Lambda Therapeutic Research Inc. (Toronto, Ontario, Canada) for Studies 3739 and 3740 be accepted for review.

A Memorandum of inspection findings was issued by OSI - Charles R. Bonapace, Pharm.D, dated September 2, 2011. Although regulatory violations were noted, OSI stated that they were unlikely to have a significant impact on data integrity. The OSI Memorandum of inspection findings was reviewed by the clinical and clinical pharmacology reviewers, who concurred violations noted were unlikely to have a significant impact on data integrity.

The Final Classification by OSI was VAI, voluntary action indicated.

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3.3 Financial Disclosures

The applicant submitted form FDA 3454 for studies 3739 and 3740, certifying that they, the applicant, had not entered into any financial arrangements with the clinical investigators. A list of the clinical investigators for studies 3739 and 3740 was provided.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see chemistry review by Yichun Sun, Ph. D., dated September 28, 2011.

Drug Product:
To produce the drug product, gelatin capsules are filled with extended release minitablets as outlined in the following table:

Table 2: Configuration of Minocycline Extended Release Capsules

Strength of Capsule	Number of Minocycline HCl Extended Release Minitabs			Capsule
	45 (mg)	56.25 (mg)	67.5 (mg)	
45 (mg)	1	-	-	One EG (Size 0) capsule shell - Opaque bluish green cap and opaque yellow body hard gelatin capsule (size 0) with 'RI18' imprinted on both cap and body in black ink.
67.5	-	-	1	One EG (Size 0) capsule shell - Opaque bluish green cap and white body hard gelatin capsule (size 0) imprinted with 'RI92' on both cap and body in black ink
90	2	-	-	One EG (Size 0) capsule shell - Opaque light blue cap and body hard gelatin capsule (size 0) with 'RI19' imprinted on both cap and body in black ink.
112.5	-	2	-	One EG (Size 0) capsule shell - Opaque light blue cap and white body hard gelatin capsule (size 0) imprinted with 'RI93' on both cap and body in black ink.
135	3	-	-	One EG (Size 0) capsule shell - Opaque bluish green cap and opaque light blue body hard gelatin capsules (size 0) with 'RI20' imprinted on both cap and body in black ink

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Source: Chemistry Review NDA 20-1922, Yichun Sun, Ph.D., from Table on p. 41.

The composition of minocycline hydrochloride extended release capsules is shown in the following table:

Table 3: Composition of Minocycline Extended Release Capsules

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 Silcon Dioxide						
Total (Core Tablet)						
Film Coating						
Opadry (b) (4) (Clear)[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] Based on (b) (4) assay on anhydrous basis as minocycline (b) (4),
The exact quantity of minocycline HCl for each strength of extended release tablets to be calculated by:

(b) (4)

2 (b) (4)

Source: Chemistry Review NDA 20-1922, Yichun Sun, Ph.D., modified by clinical reviewer from Table on p. 42.

Regarding excipients, the choice of the qualitative formulation of the extended release minitablets, was based on the ingredients used in the listed drug formulation [ingredients listed in the package insert of Solodyn® (minocycfine HCl) Extended Release Tablets (NDA 50-808)]. The following table provides a comparison of excipients between Ranbaxy's extended release minitablets and the listed drug, Solodyn®, an extended release tablet.

Table 4: Comparison of Excipients

Listed Drug ***(Extended Release Tablet)***	**Ranbaxy's Drug Product*** ***(Extended release Minitablets)***	**Function**
Lactose Monohydrate NF	Lactose Monohydrate NF	(b) (4)
Hypromellose type 2910 USP	Hypromellose type (b) (4)	
Colloidal silicon dioxide NF	Colloidal silicon dioxide NF	
Magnesium stearate NF	Magnesium stearate NF	
Carnauba wax	-	
Opadry II pink: Lactose monohydrate NF Hypromellose 2910 USP Titanium dioxide USP Triacetin USP PEG 3350 NF Iron Oxide Red, NF	Opadry (b) (4) Lactose monohydrate NF Hypromellose (b) (4) Talc USP PEG 400 PEG 6000	Film coating

* The listed drug is an extended release tablet. The applicant's drug products are hard gelatin capsules filled with the extended release minitablets.

Source: Chemistry Review NDA 20-1922, Yichun Sun, Ph.D., from Table on p. 48.

Novel excipients: There are no novel excipients used in the drug product.

Container closure system: The evaluation by the chemistry reviewer is; acceptable. All components used in the container closure system comply with FDA 21 CFR regulations and the blister pack is child-resistant.

Manufacturers: The Establishment Evaluation for the manufacturing facilities is complete as of December 9, 2011. The Office of Compliance has given an overall acceptable recommendation for the manufacturing facilities.

Regarding Control of Drug Product (Specifications)

In the early phases on NDA review a number of issues were noted:

A) The applicant proposed a specification limit [redacted] (b) (4) for any unknown impurity which is much higher than the one [redacted] (b) (4) set for the listed drug product (Solodyn®) and the proposed acceptance criterion of [redacted] (b) (4) for any unknown impurity was not justified by nonclinical toxicology data.

B) Ximino (minocycline hydrochloride) Extended Release Capsules were not tested for microbial limits.

C) The specification limit set for [redacted] (b) (4) (a degradant impurity) at [redacted] (b) (4) was higher than that [redacted] (b) (4) for the listed drug product Solodyn®.

To resolve these issues, a T-con was held (August 3, 2011), an Information request was sent (August 4, 2011), and amendments were received August 10 and 30, 2011.

Amendment of August 10, 2011:

The applicant updated the drug product specification for all strengths of the extended release capsules with inclusion of revised limits for [redacted] (b) (4) and tightened the specification for any unknown impurity to [redacted] (b) (4) Updated drug product specifications included the microbial limit test (USP <1111>). The CMC reviewer found the proposed acceptance criteria acceptable.

The drug substance specification was updated to include four newly identified impurities, which are [redacted] (b) (4) Two of the newly identified impurities [redacted] (b) (4) co-elute with the minocycline peak in the HPLC method used for identification and assay (strength). The CMC reviewer noted that, in terms of baseline, the chromatograms of the revised HPLC method used for quantitation of impurities in the stability samples are different from those provided in the HPLC method validation report. Per the CMC reviewer, due to the baseline changes, the accuracy and precision of the revised HPLC method for impurities are questionable and, therefore, the accuracy data obtained using the revised HPLC method for impurities can not be ascertained.

Amendment of August 30, 2011:

In this amendment the applicant proposed to monitor all the known impurities of the drug substance (process impurities as well as degradants) in the drug product. The [redacted] (b) (4) impurity, which was unknown in the original HPLC method, is re-categorized as a related substance/degradant.

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According to the CMC reviewer, 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.

Table 5: Specification of Minocycline HCl Extended Release Capsules

Related Substances (%w/w) by HPLC	Regulatory	Shelf Life
(b) (4)		

Source: Chemistry Review NDA 20-1922, Yichun Sun, Ph.D., adapted from Table on p. 112.

Revised specifications (from amendment of August 30, 2011) for the drug product included those for related substances (see Table 5 above). The pharmacology/toxicology reviewer found these acceptable. Please see pharmacology/toxicology review by Renqin Duan, Ph.D., dated October 4, 2011.

The CMC reviewer concludes, regarding drug product specifications (CMC review section, P.5.1 Specifications), that this section of the application is unacceptable. While monitoring all the impurities (drug substance related and degradants) is acceptable, the proposed changes in the amendment of August 30 did not resolve issues regarding the regulatory test methods used to assess identity, strength and purity of the drug product.

Regarding Analytical Procedures (P.5.2)
The CMC reviewer has evaluated the HPLC method as unacceptable for identification. Because the retention time of the major peak in the HPLC chromatogram is not specific to minocycline hydrochloride, the identity of the drug substance can not be reasonably assured by the HPLC method.

The CMC reviewer has found the evaluation of related substances by the applicant to be unacceptable. The chromatograms of the revised HPLC method used for quantitation of impurities in the stability samples are noted to be different from those provided in the HPLC method validation report. While the baseline was fairly flat in the chromatograms shown in the validation report, the baseline of the actual stability samples has “large bumps”. Because of the baseline changes, the accuracy and

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precision of the revised HPLC method for impurities are questionable. In addition, the revised HPLC method, which is proposed to be employed to quantitate all the impurities (related and degradants), has not been fully validated for quantitation of all the impurities. According to the CMC reviewer, the purity of the drug product can not be adequately assured by the drug product specification.

Regarding Stability (P.8)

Stability Summary and Conclusion

According to the CMC reviewer, the applicant's proposal to monitor all the process related impurities of the drug substance and its degradation products in the drug product is acceptable. The proposed acceptance criterion of NMT (b) (4) for the (b) (4) impurity is acceptable to the Pharm/Tox review team, Drs. Renqin Duan and Barbara Hill based on non-clinical data. The stability samples have been analyzed using the revised HPLC method (for impurities) only at the current time point (month 22 for 45, 90 and 135 mg Ximino Extended Release Capsules; 15 months for 67.5 mg and 112.5 mg Ximino Extended Release Capsules). However, according to the CMC reviewer, the revised HPLC for impurities has not been properly developed and validated for quantitation of all the impurities; therefore, the purity of the drug product can not be assessed during its shelf-life.

The CMC reviewer concludes that the proposed expiration dating period of 24 months for the drug product is not supported by stability data provided because of the deficiencies in the regulatory analytical methods for identity, purity and strength.

Recommendation of Primary Chemistry Reviewer:

Recommendation and Conclusion on Approvability

This NDA has NOT provided sufficient CMC information to assure the identity, strength, purity, and stability of the drug product as required by 21 CFR 314.25 (b)(1).

The overall acceptable recommendation of Establishment Evaluation is still pending.

There are issues on the label/labeling that need to be resolved.

Therefore, from a CMC perspective, this NDA is not recommended for "Approval" in its present form until all the CMC issues have been adequately addressed, and the Office of Compliance issues an overall "Acceptable" recommendation for all the manufacturing and test facilities, and all the issues on label/labeling are resolved.

Evaluation by Chemistry Branch Chief, DNDQA II/ONDQA

Please see Memorandum by Moo-Jhong Rhee, Ph.D., dated September 28, 2011.

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Dr. Moo-Jhong Rhee reevaluated the analytical methods in the NDA application as follows:

Identity:
Two of the newly identified impurities [redacted] (b) (4) co-elute with the minocycline peak in the HPLC method used for identification and assay. These are to be controlled within [redacted] (b) (4) respectively. In Dr. Rhee's opinion, "…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 also that a second test utilizing an UV spectroscopic method is used to further assure the identity of the drug substance.

Strength:
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 [redacted] (b) (4) together) could potentially compromise the strength of the drug product."

Purity:
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 *(sic)* negligible as long as the calculated levels are within the approved acceptance criteria." Dr Rhee recommends, to assure that the method is appropriate, that it be evaluated by the Office of Testing and Research, Division of Pharmaceutical Analysis (DPA). ONDQA will coordinate the evaluation of evaluation of the method by DPA. The need for evaluation of the method does not affect the approvability of the current application, NDA 201922.

Branch Chief Conclusion and Recommendation:

> ….It is my conclusion that 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.
>
> Therefore, my recommendation for this application is a Complete Response based on the following two pending issues:
>
> 1. Lack of an "Acceptable" recommendation from the Office of Compliance
> 2. Unresolved label/labeling issues.
>
> Furthermore, I recommend that the analytical method for impurities be submitted to DPA for evaluation (this process will be done via ONDQA).

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Evaluation by Director, Division of New Drug Quality Assessment II, ONDQA
Please see memorandum by Terrance Ocheltree, Ph.D., R.Ph., dated September 30, 2011.

> I have reviewed Dr. Moo-Jhong Rhee's conclusion regarding suitability and method validation of the HPLC methods for NDA 201922 (see Memo in DARRTS dated September 28, 2011) and discussed this topic with both Dr. Rhee and Dr. Yichun Sun. 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.

Overall CMC recommendation:
On January 31, 2012 the primary CMC reviewer (Yichun Sun, Ph.D., Review Chemist, ONDQA, Premarketing Assessment Division II) issued a Memorandum to the CMC Review #1. In this memorandum, Dr. Sun acknowledges the review by Dr. Moo-Jhong Rhee, Branch Chief, DNDQA II/ONDQA and the concurring review by Dr. Terrance Ocheltree, Director, DNDQA. Dr Sun also notes that that the Office of Compliance gave an overall "Acceptable" recommendation (December 9, 2011) for all the facilities involved in the manufacture and test of the drug substance and drug product. Regarding labels and labeling, Dr. Sun that the January 18, 2012 amendment submitted by the applicant provided finalized mock up carton and container labels that have the required information. Additionally, he notes that that the applicant has agreed to all the CMC changes made to the package insert. Dr. Sun now concludes that from the CMC perspective that NDA 201922 is now recommended for approval.

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

See pharmacology/toxicology review by Renqin Duan, Ph.D., dated October 4, 2011. The reader is also referred to the discussion in this review under CMC, section 4.1.

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Conclusion
The applicant did not submit any nonclinical studies conducted with their drug product. The applicant is relying on the Agency's findings of safety for Solodyn (minocycline HCl) Extended Release Tablets through generation of a clinical bridge to support a 505(b)(2) NDA submission by conducting a comparative clinical pharmacokinetic trial with Solodyn tablets and their minocycline HCl capsules. Therefore the applicant will be able to rely on the nonclinical information contained in Solodyn® tablets labeling.

Pharmacology/Toxicology Recommendations:

Approvability

The product is approvable with respect to nonclinical concerns.

4.4 Clinical Pharmacology

Please see review by Chinmay Shukla, Ph.D., dated October 4, 2011.

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

The applicant conducted two Bioavailability (BA)/Bioequivalence (BE) studies with the highest proposed strength (135mg). A biowaiver request was submitted for the lower strengths (45, 67.5, 90, and 112.5 mg) based on dissolution profile comparisons with the 135 mg strength. The biowaiver was reviewed by ONDQA biopharmaceutics reviewer, John Duan, Ph.D.

Trial 3739:
This was a single-center, randomized, open-label, 3-treatment, 3-period, 3-sequence crossover, single-dose, trial conducted under fasting conditions.
The objectives under fasting conditions were to:
1) Demonstrate bioequivalence between Ximino (minocycline HCl) 135 mg ER Capsules and Solodyn® 135 mg ER Tablets.
2) Assess dose proportionality between Ximino (minocycline HCl) 45 mg ER Capsules and Ximino (minocycline HCl) 135 mg ER Capsules.

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Table 6: Relative Bioavailability Analysis – Trial 3739: Fasting

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 NDA 20-1922, Chinmay Shukla, Ph.D., p. 12.

The results (see Table 6), according to the pharmacology reviewer, indicate that the 90% CI of the ratio of the geometric mean of AUC_{0-t}, AUC_{0-inf} and C_{max} of Ximino (minocycline HCl) 135 mg ER capsule versus Solodyn® 135 mg ER tablets are within the no effect range of 80 – 125 % under fasted conditions. Thus Ximino (minocycline HCl) 135 mg ER capsules are bioequivalent to Solodyn® 135 mg ER tablets under fasted conditions.

Examination of dose proportionality indicates that PK of minocycline increases linearly in a dose proportional manner following oral administration of Ximino capsules between the 45 mg and the 135 mg dose. As noted by the clinical pharmacology reviewer, the Ximino 135 mg capsules contain three of the same 45 mg mintablets and therefore the data indicate that Ximino exhibits linear PK within the dose range of 45 to 135 mg. Please see Table 7.

Table 7: Ratio of dose normalized geometric mean values – Trial 3739: Fasting

Dose normalized PK parameter	A = 45 mg dose	B = 135 mg dose	Ratio (A/B)
AUC_{0-t} (hr*ng/mL)	105.70	104.43	1.01
AUC_{0-inf} (hr*ng/mL)	108.90	106.03	1.03
C_{max} (ng/mL)	6.61	5.96	1.11

Source: Clinical Pharmacology Review NDA 20-1922, Chinmay Shukla, Ph.D., p. 14.

Trial 3740:
This was a single-center, randomized, open-label, 3-treatment, 3-period, 3-sequence crossover, single-dose, trial conducted under fed conditions.

The objectives under fed conditions were to:

1) Demonstrate bioequivalence between Ximino (minocycline HCl) 135 mg ER Capsules and Solodyn® 135 mg ER Tablets.
2) Assess the effect of food on Ximino (minocycline HCl) 135 mg ER capsules.

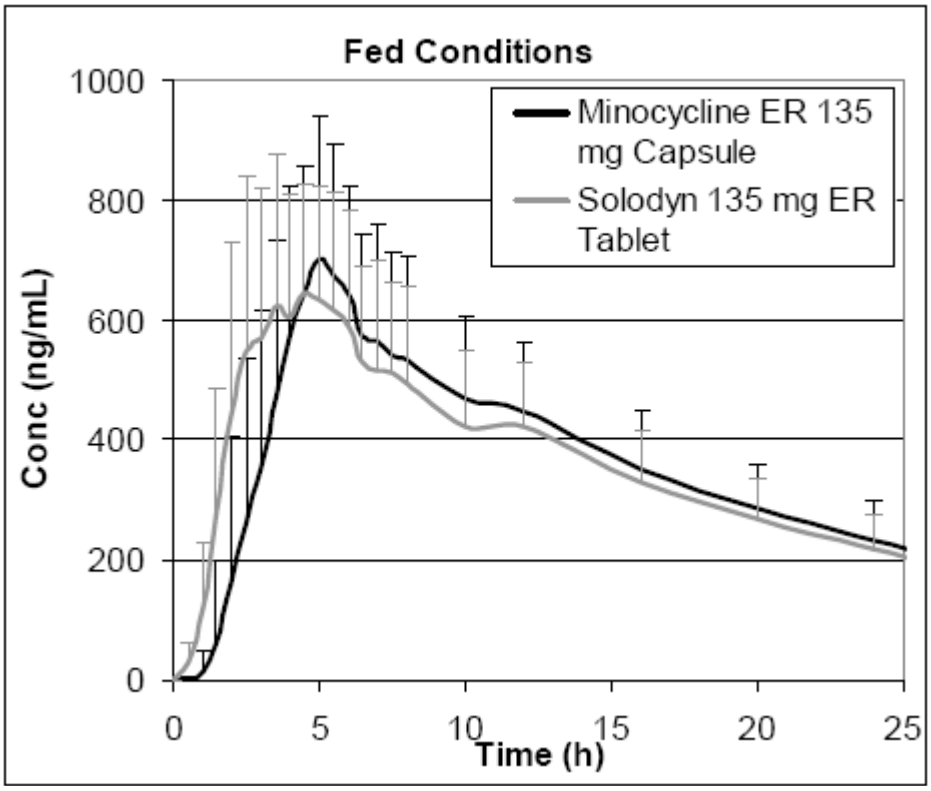
Trial results show that the 90% CI of the ratio of the geometric mean of AUC_{0-t}, AUC_{0-inf} and C_{max} of Ximino (minocycline HCl) 135 mg ER capsules versus Solodyn® 135 mg ER tablets are within the range of 80 - 125 % under fed conditions. This indicates that Ximino (minocycline HCl) 135 mg ER capsules are bioequivalent to Solodyn® 135 mg ER tablets under fed conditions. See Table 8.

Table 8: Relative Bioavailability Analysis – Trial 3740: Fed

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 NDA 20-1922, Chinmay Shukla, Ph.D., p. 15.

Figure 1: Plasma Minocycline Conc. (Mean ± SD) versus time: Trial 3940



Source: Clinical Pharmacology Review NDA 20-1922, Chinmay Shukla, Ph.D., p. 16.

As demonstrated in Figure 1, there appears to be a delay of approximately 1 hour in drug absorption with with Ximino (minocycline HCl) 135 mg ER capsules compared to Solodyn® 135 mg ER tablets under fed conditions. Bioequivalence criteria were, however, met.

The clinical pharmacology reviewer has commented that:

> This is unlikely to have any effect on drug efficacy because the proposed treatment regimen is a chronic regimen to treat moderate to severe acne vulgaris. Such a delay in drug absorption might be more relevant in case of time sensitive therapy, e.g. treatment of acute pain.

This reviewer (clinical) concurs with this assessment.

Food Effect Trial (part of Trial 3740):
Examination of the effect of food indicated that comparing Ximino (minocycline HCl) 135 mg ER capsules under fed versus fasted conditions showed that the 90% 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%. See Table 9 below.

Table 9: Relative Bioavailability Analysis – Trial 3740: Ximino (minocycline ER capsule) fed versus fasting

Parameter	Minocycline 135 mg ER Capsule Geometric Mean (% CV)		90% C.I.	Ratio of Means
	Fasting	Fed		
AUC_{0-t} (ng*hr/mL)	11942.26 (31.72)	13546.24 (21.91)	104.58 % to 121.15%	112.56%
AUC_{0-inf} (ng*hr/mL)	12196.75 (31.38)	13850.54 (21.91)	104.72% to 121.28%	112.70%
C_{max} (ng/mL)	640.28 (36.64)	824.57 (24.12)	118.22% to 137.61%	127.55%

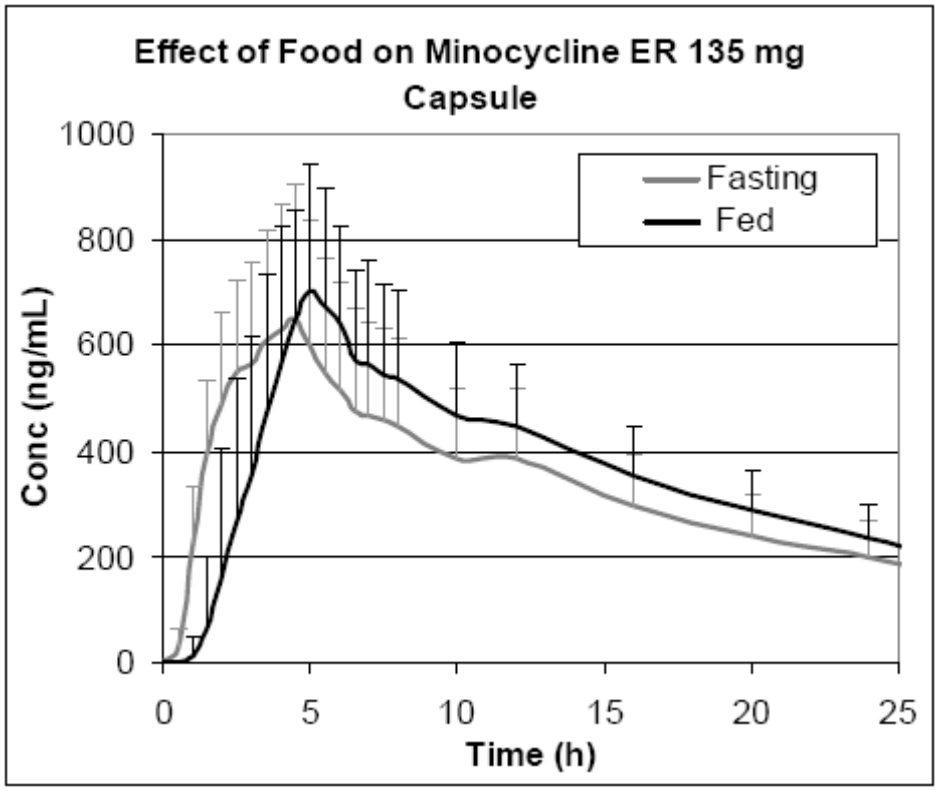
Source: Clinical Pharmacology Review NDA 20-1922, Chinmay Shukla, Ph.D., p. 17.

The clinical pharmacology reviewer has commented that:

> 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.

This reviewer (clinical) concurs with this assessment.

Figure 2: Plasma Minocycline Concentration (Mean ± SD): Trial 3940



Source: Clinical Pharmacology Review NDA 20-1922, Chinmay Shukla, Ph.D., p. 19.

As demonstrated in Figure 2, there appears to be a delay of approximately one hour in drug absorption with Ximino (minocycline HCl) 135 mg ER capsules under fed conditions compared to (Ximino minocycline HCl 135 mg ER capsules under) fasted conditions.

The clinical pharmacology reviewer has commented that:

> This delay in drug absorption with food is unlikely to have any effect on drug efficacy because the proposed treatment regimen is a chronic regimen to treat moderate to severe acne vulgaris. Such a delay in drug absorption might be more relevant in case of time sensitive therapy, e.g. treatment of acute pain.

This reviewer (clinical) concurs with this assessment.

Clinical Pharmacology Labeling Recommendations:

The **bold and underlined** text indicates insertion recommended by the clinical pharmacology 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 non-modified 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) $AUC_{(0-\infty)}$ and C_{max} 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) $AUC_{(0-\infty)}$ and C_{max} 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.

Clinical Pharmacology Recommendation:

From a Clinical Pharmacology Standpoint, the Sponsor has met the requirements under 21 CFR 320 and the application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

Biowaiver of Lower Strengths:
Please also see ONDQA Biopharmaceutics Review by John Duan, Ph.D.

The applicant submitted a biowaiver request for the lower strengths of Ximino (minocycline HCl) ER capsules (45, 67.5, 90, and 112.5). This was found acceptable based on dissolution profile comparisons with the highest strength, 135 mg. An in-vitro in-vivo correlation (IVIVC) study submitted by the applicant was not found to be acceptable. The acceptability of the biowaiver was not based on the IVIVC study; rather, biowaiver acceptability was based on dissolution profile comparisons.

The biopharmaceutics reviewer concluded, that if the bioequivalence studies involving the Ximino 135 mg strength are acceptable, then he would recommend approval of the lower strengths.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol #	Type of trial	Trial Design	Subject population	Sites	# of subjects
3739	BE and Dose Proportionality	Open-label, randomized, single dose	Males and females, age range 22 to 62 years	(1) Toronto, Canada	42 dosed 39 BE assessed 37 Dose-proportionality assessed
3740	BE and food effect	Open-label, randomized, single dose	Males and females, age range 22 to 62 years	(1) Toronto, Canada	42 dosed 37 BE and food effect assessed

5.2 Review Strategy

The bioavailability (BA)/bioequivalence (BE) trials, 3739 and 3740 were reviewed in detail for safety.

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5.3 Discussion of Individual Studies/Clinical Trials

BA/BE Trials: Review of Trials 3739 and 3740:
The two pivotal trials performed as part of the development program were of similar design. They were both three-way, crossover, open-label, balanced, randomized, single dose trials.

Please see clinical pharmacology review by Chinmay Shukla, Ph.D., dated October 4, 2011, for further details.

Results:
Demographics:

Trial 3739:
Of the 42 subjects who were dosed in the trial, 37 subjects (21 males and 16 females) with a mean age of 43.5 years (range = 22 to 62 years) completed the trial and were included in the dose-proportionality assessment. The completing subjects consisted of 18 Caucasians, 5 Asians/Orientals, 6 Blacks, and 8 Hispanics.

Of the 42 subjects who were dosed in the trial, 39 subjects (22 males and 17 females) with a mean age of 43.3 years (range = 22 to 62 years) were included in the bioequivalence assessment. The subjects included in these bioequivalence analyses consisted of 18 Caucasians, 6 Asians/Orientals, 6 Blacks and 9 Hispanics.

Table 10: Demographic Summary (Trial 3739)

	Treatment					
Parameter	**Solodyn 135 tab N=39**	**Mino 135 Cap N=41**	**Mino 45 Cap N=38**	**Completed subjects N=37**	**Subj in PK analysis N=39**	**All Subjects N=42**
Age (years)						
Mean ± SD	43.3 ± 9.7	43.6 ± 9.5	43.5 ± 9.8	43.5 ± 9.9	43.3 ± 9.7	43.5 ± 9.4
Median	44.0	44.0	43.5	44.0	44.0	44.0
Height (cm)						
Mean ± SD	168.3±11.5	167.8±11.7	168.5±11.5	168.6±11.7	168.3±11.5	167.7±11.6
Median	168.0	168.0	169.0	170.0	168.0	168.0
Weight (kg)						
Mean ± SD	73.2 ± 12.3	73.0 ± 12.6	73.7 ± 12.1	73.6 ± 12.2	73.2 ± 12.3	73.1 ± 12.5
Median	73.7	73.7	74.0	73.7	73.7	74.0
BMI (kg/m^2)						
Mean ± SD	25.7 ± 2.2	25.8 ± 2.2	25.8 ± 2.1	25.8 ± 2.1	25.7 ± 2.2	25.8 ± 2.2
Median	25.9	25.9	26.2	25.9	25.9	26.2
Sex						
Male	22 (56.4%)	23 (56.1%)	22 (57.9%)	21 (56.8%)	22 (56.4%)	24 (57.1%)
Female	17 (43.6%)	18 (43.9%)	16 (42.1%)	16 (43.2%)	17 (43.6%)	18 (42.9%)

Reference ID: 3151134

	Treatment					
Parameter	**Solodyn 135 tab N=39**	**Mino 135 Cap N=41**	**Mino 45 Cap N=38**	**Completed subjects N=37**	**Subj in PK analysis N=39**	**All Subjects N=42**
Race						
Caucasian	18 (46.2%)	19 (46.3%)	18 (47.4%)	18 (48.6%)	18 (46.2%)	19 (45.2%)
Black	6 (15.4%)	6 (14.6%)	6 (15.8%)	6 (16.2%)	6 (15.4%)	6 (14.3%)
Hispanic	9 (23.1%)	9 (22.0%)	9 (23.7%)	8 (21.6%)	9 (23.1%)	10 (23.8%)
Asian/ Oriental	6 (15.4%)	7 (17.1%)	5 (13.2%)	5 (13.5%)	6 (15.4%)	7 (16.7%)

Source: Applicant's NDA, adapted from Table 14.1.1, Clinical Study Report 3739.

Demographic features of the populations studied generally appear balanced across treatment groups.

Trial 3740:
Of the 42 subjects who were dosed in the trial, 36 subjects (28 males and 8 females) with a mean age of 42.7 years (range = 20 to 63 years) completed the trial. The completing subjects consisted of 18 Caucasians, 7 Hispanics, 6 Asians/Orientals, 4 Blacks, and 1 Mulatto.

Of the 42 subjects who were dosed in the trial, 37 subjects (29 males and 8 females) with a mean age of 42.2 years (range = 20 to 63 years) were included in the pharmacokinetic and statistical analyses. The subjects included in these analyses consisted of 18 Caucasians, 7 Hispanics, 6 Asians/Orientals, 5 Blacks, and 1 Mulatto.

Table 11: Demographic Summary (Trial 3740)

	Treatment					
Parameter	**Solodyn 135 tab fed N=41**	**Mino 135 Cap fast N=37**	**Mino 135 Cap fed N=38**	**Completed subjects N=36**	**Subj in PK analysis N=37**	**All Subjects N=42**
Age (years)						
Mean ± SD	42.4 ± 10.3	42.2 ± 11.1	42.1 ± 11.0	42.7 ± 10.9	42.2 ± 11.1	42.0 ± 10.5
Median	42.0	42.0	42.0	43.5	42.0	42.0
Height (cm)						
Mean ± SD	171.6±8.6	171.9±8.8	171.9±8.7	171.8±8.9	171.9±8.8	171.7±8.5
Median	173.6	174.0	173.8	173.8	174.0	173.8
Weight (kg)						
Mean ± SD	75.8 ± 12.4	75.7 ± 12.8	75.4 ± 12.7	75.6 ± 12.9	75.7 ± 12.8	75.9 ± 12.2
Median	76.1	76.1	75.8	75.8	76.1	76.8
BMI (kg/m^2)						
Mean ± SD	25.6 ± 2.5	25.5 ± 2.5	25.4 ± 2.5	25.5 ± 2.6	25.5 ± 2.5	25.6 ± 2.5
Median	26.1	26.0	25.9	26.1	26.0	26.1

	Treatment					
Parameter	**Solodyn 135 tab fed N=41**	**Mino 135 Cap fast N=37**	**Mino 135 Cap fed N=38**	**Completed subjects N=36**	**Subj in PK analysis N=37**	**All Subjects N=42**
Sex						
Male	32 (78.0%)	29 (78.4%)	29 (76.3%)	28 (77.8%)	29 (78.4%)	33 (78.6%)
Female	9 (22.0%)	8 (21.6%)	9 (23.7%)	8 (22.2%)	8 (21.6%)	9 (21.4%)
Race						
Caucasian	19 (46.3%)	18 (48.6%)	19 (50.0%)	18 (50.0%)	18 (48.6%)	19 (45.2%)
Black	6 (15.4%)	6 (14.6%)	6 (15.8%)	6 (16.2%)	6 (15.4%)	6 (14.3%)
Hispanic	9 (22.0%)	7 (18.9%)	7 (18.4%)	7 (19.4%)	7 (18.9%)	9 (21.4%)
Asian/ Oriental	7 (17.1%)	6 (16.2%)	6 (15.8%)	6 (16.7%)	6 (16.2%)	7 (16.7%)

Source: Applicant's NDA, adapted from Table 14.1.1, Clinical Study Report 3740.

Demographic features of the populations studied generally appear balanced across treatment groups.

Subject Disposition: Trial 3739

Table 12: Summary of Subject Disposition (Trial 3739)

	Sequence			Total
	XYZ	YZX	ZXY	
Subjects randomized	14	14	14	42
Subjects completed trial	12	12	13	37
Subjects withdrawn	2	1	1	4
Subjects dismissed	0	1	0	1
Primary reason for not completing trial	Personal reasons	Emesis within 24 hours of dosing Personal reasons	Personal reasons	

Treatment Z: 1 Minocycline HCl 45 mg ER Capsule-fasting
Treatment Y: 1 Minocycline HCl 135 mg ER Capsule-fasting
Treatment X: Reference (R): 1 Solodyn® 135 mg ER Tablet
Source: Clinical Study Report, Study 3739, Table 10.1.2.

In Trial 3739 the primary reasons for not completing the trial were personal reasons. Subjects not completing the trial were generally balanced across treatment sequences.

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Subject Disposition: Trial 3740

Table 13: Summary of Subject Disposition (Trial 3740)

	Sequence			Total
	XYZ	YZX	ZXY	
Subjects randomized	14	14	14	42
Subjects completed trial	10	13	13	36
Subjects withdrawn	2	1	1	4
Subjects dismissed	2	0	0	2
Primary reason for not completing trial	Personal reasons Administrative reason (positive drug tests)	Personal reasons	Personal reasons	

Treatment **X:** Reference (R): 1 Solodyn® 135 mg ER Tablet-fed
Treatment **Y:** 1 Minocycline HCl 135 mg ER Capsule-fasting
Treatment **Z:** 1 Minocycline HCl 135 mg ER Capsule-fed
Source: Applicant's NDA, adapted from Table 10.1.2, Clinical Study Report 3740

In Trial 3740 the primary reasons for not completing the trial were personal reasons; however, two subjects were dismissed because of positive drug test results.

For further details, please also see section 4.4.3 and Clinical Pharmacology Review of NDA 201922 by Chinmay Shukla, Ph.D.

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 Solodyn®. The scientific justification for this reliance is provided by data from two bioequivalence trials performed in humans, trials 3739 and 3740.

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 Solodyn®. The scientific justification for this reliance is provided by data from two bioequivalence studies performed in humans, studies 3739 and 3740.

The safety of minocycline hydrochloride extended release, 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 applicant submitted additional safety data from the two pharmacokinetic studies performed to evaluate bioequivalence, studies 3739 and 3740.

There were no deaths or serious adverse events. One subject was discontinued due to vomiting within 24 hours of dosing with Ximino 135mg. Liver function tests for this subject were within reference range at screening and 3 days after the adverse event.

Attribution of adverse events to specific treatment whether Ximino or Solodyn is rendered imprecise by the cross-over design of studies 3739 and 3740.
The most common adverse event reported in subjects exposed to Ximino (all doses, fed, and fasting) was headache 8/84 (9.5%). The next common event in subjects exposed to Ximino (all conditions) were elevated AST 3/84 (3.6%) and elevated 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.

7.1 Methods

Safety data, including adverse events and laboratory testing, from the two pharmacokinetic studies, 3739 and 3740, was evaluated.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Protocol #	Type of trial	Trial Design	Subject population	Sites	# of subjects
3739	BE and Dose Proportionality	Open-label, randomized, single dose	Males and females, age range 22 to 62 years	(1) Toronto, Canada	42 dosed 39 BE assessed 37 Dose-proportionality assessed
3740	BE and food effect	Open-label, randomized, single dose	Males and females, age range 22 to 62 years	(1) Toronto, Canada	42 dosed 37 BE and food effect assessed

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7.1.2 Categorization of Adverse Events

For studies 3739 and 3740, adverse events were coded using the MedDRA dictionary (version 13.1) for preferred terms, and system organ class. The adverse event categorization and preferred terms used in studies 3739 and 3740 appear satisfactory.

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

The applicant did not pool adverse event data from the two pharmacokinetic studies, 3739 and 3740.

7.2 Adequacy of Safety Assessments

Clinical safety assessments included monitoring of adverse events, vital signs (BP, heart rate, temp, respirations), and query regarding health status. A physical examination was performed at screening and the other clinical assessments were performed at regular predetermined intervals. At screening the following testing was performed; ECG, Hepatitis B surface antigen, Hepatitis C, HIV, pregnancy testing, drug and nicotine screens, and biochemistry, hematology and urinalysis. At check in periods I,II,III the following tests were performed: drug and nicotine screens, alcohol screen, and pregnancy testing. At end of trial hematology and AST and ALT were performed. At any time during the studies the Principal Investigator or Sub-Investigator was able to order testing deemed necessary based on medical discretion.

The safety assessments noted above were adequate for the type of studies performed, single-center, open-label, 3-treatment, 3-period, 3-sequence, crossover, single-dose studies.

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

Ximino was administered to 84 healthy volunteers. A total of 74 (88%) received two doses of Ximino (either 135 mg x 2, or 135 and 45 mg). A total of 6 (7%) received one dose (either 135mg or 45 mg). There was a 14 day washout period between study treatments for both studies 3739 and 3740. Because these were crossover studies, most subjects also received a dose of Solodyn 135 mg ER tablet (76/84). Please see following tables.

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Table 14: Exposure (Trial 3739)

Subjects Who Completed the Trial				
Subjects		**Total Number of Doses Taken**	**Treatment Dose**	**Total Exposure**
37		3	45 mg 135 mg 135 mg	315 mg
Subjects Who Discontinued Prematurely				
Subject Number	**Treatment(s) Received**	**Total Number of Doses Taken**	**Treatment Dose**	**Total Exposure**
004	XY	2	135 mg 135 mg	270 mg
005	Z	1	45 mg	45 mg
018	Y	1	135 mg	135 mg
029	XY	2	135 mg 135 mg	270 mg
034	Y	1	135 mg	135 mg

Treatment **Z**: 1 Minocycline HCl 45 mg ER Capsule-fasting
Treatment **Y**: 1 Minocycline HCl 135 mg ER Capsule-fasting
Treatment **X**: Reference (R): 1 Solodyn® 135 mg ER Tablet-fasting
Source: Applicant's NDA, adapted from Table 12.1.1, Clinical Study Report 3739

Table 15: Exposure (Trial 3740)

Subjects Who Completed the Trial				
Subjects		**Total Number of Doses Taken**	**Treatment Dose**	**Total Exposure**
36		3	135 mg	405 mg
Subjects Who Discontinued Prematurely				
Subject Number	**Treatment(s) Received**	**Total Number of Doses Taken**	**Treatment Dose**	**Total Exposure**
001	X	1	135 mg	135 mg
005	X	1	135 mg	135 mg
010	ZX	2	135 mg	270 mg
019	X	1	135 mg	135 mg
025	YZ	2	135 mg	270 mg
033	X	1	135 mg	135 mg

Treatment **X:** Reference (R): 1 Solodyn® 135 mg ER Tablet-fed
Treatment **Y:** 1 Minocycline HCl 135 mg ER Capsule-fasting
Treatment **Z:** 1 Minocycline HCl 135 mg ER Capsule administered-fed
Source: Applicant's NDA, adapted from Table 12.1.1, Clinical Study Report 3740

Table 16: Demographics of Safety Population

	Trial 3739	Trial 3740	
Parameter	**All Subjects Dosed N=42**	**All Subjects Dosed N=42**	
Age (years)			
Mean ± SD	43.5 ± 9.4	42.0 ± 10.5	
Median	44.0	42.0	
Min, Max	22, 62	20, 63	
Height (cm)			
Mean ± SD	167.7±11.6	171.5 ± 8.5	
Median	168.0	173.8	
Weight (kg)			
Mean ± SD	73.1 ± 12.5	75.9 ± 12.2	
Median	74.0	76.8	
BMI (kg/m^2)			
Mean ± SD	25.8 ± 2.2	25.6 ± 2.5	
Median	26.2	26.1	
Sex			
Male	24 (57.1%)	33 (78.6%)	
Female	18 (42.9%)	9 (21.4%)	
Race			U.S. Population[1]
Caucasian	19 (45.2%)	19 (45.2%)	74% Caucasian
Black	6 (14.3%)	6 (14.3%)	12.4 % Black
Hispanic	10 (23.8%)	9 (21.4%)	14.7 % Hispanic[2]
Asian/Oriental	7 (16.7%)	7 (16.7%)	4.3 % Asian

[1] U.S. Census Bureau, 205-2007 American community Survey, Detailed Tables – American Fact Finder; B02001.Race and B03001.Hispanic or Latino by Specific Origin
[2] In the American Community Survey, "Hispanic or Latino" was employed as a category for ethnicity. In this table, "Hispanic" is a category for race.

Source: Applicant's NDA, adapted from Table 14.1.1, Clinical Study Reports 3739 and 3740

The subject population consisted of male and female subjects, ages to be included 18 to 65 years, healthy, non-smoking.

As compared with the U. S. population, the demographics of the populations dosed in studies 3739 and 3740 show an under representation of Caucasians and an over representation of Hispanics and Asians. The majority were male 68% (57/84) with a mean age of 42.8 (range 20 to 63 years).

7.2.2 Explorations for Dose Response

Dose response for adverse events was not explored in the 3 dose pharmacokinetic studies, 3739 and 3740.

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 preformed was appropriate for the 3 dose pharmacokinetic studies, 3739 and 3740.

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, 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 studies, 3739 and 3740, 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 studies 3739 or 3740

7.3.2 Nonfatal Serious Adverse Events

No Serious Adverse Events were reported in studies 3739 or 3740.

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7.3.3 Dropouts and/or Discontinuations

Trial 3739:
One subject (ID # 34: 49 year old Asian/Oriental female) was dismissed due to emesis within 24 hours of dosing (135 mg ER Capsule). The subject was dosed 10/12 8:06 and onset was 10/12 18:00. Liver function tests including ALT and AST were within reference range at screening on 10/10 and on 10/15.

7.3.4 Significant Adverse Events

No clinically significant adverse events were reported for studies 3739 or 3740.

7.3.5 Submission Specific Primary Safety Concerns

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

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In trial 3739, 42 subjects were dosed at least once and 11 subjects had a total of 18 adverse events.

Table 17: Adverse Events (Timing, Severity, Relationship) Trial 3739 - Fasting

Ximino 45 mg ER Capsules (4 subjects/4 AEs)						
Subject	**AE**	**Tx given**	**Onset**	**Duration**	**severity**	**relationship**
005/42 yo/H	Elevated ALT	10/12	11/04	10d 19:18	mild	possibly
	This subject only received Ximino 45 mg – no cross over					
020/56 yo/C	Headache	10/12 7:38	10/12 11:15	18:45	mild	possibly
024/44 yo/A	Headache	11/9 7:46	11/10 6:30	1d 8:00	Mild	possibly
026/33 yo/C	Vasovagal rxn	10/26 7:50	10/26 9:06	06 min	Mild	possibly
Ximino 135 mg ER Capsules (6 subjects/9 AEs)						
016/32 yo/A	Headache	10/26 7:30	10/26 19:13	4:17	Mild	possibly
020/56 yo/C	Headache	11/9 7:38	11/10 1:30	14:30	Mild	possibly
022/50 yo/C	Chest heaviness	11/9 7:42	11/9 23:30	7:15	Mild	possibly

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	Headache	11/9 7:42	11/10 1:00	6:45	Mild	possibly
026/33 yo/C	Sneezing	10/12 7:50	10/12 17:30	6:00	Mild	unlikely
029/44 yo/H	Somnolence	10/26 7:56	10/26 10:00	4:00	Mild	possibly
034/49 yo/A	Vomiting	10/12 8:06	10/12 21:00	1:15	Moderate	possibly
	Headache	10/12 8:06	10/12 18:00	9:00	Mild	possibly
	Stomach ache	10/12 8:06	10/12 18:30	8:30	Mild	possibly
Solodyn® 135 mg ER Tablets (3 subjects/3 AEs)						
020/56 yo/C	Headache	10/26 7:38	10/26 14:35	15:25	Mild	possibly
026/33 yo/C	Heartburn	11/9 7:50	11/9 8:34	2:56	Mild	possibly
031/58 yo/C	Somnolence	10/12 8:00	10/12 9:39	9:02	Mild	probably
End of Trial Medical Examination (2 subjects/2 AEs)						
	AE	**Tx given**	**Onset**	**Duration**	**Severity**	**Relationship**
019/36 yo/B	Elevated AST	Ximino 45 mg tab				
		11/09 7:36	11/13 7:36	4d 11:04	mild	possibly
		Ximino 135 mg cap				
		10/26 7:36				
		Solodyn 135 mg tab				
		10/12 7:36				
030/51 yo/B	Elevated AST	Ximino 135 mg cap				
		11/09 7:58	11/13 7:58	4d 3:49	mild	possibly
		Solodyn 135 mg tab				
		10/26 7:58				
		Ximino 45 mg cap				
		10/12 7:58				

Source: Applicant's NDA, complied by reviewer from line listings, Clinical Study Report 3739

Table 18: Adverse Events Trial 3739 - Fasting

Event	Ximino 45 mg N = 38		Ximino 135 mg N = 41		Solodyn 135 mg N = 39	
Headache	2	5%	4	10%	1	3%
Elevated ALT	1	3%				
Elevated AST (From end of trial)	1	3%	1	2%		
Somnolence			1	2%	1	3%
Chest heaviness			1	2%		
Heartburn					1	3%
Sneezing			1	2%		
Stomach ache			1	2%		
Vasovagal reaction	1	3%				
Vomiting			1	2%		

Source: Applicant's NDA, compiled by reviewer from line listings, Clinical Study Report 3739

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In trial 3740, 42 subjects were dosed at least once and 9 subjects experienced 14 adverse events.

Table 19: Adverse Events (Timing, Severity, Relationship) Trial 3740

Ximino 135 mg ER Capsules - Fed (1 subject/1 AE)						
Subject	**AE**	**Tx given**	**Onset**	**Duration**	**Severity**	**Relationship**
042/41 yo/C	Headache	10/28 9:52	10/28 13:30	11:00	mild	unlikely
Ximino 135 mg ER Capsules - Fasting (3 subjects/5 AEs)						
034/55 yo/A	Headache	11/11 9:36	11/11 13:30	5:00	Mild	unlikely
035/57 yo/C	Leg cramps	10/14 9:38	10/14 19:00	2d 21:00	Mild	unlikely
	Back pain		10/15 10:16	2d 5:44	Moderate	unlikely
	Joint pain		10/15 1:00	2d 15:00	Mild	possibly
037/50 yo/C	Nail infection	10/28 9:42	11/4 20:00	Unknown	Moderate	unrelated
Solodyn® 135 mg ER Tablets - Fed (no subjects had AEs)						
End of Trial Medical Examination (6 subjects/8 AEs)						
	AE	**Tx given**	**Onset**	**Duration**	**Severity**	**Relationship**
002/27 yo/B	Elevated ALT	Ximino135 mg cap - Fasting				
		11/11 8:32	11/15 8:32	Unknown	mild	possibly
		Solodyn 135 mg tab - Fed				
		10/28 8:32				
		Ximino 135 mg cap - Fed				
		10/14 8:32				
008/29 yo/C	Decr. plt count	Ximino 135 mg cap - Fasting				
		11/11 8:44	11/15 8:44	3d 4:46	Mild	possibly
		Solodyn 135 mg tab - Fed				
		10/28 8:44				
		Ximino 135 mg capsule - Fed				
		10/14 8:44				
013/58 yo/C	Elevated ALT	Solodyn 135 mg tab - Fed				
		11/11 8:54	11/15 8:54	18d 23:57	Mild	possibly
		Ximino135 mg cap - Fed				
		10/28 8:54				
		Ximino 135 mg cap - Fasting				
		10/14 8:54				
030/36 yo/C	Elevated AST	Ximino 135 mg cap - Fasting				

		11/11 9:28	11/15 9:28	6d 3:43	Mild	possibly
	Decr Hgb		11/15 9:28	6d 3:43	Mild	unlikely
		Solodyn 135 mg tab - Fed				
		10/28 9:28				
		Ximino 135 mg cap - Fed				
		10/14 9:28				
037/50 yo/C	Decr WBC	Ximino 135 mg cap - Fed				
		11/11 9:42	11/15 9:42	Unknown	mild	possibly
		Ximino 135 mg cap - Fasting				
		10/28 9:42				
		Solodyn 135 mg tab - Fed				
		10/14 9:42				
038/30 yo/H	Elevated AST	Solodyn 135 mg tab - Fed				
		11/11 9:44	11/15 10:15	Unknown	Mild	possibly
	Elevated ALT		11/15	Unknown	Mild	possibly
		Ximino 135 mg cap - Fed				
		10/28 9:44				
		Ximino 135 mg cap - Fasting				
		10/14 9:44				

Source: Applicant's NDA, complied by reviewer from line listings, Clinical Study Report 3740

Table 20: Adverse Events Trial 3740 – BE and Food Effect

Event	Ximino 135 mg Fed N = 38		Ximino 135 mg Fasting N = 37		Solodyn 135 mg Fed N = 41	
Headache	1	3%	1	3%		
Elevated ALT (from end of trial)			1	3%	2	5%
Elevated AST (From end of trial)			1	3%	1	2%
Back pain			1	3%		
Decreased hemoglobin (from end of trial)			1	3%		
Decreased platelet count (from end of trial)			1	3%		
Decreased WBC (from end of trial)	1	3%				
Leg cramps			1	3%		
Joint pain			1	3%		
Nail infection			1	3%		

Source: Applicant's NDA, compiled by reviewer from line listings, Clinical Study Report 3740

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Because these were crossover studies with each subject receiving both Ximino 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. Regarding laboratory testing, the applicant states that laboratory tests were performed only at the end-of-trial medical examination and subjects were exposed to all treatments before testing. Therefore abnormal laboratory results can only be related to the trial and not to the specific treatment received. This reviewer has attempted to provide more precise accounting for this by assigning laboratory adverse events to the most recent treatment as shown in the tables above under end-of-trial medical examination. With washout periods between treatments being 14 days this approach may reveal some associations; however, it is acknowledged that the cross-over design does lead to confounding between one treatment (Ximino) and the other (Solodyn®).

For trial 3739, all adverse events are described as resolved. For trial 3740, all adverse events, where follow up is available, are described as resolved with the exception of the nail infection (subject # 37) and the decreased WBC (subject #37). For this subject WBC was below reference range at screening. Also in trial 3740, two subjects were lost to follow-up, # 2 having increased ALT and # 38 having increased ALT and AST. Outcomes for these two subjects are not known.

The most common adverse event reported in subjects exposed to Ximino (all doses, fed, and fasting) was headache 8/84 (9.5%). The next most common event in subjects exposed to Ximino (all conditions) were elevated AST 3/84 (3.6%) and elevated ALT 2/84 (2.3%). These adverse events are currently included in labeling for the listed drug Solodyn®.

When adverse events are analyzed per dose received (subjects generally received two doses of Ximino and one dose of Solodyn®) the findings are as follows:
The most common adverse event reported in subjects exposed to Ximino (all doses, fed, and fasting) was headache 8/154 (5.2%). By comparison, the number of subjects reporting headache exposed to Solodyn® 135 mg (fed or fasting) was 1/80 (1.2%). The next common event in subjects exposed to Ximino (all conditions) were elevated AST 3/154 (1.9%) and elevated ALT 2/154 (1.3%). By comparison, the number of subjects exposed to Solodyn® 135 mg (fed or fasting) reporting elevated AST was 1/80 (1.2%) and elevated ALT was 3/80 (3.8%).

The remaining adverse events (somnolence, chest heaviness, heartburn, sneezing, stomach ache, vasovagal reaction, vomiting, back pain, decreased hemoglobin, decreased platelet count, decreased WBC, leg cramps, joint pain, and nail infection) occurred only in 1/84 subjects (or in 1/154 doses) for those exposed to Ximino. Of these; somnolence, decreased hemoglobin, and decreased platelet count are labeled. All adverse events were of mild severity except for one case each of vomiting, back

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pain, and nail infection, described as moderate in severity. Due to low numbers, patterns seen are most likely the result of chance.

7.4.2 Laboratory Findings

The majority of changes in laboratory findings were reported as adverse events and are also discussed above.

In subjects exposed to Ximino (all doses and conditions) the most common changes reported are elevations in AST and ALT. In general changes in laboratory findings for subjects exposed to Ximino do not represent significant departures from reference range values and in many cases were shown to return to within reference range on subsequent testing.

Trial 3739:
Elevated AST was noted as adverse event in two subjects (# 19 and # 30) at the end of trial examination (proximate treatments were Ximino 45 mg ER Capsules and Ximino 135 mg ER Capsules).
19: AST 26 on 10/4, 43 on 11/13, 28 on 11/17 (ref range < 37 U/L) Ximino 45 mg
30: AST 35 on 9/30, 37 on 11/13, 27 on 11/17 Ximino 135 mg

<u>Not noted as adverse event</u>: Subject 36 (Female, 51 y/o, Caucasian), at end of trial had depression of neutrophils (Proximate treatment was Ximino 45 mg ER Capsule on 11/09):
36 neutrophils: screening 2.32 (10/1) to 1.37 (11/13) (ref range: 1.8 - 7)
WBC: screening 4.3 (10/1) to 3.8 (11/13) (ref range: 4 - 11)

Trial 3740:
Elevated ALT was noted as an AE in three subjects (# 2, #13, and # 38) at the end of trial examination. Proximate treatments were Ximino 135 mg ER Capsules-fasting, Solodyn 135 mg ER Tablets-fed, and Solodyn 135 mg ER Tablets-fed, respectively.
2: ALT 17 on 10/4, 48 on 11/15 (ref range F<36 U/L) Ximino 135 mg
#13: ALT 39 on 10/4, 60 on 11/15, 44 on 12/4 (ref range M <46 U/L) Solodyn 135 mg
#38: ALT 48 on 10/4, 107 on 11/15, 131 on 11/17 (ref range M <46) Solodyn 135 mg

Elevated AST was noted in two subjects (#30 and # 38) at the end of trial examination (11/15); proximate treatments were Ximino 135 mg ER Capsules-fed and Solodyn 135 mg ER Tablets-fed, respectively.
30: AST 24 on 10/5, 42 on 11/15, 25 on 11/21 (ref range <37) Ximino 135 mg
38: AST 31 on 10/4, 48 on 11/15, 55 on 11/17 Solodyn 135 mg

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One subject (#8) had decreased platelets (139 x 10^9/L with a reference range of 145-400, platelets were 147 at screening) at the end of trial examination and proximate treatment was Solodyn 135 mg ER Tablets-fed.

One subject (#30) had decreased hemoglobin at the end of trial examination (11/15) and proximate treatment was Ximino 135 mg ER Capsules-fed.
Hgb 142 on 10/5, 120 on 11/15, 137 on 11/21 (ref range 135 – 170 g/L)

One subject (#37) had decreased WBC at the end of trial examination and proximate treatment was Ximino 135 mg ER Capsules-fed.
WBC 3.5 on 10/5, 3.4 on 11/15, 3.3 on 11/21 (ref range 4-11x 10^9/L)
(For this subject note that WBC was below reference range at screening)

<u>Not noted as adverse event:</u>
Subject 3 (Male 28 y/o, Hispanic) had decreased neutrophils and decreased WBC at end of trial. Proximate treatment was Solodyn 135 mg ER Tablet on 11/11.
Neutrophils: 2.39 on 10/6, 1.58 on 11/15 (ref range 1.8 – 7x10^9/L)
WBC: 4.6 on 10/6, 3.6 on 11/15 (ref range 4-11x10^9/L)

7.4.3 Vital Signs

Studies 3739 and 3740:
Clinically significant changes from screening to clinic exit in mean heart rate, diastolic blood pressure, and systolic blood pressure were not seen for any of the treatments administered; Ximino (minocycline hydrochloride) 135 mg ER Capsules, Ximino (minocycline hydrochloride) 45 mg ER Capsules, or Solodyn® 135 mg ER Tablets. Individual shifts of vital signs to abnormal values were sporadic and usually corrected upon repeat measurement.

7.4.4 Electrocardiograms (ECGs)

ECGs were performed only at screening.

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 3739 and 3740 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 3739 and 3740 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, Solodyn®.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant women were excluded from studies 3739 and 3740 and instances of pregnancy during these studies were not reported.

Labeling proposed by the applicant is the same as that for the listed drug Solodyn® (minocycline HCl) Extended Release Tablets for section 5.1 Teratogenic Effects

(WARNINGS AND PRECAUTIONS) and for section 8.1 Pregnancy (USE IN SPECIFIC POPULATIONS).

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant originally requested a waiver for pediatric age group [redacted] (b) (4). Reasons cited were: [redacted] (b) (4)

Upon review, it was determined that it would be more appropriate to request a waiver, for the following reasons:

a) Age 0 to age 7 since the product would be unsafe
b) Age 8 to 11 since studies are impossible or highly impractical
c) Age 12 to 16 since bioequivalence with reference product, Solodyn®, has been established. Solodyn® is approved for same indication for patients age 12 and older.

Justification for waiver:

0-7 yr. old: NDA 201922 was submitted pursuant to 505(b)(2) and refers to clinical studies performed by the listed drug, Solodyn® (minocycline HCl) Extended Release Tablets, 135 mg (NDA 050808). Per the approved listed drug labeling, 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 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.

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.

8-11 yr. old: The greatest number of acne cases is seen during the middle and late teenage years. The onset of acne is associated with a rise in serum levels of DHEAS and is associated with an increase in 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 all 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: Bioequivalence with reference product, Solodyn®, has been established. Solodyn® is approved (safety and effectiveness have been established) for the same indication for patients age 12 and older (treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older). The proposed drug product is appropriately labeled for ages 12 to 16.

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 Ximino and Solodyn® the pediatric and adult formulations are the same).

Pediatric Review Committee:
The application was presented to the Pediatric Review Committee (PeRC) on September 7, 2011. The Pediatric Review Committee agreed that it was appropriate to waive the pediatric age groups as follows:

a) Age 0 to age 7 since the product would be unsafe
b) Age 8 to 11 since studies are impossible or highly impractical
c) Age 12 to 16 since bioequivalence with reference product, Solodyn®, has been established. Solodyn® is approved for same indication for patients age 12 and older.

(b) (4)

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.

Reference ID: 3151134

7.7 Additional Submissions / Safety Issues

The applicant did not submit a 120 day safety update. An information request was submitted September 1, 2011 requesting that the applicant provide a safety update under 21 CFR 314.50(d)(5)(vi)(*b*).

On September 23, 2011 the applicant responded to this information request with a submission (Supporting document 25, received September 26, 2011) that was considered an unsolicited major amendment. Because the receipt date was within three months of the user fee goal date, the goal date was extended by three months to provide time for a full review of the submission.

Ranbaxy's Response to Agency Request for NDA Safety Update:
This response contains two parts:
Part A): Safety related information for minocycline on the basis of published literature regardless of indication, dosage form or dose level. Data analysis includes both clinical and non-clinical data.
Part B): Review of safety data available from applicant's in house safety database with respect to the drug minocycline.

Part A): For published literature:
The applicant performed an online search, September 6, 2011, of published biomedical literature using the PubMed database of the US National library of Medicine. The search term was "Minocycline." No limits were placed on time.

Indication acne:
A total of 193 publications were identified containing information relevant to safety; 21 safety and efficacy studies, 149 case reports, and 23 review articles.

In the 21 safety and efficacy studies, adverse events reported are consistent with those included in current labeling for the listed drug Solodyn®. Examples of events reported include; drug induced lupus, pseudotumor cerebri, photosensitivity, pigmentation of various tissues.

Adverse events described in the 149 case reports are presently included in product labeling for the listed drug Solodyn®, with minor exceptions mostly consisting of those events that the applicant identified as unlisted (see section B discussion below). The most common adverse events reported include; hypersensitivity reactions (including DRESS), pigmentation of various tissues including thyroid, pseudotumor cerebri, hepatotoxicity, vasculitis, drug induced lupus-like syndrome, and autoimmune syndromes.

Adverse events discussed in the 23 review articles are consistent with those present in current product labeling for the listed drug Solodyn®. Adverse events described as drug

Reference ID: 3151134

related discussed most frequently in the review articles included; hypersensitivity reactions, pigmentation of various tissues, autoimmune syndromes including hepatotoxicity, pseudotumor cerebri, and drug induced lupus-like syndrome.

Part B): Use of in house safety database:
The applicant extracted from their in house safety database all Adverse Drug Eruptions (ADR) cases where minocycline was a suspect drug. Indications for use included all minocycline indications including infections due to susceptible stains of microorganisms (e.g. Rocky Mountain spotted fever caused by rickettsiae, respiratory tract infections caused by *Mycoplasma pneumoniae*, lymphogranuloma venereum caused by *Chlamydia trachomatis*, etc.) and severe acne, as adjunctive therapy. The time period search was since the first authorization of the applicant's minocycline containing products, which was November 30, 2000 for ANDA # 065062 and January 7, 2004 for ANDA # 065156.

The applicant has received 403 ADR cases with minocycline as the suspect drug. A total of 9 cases were reported with fatal outcome, 8 of which were reported from literature sources and one from the United Kingdom Regulatory Authority. In 6 of the fatal cases patients, following treatment with minocycline, developed Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome and died due to systemic manifestations of DRESS syndrome. In 3 cases black pigmentation of the thyroid gland was a coincidental finding.

The 403 ADR cases with minocycline as the suspect drug included 869 ADRs. The highest number of ADRs, 163 (18.75%), was reported from the skin and subcutaneous disorders SOC, with principal subcategories being; pigmentation disorder (45 ADRs), DRESS syndrome (31 ADRs), and skin hyperpigmentation (14 ADRs). The second highest number of ADRs, 142 (16.34%) was reported from the musculoskeletal and connective tissue disorders SOC, with principal subcategories being; arthralgia (59 ADRs), lupus-like syndrome (39 ADRs) and arthritis (19 ADRs).

After review of the 403 ADR cases, 8 ADRs were identified which the applicant considers to be unlisted per US prescribing information (PI) of Ranbaxy's minocycline hydrochloride tablets 50, 75, 100mg, dated February 2011 and/or the US PI for SOLODYN® (minocycline HCl) Extended Release Tablets, 45, 55, 65, 80, 90, 105, 115, and 135 mg. These include the following:

- Hypertriglyceridemia following drug interaction between minocycline and antiretroviral therapy (including protease inhibitors and NRTIs)
- Myopathy
- Cytotoxic edema
- Depersonalization
- Metrorrhagia
- Dermatomyositis
- Lymphomatoid papulosis

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- Acute febrile neutrophilic dermatosis

The Office of Surveillance and Epidemiology (OSE) was consulted regarding whether the above ADRs should be incorporated into product labeling. A review[1] was completed on January 18 2012 by Jessica Weintraub, Pharm. D., OSE, Division of Pharmcovigilance I (DPV I). The OSE reviewer searched the Adverse Event Reporting System (AERS) database for postmarketing reports dating from June 30, 1971 through October 28, 2011 for drug names; Solodyn, Dynacin, Minocin, Arestin, minocycline, and all associated verbatim names. The following events were searched; hypertriglyceridemia following drug interaction with antiretroviral therapy, myopathy, cytotoxic edema, depersonalization, metrorrhagia, dermatomyositis, lymphomatoid papulosis, acute febrile neutrophilic dermatosis.

OSE also performed a literature search of Embase on October 21, 2011 using the search string: minocycline AND (hypertriglyceridemia OR myopathy OR cytotoxic edema OR depersonalization OR metrorrhagia OR dermatomyositis OR polymyositis OR lymphomatoid papulosis OR acute febrile neutrophilic dermatosis).

B) Over All Conclusion for Applicant's Review of Safety Data Available from their In House Safety Database:

For the individual events considered, the number of cases is limited, up to at most 13 AERS cases and with limited additional cases found by literature search. Many of the cases are confounded. Data to support biologic plausibility is not present for many of the eight adverse events. Therefore there is inadequate data to support the belief that a causal relationship exists between the use of minocycline and the occurrence of these eight events. At the same time an association can not be definitively ruled out between minocycline use and the occurrence of these eight events. This reviewer concurs with the OSE plan to monitor for these eight events and for other potential safety signals associated with minocycline use. No new labeling changes are recommended at this time.

[1] Office of Surveillance and Epidemiology: "Hypertriglyceridemia following drug interaction with antiretroviral therapy, myopathy, cytotoxic edema, depersonalization, metrorrhagia, dermatomyositis, lymphomatoid papulosis, acute febrile neutrophilic dermatosis" for minocycline hydrochloride extended release capsules. Jessica Weintraub, Pharm. D., Safety Evaluator; OSE RCM #: 2011-3990, 18, 2012

Reference ID: 3151134

8 Postmarket Experience

The applicant's product, Ximino (minocycline hydrochloride) Extended Release Capsules, 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. Changes to the applicant-proposed labeling include:

Full Prescribing Information
1.1 Indication
Moving the statement "To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, Ximino should be used only as indicated *[see Warnings and Precautions (5.11)]*" from section, 1.2 Limitations of Use, to section, 1.1 Indication.

2 Dosage and Administration
Addition of the sentence: "The capsules should be swallowed whole without chewing, crushing or splitting." This is done to correct a discrepancy in the PI between section 2 and section 17 Patient Counseling Information.

Comment regarding Dosing table:
The following dosing table differs from that for Solodyn® due to the presence of different proposed capsule strengths.

Table 1: Dosing Table for Minocycline Hydrochloride Extended-Release Capsules

Patient's Weight (lbs.)	Patient's Weight (kg)	Capsule Strength (mg)	Actual mg/kg Dose
99 to 122	45 to 55	45	1 to 0.82
123 to 164	56 to 74	67.5	1.21 to 0.91
165 to 212	75 to 96	90	1.20 to 0.94
213 to 276	97 to 125	112.5	1.16 to 0.90
277 to 300	126 to 136	135	1.07 to 0.99

5 Warnings and Precautions
5.1 Teratogenic Effects
Changing the following text from all capitals to sentence case letters as recommended by SEALD reviewer:

A. Minocycline, like other tetracycline-class drugs, can cause fetal harm when administered to a pregnant woman. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus.

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).

5.2 Pseudomembranous Colitis
Replacement of current labeling with class labeling recommended by Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogens and transplant Products:

Clostridium difficile associated diarrhea (CDAD) has been reported with nearly all antibacterial agents, including minocycline, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated *[see Patient Counseling Information (17)]*.

6 Adverse Reactions
The current NDA is a 505(b)2 application therefore safety data are the same as the listed drug Solodyn®.

7.5 Low Dose Oral Contraceptives
Addition of phrase, "administered as another extended release formulation which is bioequivalent to Ximino," to following text to improve clarity:

In a multi-center trial to evaluate the effect of minocycline hydrochloride (administered as another extended release formulation which is bioequivalent to Ximino) on low dose oral contraceptives, hormone levels over one menstrual cycle with and without minocycline hydrochloride 1 mg/kg once-daily were measured.

12 Clinical Pharmacology
12.3 Pharmacokinetics

- The following applicant proposed language was deleted:

(b) (4)

- The deleted language was replaced with that proposed by clinical pharmacology:

Ximino is not bioequivalent to immediate release minocycline products.

Following administration of a single dose of Ximino (135 mg) to healthy male and female adult subjects, the mean (SD) $AUC_{(0-\infty)}$ and C_{max} were 12.87 (4.04) mcg x hr/mL and 0.68 (0.25) mcg/mL, respectively, under fasting conditions.

When a single dose of Ximino (135 mg) was administered with a high fat meal to the same subjects in the same trial in a crossover design, the mean (SD) $AUC_{(0-\infty)}$ and C_{max} were 14.16 (3.10) mcg x hr/mL and 0.85 (0.20) mcg/mL, respectively.

14 Clinical Studies

The current NDA is a 505(b)2 application therefore efficacy data are the same as the listed drug Solodyn®.

17 Patient Counseling Information
The following sentence was added to improve communication with patients: To avoid contraceptive failure, female patients on low dose oral contraceptives should be advised to use a second form of contraception during treatment with minocycline.

- Concurrent use of tetracycline may render oral contraceptives less effective. To avoid contraceptive failure, female patients on low dose oral contraceptives should be advised to use a second form of contraception during treatment with minocycline *[see Drug Interactions (7.5)]*.

Patient Package Insert
The Patient Package Insert (PPI) was evaluated by Division of Risk Management (DRISK), review dated October 3, 2011 and Office of Prescription Drug promotion (OPDP), review dated October 6, 2011. The PPI follows the question and answer Med Guide format and is reflective on information in the Physician Insert.

9.3 Advisory Committee Meeting

No Advisory Committee was convened in response to this application

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/s/

PATRICIA C BROWN
06/26/2012

GORDANA DIGLISIC
06/26/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 20-1922

Applicant: Ranbaxy Laboratories, Limited

Stamp Date: Feb 4, 2011

Drug Name: (minocycline hydrochloride) Extended Release Capsules: 45, 67.5, 90, 112.5, & 135 mg

NDA Type: Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			Clinical study reports do not have page numbers
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the listed drug?	505(b)(2): Solodyn®			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	

Reference ID: 2926685

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study #1 3739; Fasting Bioequivalence study Indication: Acne Pivotal Study #2 3740; Food-Effect Bioequivalence study Indication: Acne				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Open safety issues with Solodyn® will become open safety issues for new product
25.	Have narrative summaries been submitted for all deaths and			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 2926685

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Applicant has submitted case report forms for all subjects.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comments to be sent to the applicant: None.

Reference ID: 2926685

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Patricia C. Brown, M.D.	March 31, 2011
Reviewing Medical Officer	Date
Gordana Diglisic, MD	see sign-off date
Clinical Team Leader	Date

Reference ID: 2926685

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
03/31/2011

GORDANA DIGLISIC
04/01/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 20-1922 **Applicant:** Ranbaxy Laboratories, Limited **Stamp Date:** May 20, 2010

Drug Name: (minocycline hydrochloride) Extended Release Capsule, 135 mg **NDA Type:** Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the listed drug?	505(b)(2): Solodyn® The application per 21 CFR 314.101(d)(3) is incomplete because information required under CFR 314.50 is not present. (See statement under fileability.)			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study #1 1974/09 Bioequivalence study Indication: Acne Pivotal Study #2 1975/09 Bioequivalence study Indication: Acne				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			Explanation offered but not adequate for bioequivalence
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the			X	Open safety issues with Solodyn® will

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				become open safety issues for new product
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				Statistics/Clin Pharm
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				“
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				“
34.	Are all datasets to support the critical safety analyses available and complete?				“
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				“
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Applicant has submitted case report forms for all subjects.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?		X		Form FDA 3454 is provided, however it is signed by an agent, not the applicant.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? No

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The application per 21 CFR 314.101(d)(3) is incomplete because information required under CFR 314.50 is not present. Per 21 CFR 314.50 (d)(5)(v) the application is required to have: "An integrated summary of the data demonstrating substantial evidence of effectiveness for the claimed indications." Since the sponsor is proposing a 505(b) (2) application with Solodyn® as the listed drug, the claimed indication will be the same as that for Solodyn®. The indication for Solodyn® is to treat 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 daily for 12 weeks. The sponsor plans to establish bioequivalence based only on study of a 135mg formulation and the recommended dosage of approximately 1 mg/kg can only be fulfilled for patients who weigh 200 to 300 pounds (91 – 136 kg), a subset of the population of patients aged 12 and older having inflammatory lesions of non-nodular moderate to severe acne vulgaris.

Comments to be sent to the applicant:

21 CFR 314.101(d)(3): The application is incomplete because it does not on its face contain information required under section 505(b) and 21 CFR 314.50.

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

The following information should be requested when the sponsor resubmits the application:

a) a pediatric assessment

b) a narrative summary for each adverse dropout

c) financial disclosure form FDA 3454 signed by the applicant

Patricia C. Brown, M.D.	7/14/10
Reviewing Medical Officer	Date
Jill Lindstrom	see sign-off date
Clinical Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201922	ORIG-1	RANBAXY LABORATORIES LTD	MINOCYCLINE ER CAPSULES 135 mg

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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
07/14/2010

JILL A LINDSTROM
07/14/2010