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RESEARCH**

*APPLICATION NUMBER:*  
**201922Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 201922  
Supporting document/s: 6  
Applicant's letter date: 02-04-2011  
CDER stamp date: 02-04-2011  
Product: Minocycline hydrochloride extended release capsule, 135 mg  
Indication: Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris  
Applicant: Ranbaxy Lab. Ltd.  
Review Division: Dermatology and Dental Products  
Reviewer: Renqin Duan, Ph.D.  
Supervisor/Team Leader: Barbara Hill, Ph.D.  
Division Director: Susan Walker, M.D.  
Project Manager: Matthew White

*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

The sponsor submitted a 505(b)(2) NDA application for minocycline hydrochloride (HCl) capsules (a new dosage form).

## 1.2 Brief Discussion of Nonclinical Findings

The sponsor did not submit any nonclinical studies conducted with their drug product. The sponsor is relying on the Agency's findings of safety for Solodyn (minocycline HCl) tablets through generation of a clinical bridge to support a 505(b)(2) NDA submission. The sponsor has generated a clinical bridge to Solodyn tablets by conduct of a comparative clinical pharmacokinetic study with Solodyn tablets and their minocycline HCl capsules. The sponsor will be able to rely on the nonclinical information contained in the Solodyn tablets label (refer to Section 1.3.3).

## 1.3 Recommendations

### 1.3.1 Approvability

The product is approvable with respect to nonclinical concerns.

### 1.3.2 Additional Non Clinical Recommendations

None

### 1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the minocycline HCl capsules label reproduced below. The nonclinical portions of the label (i.e., sections 8.1, 12.1 and 13.1) are the same as in the recently approved Solodyn tablets label. The pharmacologic class designation for minocycline HCl in the Highlights section of the label (i.e., tetracycline-class drug) is acceptable.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

### INDICATIONS AND USAGE

(b) (4) Tradename is a tetracycline-class drug indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

### 8.1 Pregnancy

*Teratogenic Effects: Pregnancy category D [see Warnings and Precautions (5.1)]*

(b) (4) Tradename should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and stop treatment immediately.

There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class drugs, crosses the placenta and may cause fetal harm when administered to a pregnant woman.

Rare spontaneous reports of congenital anomalies including limb reduction have been reported with minocycline use in pregnancy in postmarketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established.

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits in doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients as a result of use of (b) (4) -Tradename). Reduced mean fetal body weight was observed in studies in which minocycline was administered to pregnant rats at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients who use (b) (4) Tradename).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats from day 6 of gestation through the period of lactation (postpartum day 20), at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients as a result of use of (b) (4) Tradename). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

## 12.1 Mechanism of Action

The mechanism of action of minocycline hydrochloride for the treatment of acne is unknown.

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis**-Long-term animal studies have not been performed to evaluate the carcinogenic potential of minocycline. A structurally related compound, oxytetracycline, was found to produce adrenal and pituitary tumors in rats.

**Mutagenesis**-Minocycline was not mutagenic *in vitro* in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic *in vitro* using human peripheral blood lymphocytes or *in vivo* in a mouse micronucleus test.

**Impairment of Fertility**-Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (which resulted in up to approximately 40 times the level of systemic exposure to minocycline observed in patients as a result of use of (b) (4) Tradename). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients as a result of use of (b) (4) Tradename) adversely affected spermatogenesis. Effects observed at 300 mg/kg/day included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis.

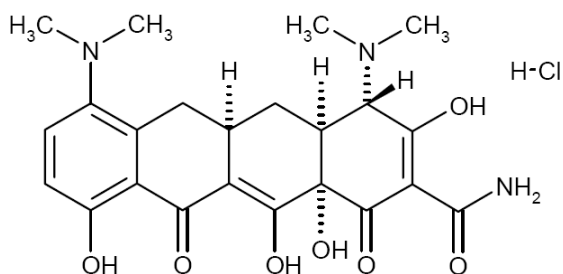
(b) (4) Tradename should not be used by individuals of either gender who are attempting to conceive a child.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number (Optional):	13614-98-7
Generic Name:	Minocycline HCl Extended Release Capsules
Code Name:	N/A
Chemical Name:	4,7-Bis(dimethylamino)- 1,4,4a,5,5a,6, 1 1, 1 2a-octahydro-3, 10, 12, 12a-tetrahydroxy- 1, 11-dioxo-2-naphthacenecarboxamide monohydrochloride
Molecular Formula/Molecular Weight:	C <sub>23</sub> H <sub>27</sub> N <sub>3</sub> O <sub>7</sub> •HCl/493.95

Structure:



Pharmacologic Class: Antibiotics

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 50-808 (Solodyn tablets)

## 2.3 Drug Formulation

Five formulations of minocycline HCl extended release capsules (45 mg/67.5 mg/90 mg/112.5 mg and 135 mg) have been proposed for marketing. The quantitative composition of minocycline HCl extended release capsules are provided in the following table.

Composition of Minocycline Extended Release Capsules

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

## 2.4 Comments on Novel Excipients

None

## 2.5 Comments on Impurities/Degradants of Concern

During the filing review for the resubmission of this NDA, a potential impurity issue was indentified. The following information request was contained in the Pharmacology/Toxicology NDA Filing review. This information request was sent to the sponsor on April 8, 2011.

*You should provide an impurity profile comparison between the listed drug product and your drug product. Additional nonclinical bridging toxicology studies may be needed if there are any significant differences in the impurity profile for the listed drug product compared to the impurity profile for your drug product.*

The sponsor responded with incomplete information on May 11, 2011. Therefore, the following Information Request was sent to the sponsor on May 27, 2011.

*In your response to the nonclinical information requested in the filing communication dated April 8, 2011, you provided information for the degradant impurity (b) (4) in your drug product and the listed drug product. However, you should provide a full impurity profile comparison between the listed drug product and your drug product. It should include levels for each of the degradant and non-degradant impurities, and total impurities. The degradant and non-degradant impurities should be identified by their name and not by their code number.*

On June 1, 2011, the sponsor provided a comparison of the impurity levels in the listed drug product, Solodyn, compared to their drug product. Four impurities were identified in this submission which included: (b) (4) and 4) unknown impurities. The highest level of each of the impurities noted in the listed drug (Solodyn) compared to the highest level noted in the sponsor's drug product are provided in the following table.

Impurity	Solodyn (% w/w)	Minocycline HCl capsules (% w/w)
(b) (4)		

The highest level of unknown impurities in the sponsor's drug product was greater than (b) (4) which is higher than the specification for the listed drug product (NMT (b) (4)). The sponsor proposed a drug product specification for unknown impurities of (b) (4). This higher unknown impurity specification is not supported by nonclinical toxicology data. This concern was shared with the review team during the Mid-Cycle meeting held on June 7, 2011.

During a teleconference conducted on August 3, 2011, the sponsor stated that they had developed a new HPLC method for quantitation of impurities in the drug product. The sponsor clarified that the new HPLC method allows for identification of additional impurities that had previously co-eluted with the unknown impurity peak using the previous HPLC method. An information request was sent to the sponsor on August 4, 2011 requesting additional information about the new HPLC method and a revision of the impurity specifications based on the data generated with the new HPLC method.

The sponsor responded to the information request on August 10, 2011. Information to validate the new HPLC method was included in the response. Dr. Moo-Jhong Rhee, Branch Chief, DNDQA II/ONDQA, determined that the new HPLC method is adequate. Dr. Rhee's conclusion contained in his review in DARRTS dated September 28, 2011 is provided below for reference purposes.

*"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."*

The sponsor stated that they have tightened the unknown impurity specification to (b) (4) based on the analysis of their drug product using the new HPLC method for quantitation of impurities in the drug product. The sponsor identified four new impurities in their drug product based on the new HPLC method. The new impurities include: (b) (4)

The drug substance, minocycline HCl, used for the manufacture of Solodyn tablets is the same drug substance used for the manufacture of minocycline HCl capsules. The DMF for the minocycline HCl drug substance provided data on the level of these impurities in several marketed minocycline drug products (including the listed drug, Solodyn). The ranges for the four new impurities are provided in the following table.

Impurity	Range (% w/w)
(b) (4)	

The sponsor provided new impurity specifications for their minocycline HCl capsules in the August 31, 2011 submission. The new impurity specifications are provided below.

Impurity	Specification (%w/w)
(b) (4)	

The proposed impurity specifications are acceptable from a Pharmacology/Toxicology perspective.

## 2.6 Proposed Clinical Population and Dosing Regimen

Patients with non-nodular moderate to severe acne vulgaris; 1 mg/kg once daily for 12 weeks.

## **2.7 Regulatory Background**

On May 10, 2010, the sponsor originally submitted a 505(b)(2) NDA application for minocycline HCl capsules. After a preliminary review, the Agency found the application was not sufficiently complete to permit a substantive review. A Refuse to File letter was sent to the sponsor on July 16, 2010.

On February 4, 2011, the sponsor resubmitted the 505(b)(2) NDA application for minocycline HCl capsules. The sponsor intends to rely on the Agency's findings of safety for Solodyn tablets. The sponsor has generated a clinical bridge to Solodyn tablets by conduct of a comparative clinical pharmacokinetic study with Solodyn tablets and their minocycline HCl capsules.

## **3 Studies Submitted**

### **3.1 Studies Reviewed**

None. The sponsor did not submit any nonclinical studies with this 505(b)(2) NDA submission.

### **3.2 Studies Not Reviewed**

N/A

### **3.3 Previous Reviews Referenced**

N/A

## **4 Pharmacology**

### **4.1 Primary Pharmacology**

Minocycline inhibits the growth of certain species of bacteria through inhibition of protein synthesis by blocking aminoacyl-tRNA binding to the mRNA-ribosome complex. Minocycline is active against a number of gram-positive and gram-negative organisms, including *Propionibacterium acnes*. The mechanism through which minocycline ameliorates acne is not fully elucidated, although reducing the bacterial count may reduce the size and quantity of lesions by reducing inflammation.

### **4.2 Secondary Pharmacology**

N/A

### **4.3 Safety Pharmacology**

No new safety pharmacology studies were submitted with this NDA. The previous clinical experience with Solodyn suggest that there is no safety pharmacology concerns associated with minocycline.

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

Minocycline is well absorbed from the GI tract, with peak serum levels observed within two to four hours. Greater than 95% of an oral dose is typically absorbed. Minocycline is highly lipid soluble, and exhibits a large volume of distribution (>80 L in humans). Minocycline is approximately 70% to 80% bound to plasma proteins, exhibits a serum half-life of 11 to 18 hours and a renal clearance rate of 9 mL/min. Minocycline is metabolized in the liver to three inactive metabolites (9-hydroxy-, N-desmethyl-, and N4-desmethyl-minocycline). Minocycline and its metabolites are primarily eliminated in the feces.

### 5.2 Toxicokinetics

N/A

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

N/A

### 6.2 Repeat-Dose Toxicity

The primary toxicological target organ for minocycline identified in repeat dose nonclinical toxicity studies appears to be the thyroid, with treatment-related effects on the thyroid manifesting (at sufficient levels of exposure) as grossly visible enlargement, increased mean weight, dark red discoloration, increased colloid content, accumulation of brown pigment in the follicular cells, follicular cell hypertrophy, and elevated plasma levels of T4 and TSH. These effects are of a minimal to mild severity in most instances, and do not appear to be toxicologically relevant at levels of exposure close to those observed clinically.

## 7 Genetic Toxicology

The following genetic toxicology information is contained in the Solodyn Tablets label.

Minocycline was not mutagenic *in vitro* in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic *in vitro* using human peripheral blood lymphocytes or *in vivo* in a mouse micronucleus test.

## 8 Carcinogenicity

The following carcinogenicity information is contained in the Solodyn Tablets label.

Long-term animal studies have not been performed to evaluate the carcinogenic potential of minocycline. A structurally related compound, oxytetracycline, was found to produce adrenal and pituitary tumors in rats.

The carcinogenic potential of minocycline HCl is being evaluated in mice and rats as a postmarketing commitment under NDA 50-808.

## 9 Reproductive and Developmental Toxicology

The following reproductive toxicology information is contained in the Solodyn Tablets label.

### **Impairment of Fertility**

Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (which resulted in up to approximately 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN®). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN®) adversely affected spermatogenesis. Effects observed at 300 mg/kg/day included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis.

SOLODYN® should not be used by individuals of either gender who are attempting to conceive a child.

### **Pregnancy**

#### *Teratogenic Effects: Pregnancy category D*

SOLODYN® should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and stop treatment immediately.

There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class drugs, crosses the placenta and may cause fetal harm when administered to a pregnant woman.

Rare spontaneous reports of congenital anomalies including limb reduction have been reported with minocycline use in pregnancy in post-marketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established.

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits in doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients as a result of use of SOLODYN<sup>®</sup>). Reduced mean fetal body weight was observed in studies in which minocycline was administered to pregnant rats at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients who use SOLODYN<sup>®</sup>).

Minocycline was assessed for effects on peri-and post-natal development of rats in a study that involved oral administration to pregnant rats from day 6 of gestation through the period of lactation (postpartum day 20), at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients as a result of use of SOLODYN<sup>®</sup>). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

## **10 Special Toxicology Studies**

N/A

## **11 Integrated Summary and Safety Evaluation**

The sponsor submitted a 505(b)(2) NDA application for minocycline HCl capsules (a new dosage form). The sponsor is relying on the Agency's findings of safety for Solodyn tablets through generation of a clinical bridge to support a 505(b)(2) NDA submission. The sponsor has generated a clinical bridge to Solodyn tablets by conduct of a comparative clinical pharmacokinetic study with Solodyn tablets and their minocycline HCl capsules. The sponsor will be able to rely on the nonclinical information contained in the Solodyn tablets label (refer to Section 1.3.3).

The carcinogenic potential of minocycline HCl is being evaluated in mice and rats as a post-marketing commitment under NDA 50-808. The results from the carcinogenicity studies conducted with minocycline HCl should be incorporated into the labels for both Solodyn tablets and minocycline HCl capsules when they are available.

## **12 Appendix/Attachments**

N/A

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/s/  
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Renqin DUAN  
10/04/2011

BARBARA A HILL  
10/04/2011  
I concur

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 201922

**Applicant:** Ranbaxy

**Stamp Date:** 02-04-2011

**Drug Name:** Minocycline  
hydrochloride extended release  
capsule, 135 mg

**NDA Type:** 505(b)(2)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Based on the agreement between the Agency and the sponsor of the listed drug Solodyn (NDA 50-808), the carcinogenic potential of the drug product is being evaluated in mice and rats post approval of NDA 50-808.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A Relying on the Agency's findings of safety for the listed drug Solodyn
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A Relying on the Agency's findings of safety for the listed drug Solodyn
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A Relying on the Agency's findings of safety for the listed drug Solodyn
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A Relying on the Agency's findings of safety for the listed drug Solodyn

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? \_Yes\_\_\_\_\_**

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

You should provide an impurity profile comparison between the listed drug product and your drug product. Additional nonclinical bridging toxicology studies may be needed if there are any significant differences in the impurity profile for the listed drug product compared to the impurity profile for your drug product.

Renqin Duan, PhD	02-28-2011
Reviewing Pharmacologist	Date
Barbara Hill, PhD	See sign off date
Supervisor	Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

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/s/  
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Renqin DUAN  
03/31/2011

BARBARA A HILL  
03/31/2011

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 201922

**Applicant:** Ranbaxy

**Stamp Date:** 05-10-2010

**Drug Name:** Minocycline  
hydrochloride extended release  
capsule, 135 mg

**NDA Type:** 505(b)(2)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		Based on the agreement between the Agency and the sponsor of the listed drug Solodyn (NDA 50-808), the carcinogenic potential of the drug product is being evaluated in mice and rats post approval of NDA 50-808.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A Relying on the Agency's findings of safety for the listed drug Solodyn
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A Relying on the Agency's findings of safety for the listed drug Solodyn
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A Relying on the Agency's findings of safety for the listed drug Solodyn
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A Relying on the Agency's findings of safety for the listed drug Solodyn

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION  
FILEABLE? \_Yes\_\_\_\_\_**

If the NDA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A

Renqin Duan, PhD	06-22-2010
Reviewing Pharmacologist	Date
Barbara Hill, PhD	See sign off date
Supervisor	Date

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

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

Renqin DUAN  
07/06/2010

BARBARA A HILL  
07/06/2010