

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209269Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 18, 2017

To: Belainesh Robnett
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Matthew J. Falter, Pharm.D.
Team Leader
Office of Prescription Drug Promotion (OPDP)

CC: Silvia Wanis, Pharm.D., CPH
Regulatory Review Officer, OPDP

Subject: **NDA 209269**
Addendum to OPDP labeling comments for MINOLIRA™
(minocycline hydrochloride) extended-release tablets, for oral use

Reference is made to DDDP's July 18, 2016, consult request for OPDP's comments regarding the proposed Package Insert (PI) and Carton and Container Labeling for MINOLIRA™ (minocycline hydrochloride) extended-release tablets, for oral use (Minolira).

Addition reference is made to OPDP's review of the proposed Minolira PI and Carton and Container labeling checked into DARRTS on March 29, 2017.

Further reference is made to the sponsor's proposed revisions to the PI submitted by the sponsor on April 12, 2017, and located in SharePoint on April 18, 2017. Reference is also made to the proposed revisions to the Carton and Container labeling submitted to FDA on April 12, 2017 and located in the EDR at:

- <\\cdsesub1\evsprod\nda209269\0015\m1\us\114-label\1141-draft-label\contain-135mg-ps-10count.pdf>
- <\\cdsesub1\evsprod\nda209269\0015\m1\us\114-label\1141-draft-label\contain-135mg-30count.pdf>

- <\\cdsesub1\evsprod\nda209269\0015\m1\us\114-label\1141-draft-label\contain-105mg-ps-10count.pdf>
- <\\cdsesub1\evsprod\nda209269\0015\m1\us\114-label\1141-draft-label\contain-105mg-30count.pdf>

This addendum serves as review of the aforementioned documents. OPDP has reviewed the proposed revisions to the PI and has no comments at this time.

OPDP has also reviewed the proposed revisions to the Carton and Container labeling and offers the following comments.

OPDP is concerned that the proposed trade dress in the Carton and Container labeling is promotional in tone and may give a misleading impression regarding the efficacy of Minolira. We note that the tittle over the first ‘i’ in the proprietary name is large and prominent but then as a circular pattern is created, becomes smaller, faint, and nearly imperceptible. This presentation may misleadingly suggest that as a result of using Minolira for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris, all patients will achieve similar improvements in inflammatory lesions, when this is not the case.

According to the draft PI, the mean percent improvement in inflammatory lesions in subjects treated with Minolira was 43-46%. In addition, only 16-17% of subjects were evaluated as either clear or almost clear on the Evaluator’s Global Severity Assessment. The graphical presentation in the trade dress of the proposed proprietary suggests a greater improvement in inflammatory lesions than what has been demonstrated, which may be misleading.

We remind the sponsor that labeling must not be promotional in tone nor false or misleading in any particular. Therefore, we recommend deleting the graphical presentation over the first ‘i’ in the trade dress of the proprietary name.

Thank you for the opportunity to review the revised PI and Carton and Container labeling. If you have any questions, please contact me at matthew.falter@fda.hhs.gov or 6-2287.

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/s/

MATTHEW J FALTER
04/18/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 13, 2017
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: NDA 209269
Product Name and Strength: Minolira (minocycline hydrochloride) extended release tablets, 105 mg and 135 mg
Applicant/Sponsor Name: Dr. Reddy's Laboratories, Inc.
Submission Date: April 12, 2017
OSE RCM #: 2016-1634-1
DMEPA Primary Reviewer: Madhuri R. Patel, Pharm.D.
DMEPA Team Leader (Acting): Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels, Prescribing Information (PI), and Instructions for Breaking Tablets for Minolira (minocycline hydrochloride) extended release tablets (NDA 209269) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised Prescribing Information (PI) and Instructions for Breaking Tablets is acceptable from a medication error perspective. However, the revised container labels are unacceptable from a medication error perspective. We note the established name is not at least half the size of the proprietary name, which could increase the risk for medication errors. Therefore, we provide a recommendation in Section 4 for the Applicant to address this concern.

3 RECOMMENDATIONS FOR DR. REDDY'S LABORATORIES, INC.

^a Patel M. Label and Labeling Review for MINOLIRA (NDA 209269). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 13. RCM No.: 2016-1634.

We recommend the following be implemented prior to approval of this NDA 209269:

- A. Container Label: The established name is not at least half the size of the proprietary name. Thus, we request you revise the established name to be in accordance with 21 CFR 201.10(g)(2).

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/s/

MADHURI R PATEL
04/14/2017

SARAH K VEE
04/14/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Drug Evaluation IV
Office of New Drugs
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MEMORANDUM TO FILE PEDIATRIC LABELING REVIEW

Date Consulted: 01/24/2017

From: Jacqueline A. Spaulding MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)

Through: Mona Khurana, MD, Acting Pediatric Team Leader

John J. Alexander M.D. M.P.H., Deputy Division Director
DPMH, ODE IV

To: Division of Dermatology and Dental Products (DDDP)

Drug: MINOLIRA™ (minocycline hydrochloride) Extended-Release
Tablets

Application Number: NDA 209269

Subject: Labeling Review for 505(b)(2) New Drug Application

Applicant: Dr. Reddy's Laboratories Limited

Proposed Indication Treatment of only inflammatory lesions of non-nodular moderate
to severe acne vulgaris in patients 12 years of age and older

Consult Question: “Please provide feedback on section 8.4 of the draft prescribing
information labeling”

Materials Reviewed

- The Labeling Review Tool Draft Guidance for Industry and Review Staff - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice for Industry and Review Staff Products Labeling Good Review Practice ¹
- The February 2013 Draft Guidance for Industry and Review Staff: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling ²
- Applicant's submitted background package and proposed package labeling for MINOLIRA minocycline hydrochloride (HCl) extended release tablets, NDA 209269
- DPMH Pregnancy and Lactation Labeling Review dated February 17, 2017; DARRTS Reference ID 3966934
- Solodyn (minocycline HCL) ER tablets Label Drugs@FDA, accessed February 2, 2017
- DPMH Pregnancy and Lactation Labeling Review dated 02/12/17 Reference ID: 4056229 accessed February 22, 2017
- Reviewer Literature Search using Embase and PubMed databases; Search terms "minocycline and tooth discoloration" "minocycline and tooth staining"

Consult Request

DDDP consulted DPMH on January 24, 2017 to provide input for appropriate format and content of the Pediatric Use section of MINOLIRA (minocycline HCl) extended-release (ER) labeling.

I. Background

MINOLIRATM (minocycline HCl) ER tablets are a semi-synthetic derivative of tetracycline. ³ The mechanism of action and pharmacodynamics of MINOLIRA in the treatment of acne are unknown. MINOLIRA is supplied as scored tablets containing (b) (4) minocycline hydrochloride equivalent to 105 milligrams (mg) and 135 mg of minocycline. ³

Minocin (minocycline HCl) was originally approved on June 30, 1971⁴ as 100 mg capsules for treatment of infections due to susceptible strains of micro-organisms. Labeling at that time also stated tetracyclines may be useful adjunctive therapy in severe acne. Minocycline HCl is

¹<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm> accessed 2 February 2017

²<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm341394.pdf> accessed November 1, 2016

³ Applicant's submitted background package and proposed package labeling for MINOLIRA [minocycline hydrochloride (HCL) extended release tablets, NDA 209269

⁴ 1971 FDA Approved package retrieved 03/01/17 search of PharmaPendium for Minocin <https://www.pharmapendium.com/#/browse/fda/Minocycline%20Hydrochloride/365a8b82452ccaf6e2d3cca1848abd2e?query=Minocin&includeSynonyms=true>

currently approved in various dosage forms (immediate-release capsule, extended-release capsule, microspheres, and injectable) for treatment of bacterial infections, for adjuvant therapy for severe acne vulgaris, for treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris, and as an adjunct to scaling and tooth planning procedures for reduction of pocket depth in adult periodontitis.⁵ Minocycline HCl is marketed under both NDAs and under more than two dozen abbreviated NDAs (ANDAs).⁶

A. Regulatory History^{3,7}

On July 8, 2016, the Applicant, Dr. Reddy's Laboratories Limited, submitted a New Drug Application (NDA 209269) for MINOLIRA [minocycline HCl] ER 105 mg and 135 mg scored tablets for the proposed indication of the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. NDA 209269 is a 505(b)(2) application which is relying on FDA's previous findings of safety and efficacy of the listed drug, Solodyn (NDA 050808).^{3,7} The initial pediatric study plan (iPSP) was submitted to the IND 120026, SN0005 on March 18, 2016. The Agency determined that the NDA for MINOLIRA will not trigger the requirement for a pediatric assessment under the Pediatric Research Equity Act (PREA).

Solodyn (minocycline HCl) ER was approved on May 8, 2006 for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.⁸ The approved dosage is 1 mg per kilogram (mg/kg) once daily for 12 weeks. The labeling states that higher doses have not been shown to be of additional benefit in the treatment of inflammatory acne lesions and may be associated with more acute vestibular side effects. The basis for the approval was demonstrated in two 12-week, multi-center, randomized, double-blind, placebo-controlled, trials in patients 12 years of age and older. In these two trials, patients treated with Solodyn at 1 mg/kg experienced statistical improvement in mean percent change in inflammatory lesion counts compared to patients treated with placebo at the 12 week timepoint. In addition, the percentage of Soldyn-treated patients with an Evaluator's Global Severity Assessment (EGSA) of clear or almost clear at 12 weeks was statistically better than placebo-treated patients.⁸

⁵ Source: July 9, 2012 Division Director Summary Review of NDA 201922 (Ximino)

⁶ Source: Orange Book Minocycline search March 2, 2017

⁷ DPMH Pregnancy and Lactation Labeling Review dated February 17, 2017; DARRTS Reference ID 3966934; accessed February 20, 2017

⁸ Approved Solodyn package insert 10/21/2013, accessed February 9, 2017

B. Acne Vulgaris^{9,10}

Acne Vulgaris (AV) is a chronic inflammatory skin disease with open or closed comedones (blackheads and whiteheads, respectively) and inflammatory lesions, including papules, pustules, or nodules (also known as cysts).⁹ Acne is a common skin disorder, especially in adolescents and young adults. Acne is the most common chronic skin disease affecting children and adolescents, with an 85% prevalence rate among those aged 12 to 24 years. A published review article stated teenagers only comprise 36.5% of patients with acne.¹⁰ The statistic on adolescents was cited from a 2010 review article¹¹ that examined the epidemiology of AV in the United States. While there is no mortality associated with acne, there is often significant physical and psychological morbidity associated with AV, such as permanent scarring, poor self-image, depression, and anxiety. Acne has been associated with anxiety, low-self-esteem, embarrassment, social withdrawal and depression.⁹

The treatment of AV is important in that it can prevent physical scarring and psychosocial distress.¹² Treatment options are available according to the severity of the disease. The majority of patients with acne can be successfully treated using topical agents such as benzoyl peroxide, topical antibiotics, and topical retinoids; however patients with moderate to severe inflammatory acne unresponsive to topical therapies may require systemic therapy with oral antibiotics such as the tetracycline class.⁹

Tetracyclines are the commonly prescribed antibacterial drugs for the treatment of AV.⁹ Compared to older tetracyclines, minocycline is thought to have better absorption and is capable of greater antimicrobial activity; and is more lipophilic thus penetrating tissue better than older tetracyclines.¹³ DDDP has approved the reference drug, Solodyn (minocycline HCl) for moderate and severe acne.

II. Safety Considerations

The Warnings and Precautions section of approved labeling for Solodyn states that use 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). The

⁹ Zaenglein AL, Pathy AL, Schlosser BJ, et al. (2016). Guidelines of care for the management of acne vulgaris. *Journal of American Academy of Dermatology*, 945-73.

¹⁰ Kim, W., & Mancini, A. (2013). Acne in Childhood: An Update. *Pediatric Annals*, 418-427.

¹¹ Yentzer, B., Hick, J., Reese, E., Uhas, A., Feldman, S., & Balkrishnan, R. (2010). Acne Vulgaris in the United States: A Descriptive Epidemiology. *Cutis*, 94-99.

¹² Park, H., & Skopit, S. (2016). Safety Considerations and Monitoring in Patients Treated with Systemic Medications for Acne. *Dermatology Clinics*, 185 - 193

¹³ Cascio, A., Di Liberto, C., D'Angelo, M., Iaria, C., Scarlata, F., Titone, L., et al. (2004). No Findings of Dental Defects in Children Treated with Minocycline. *Antimicrobial Agents and Chemotherapy*, 2739-2741.

Solodyn labeling further states that this adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses and that enamel hypoplasia has also been reported. Therefore, the labeling cautions that tetracycline drugs should not be used during tooth development.

Reviewer Comments: This reviewer conducted a literature search in PubMed and Embase using the search terms: “minocycline and tooth discoloration” and minocycline and tooth staining” to identify published reports of minocycline-induced tooth discoloration in adults and pediatric patients. The dates of the search were: February 8, 2017 and February 16, 2017. The years included in the search included up to the present time. The limits on the literature search included: English language and humans only.

The search of the PubMed database initially identified 48 articles of which 30 articles were not further evaluated by this reviewer for the reasons that follow. The search of the Embase database initially identified 142 articles of which 125 articles were not further evaluated by this reviewer for the following reasons:

- 1. The subject matter was not applicable to tetracycline and/or minocycline tooth discoloration/staining,*
- 2. The article was written in a language other than English,*
- 3. The abstract and full text article was not available*
- 4. The references were duplicates or;*
- 5. The article discussed an animal study*

Based on this approach, this reviewer identified 18 references from the combined PubMed and Embase searches that were relevant to minocycline or tetracycline tooth discoloration/staining. These references consisted of the following: 11 review articles^{9,10, 11,12, 13 14, 15, 16, 17, 18, 22,24}; five case reports^{19, 26, 27, 28,29} and two case-series.^{25,20} No information regarding minocycline tooth discoloration/staining was retrieved from controlled clinical trials.

¹⁴ Smith, K., & Leyden, J. J. (2005). Safety of Doxycycline and Minocycline: A Systematic Review. *Clinic Therapeutics*, 1329-1342.

¹⁵ Eisen, D., & Hakin, M. (1998). Minocycline-Induced Pigmentation - Incidence, Prevention and Management. *Drug Safety*, 431-440.

¹⁶ Sloan, B., & Scheinfeld, N. (2008). The use and safety of doxycycline hyclate and other second-generation tetracyclines. *Expert Opinion on Drug Safety*, 571 - 577.

¹⁷ Gannon, M., Underhill, M., & Wellik, K. E. (2011). /which oral antibiotics are bestfor acne? *The Journal of Family Practice*, 290 - 292.

¹⁸ Good, M., & Hussey, D. (2003). Minocycline: stain devil? *British Journal of Dermatology*, 237-239.

¹⁹ LaPorta, V. N., Nikitakis, N. G., Sindler, A. J., & Reynolds, M. A. (2005). Minocycline-associated intra-oral soft-tissue pigmentation; clinicopathologic correlations and review. *Journal of Clinical Peridontology*, 119-122.

Overall, the published reviews support the findings from the retrieved case-series and case-reports describing the occurrence of tooth discoloration in pediatric patients older than 8 years of age as well as in adults who received minocycline for acne treatment for prolonged periods of time and generally at doses greater than 100 mg/day. Minocycline administration under these conditions was also reported to cause pigmentation of skin, teeth, sclera, and ears in adolescents and adults post-eruption of molars. While minocycline's potential to cause hyperpigmentation in non-dental tissues is currently captured in the applicant's proposed annotated labeling and in Solodyn labeling, neither labeling currently contains information about minocycline's potential to cause tooth discoloration in pediatric patients older than 8 years of age and in adults post-eruption of molars. The intrinsic nature and color of the tooth discoloration also appears to be unique to minocycline and distinct from that of tetracycline.

The potential for the tetracycline class of antibiotics to cause tooth enamel hypoplasia currently appears to be a theoretical risk. One published review discusses the possible association of tetracycline with enamel hypoplasia. However, in the remainder of the publications retrieved by this reviewer, no findings of enamel hypoplasia associated with minocycline administration for moderate to severe acne were described. Theoretically, tooth enamel hypoplasia may have been more of an earlier class effect unique to the tetracycline under development and the population (premature or newborn infants vs. older pediatric patients) to which the tetracycline was administered. For purposes of labeling, a statement discussing the theoretical risk of the tetracycline class and enamel hypoplasia could be added to better inform prescribers about this potential adverse reaction.

A brief summary of the retrieved publications follows.

Review Articles

A 2016 review focused on safety considerations and monitoring of patients undergoing systemic treatment for moderate to severe AV.²¹ The authors noted that adverse reactions reported with minocycline use include: minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with persistent myocarditis; minocycline-induced autoimmunity (MIA); gastrointestinal events (vomiting, diarrhea, and abdominal pain), vertigo/dizziness/ataxia; candidiasis, and bluish discoloration of the skin. These adverse reactions are currently captured in the applicant's proposed annotated labeling and are

²⁰ Petrino, J., Boda, K., Bowles, W., & McClanahan. (2010). Challenges in Regenerative Endodontics. *Journal of Endodontics*, 536-541.

²¹ Park, H., & Skopit, S. (2016). Safety Considerations and Monitoring in Patients Treated with Systemic Medications for Acne. *Dermatology Clinics*, 185 - 193.

consistent with those in Solodyn labeling. The review did not specifically mention the presence or absence of reports of minocycline-induced enamel hypoplasia.²¹

A 2013 review discusses the common oral antibiotics used for acne therapy (doxycycline, minocycline, tetracycline, erythromycin, cephalexin and trimethoprim/sulfamethoxazole).¹⁰ The review highlights the recommended dose of minocycline as 50 mg to 100 mg twice daily and notes that patients should be educated to expect a 3- to 6-month period of therapy (occasionally longer) with the goal of discontinuing oral treatment as early as possible while continuing the topical maintenance regimen. Finally, the authors report on the potential adverse reactions (ARs) associated with minocycline use and discussing these potential ARs with patients. Potential ARs reported in the article include: cutaneous and mucosal hyperpigmentation, drug hypersensitivity with hepatitis and pneumonitis, lupus-like syndrome, Stevens Johnson syndrome, vaginal candidiasis, vestibular effects, dental discoloration (not recommended < 8 years of age), inflammatory bowel disease, photosensitivity (less than doxycycline), and pseudotumor cerebri. The authors did not comment on minocycline-induced ARs which are distinct from those reported with tetracycline in general. Additionally, there were no reports of enamel hypoplasia associated with minocycline use stated in the article.¹⁰

A 2012 review article discusses drug-induced tooth discoloration and notes that – unlike tetracycline - minocycline can cause generalized intrinsic tooth discoloration post-eruption and this pattern of staining is distinct from that caused by tetracycline.²² The authors note that minocycline-induced tooth discoloration appears to occur in 3% to 6% of adults taking minocycline long-term at doses greater than 100 mg per day. The authors note that the precise mechanism by which minocycline causes intrinsic tooth discoloration is still not clear but opine on four possible theories, including the intrinsic theory which suggests that minocycline binds to plasma protein and deposits in collagen-rich tissue such as teeth. This complex oxidizes slowly over time with exposure to light. This deposition in teeth occurs solely with dentin matrix as secondary and reparative dentin is formed; the drug or its metabolite does not affect the enamel itself. The authors also report that minocycline may cause abnormal pigmentation of the skin, nails, bone, sclera, and conjunctiva in adults. The authors did not report enamel or bony hypoplasia as one of the abnormalities associated with minocycline administration for acne.²²

A 2009 review describing emerging treatments for AV reports that drugs of the tetracycline class, (doxycycline, minocycline and tetracycline), erythromycin (a macrolide) and trimethoprim are most often prescribed for acne, but that the lipophilic tetracyclines, such as doxycycline and minocycline, are generally more effective than others.²³ The authors note that the tetracycline class is contraindicated in pregnancy and children younger than 10 years of age due to the

²² Kumar, A., Kumar, V., Singh, J., Hooda, A., & Dutta, S. (2012). Drug-Induced Discoloration of Teeth; An Updated Review. *Clinical Pediatrics*, 181-185.

²³ James, K. A., Burkhart, C. N., & Morrell, S. S. (2009). Emerging Drugs in Acne. *Expert Opinion*, 649-659.

concerns for yellow tooth discoloration and enamel hypoplasia but don't reference new, original studies to support this established concern with the tetracycline class. The review does not discuss minocycline-specific ARs when used for the treatment of acne.²³

A 2004 review article describes how 41 children less than <8 years of age treated for brucellosis with oral minocycline (2.5 mg/kg) twice daily for 3 weeks were recalled and examined to check for dental staining and defects.²⁴ A control group of non-exposed patients was enrolled in the same period as the recruitment of the cases during annual dental screening among students born and living in the same district. Dental staining and defects were found in 14 of 41 minocycline exposed children (34.1%) and in 30 of 82 matched controls (36.6%), respectively ($P > 0.2$). Enamel hypoplasia was detected in 1 of 41 minocycline exposed children (2.4%) compared to 7 of 82 matched controls (8.5%) respectively. This study suggests that minocycline could be used to treat infections for a maximum of three weeks in pediatric patients less than 8 years of age when indicated and that minocycline does not appear to induce enamel hypoplasia.²⁴

The remaining seven published reviews retrieved by this reviewer describe similar information regarding minocycline tooth discoloration and/or tetracycline tooth discoloration. These reviews were published between 1998 and 2011 and did not provide any additional minocycline-specific safety information.

Original Article

The Applicant's proposed language in Subsection 5.1 Teratogenic Effects – (b) (4) of the MINOLIRA annotated label is based on findings from a review article.²⁵ (b) (4)

³ The article is based on a study conducted at the University Hospital, New York University in 1962 to investigate the effect of tetracycline on the developing skeleton in the premature infant by using the Day and Silverman x-ray technique of measuring fibula growth rate. This technique involves taking x-rays of each fibula at the end of three consecutive treatment periods. Each treatment period is approximately 9 -12 days. The author states that measurement of the fibula is a reasonable index of overall skeletal growth.²⁵

²⁴ Cascio, A., Di Liberto, C., D'Angelo, M., Iaria, C., Scarlata, F., Titone, L., et al. (2004). No Findings of Dental Defects in Children Treated with Minocycline. *Antimicrobial Agents and Chemotherapy*, 2739-2741.

²⁵ Cohan, S. Q., Bevelander, G., & Tiamsic, T. (1963). Growth inhibition of Premature Receiving Tetracycline. *American Journal of Diseases of Children*, pp. 65-73.

Fibula growth rates were measured over a 30-day period in 37 otherwise healthy premature infants using the Day and Silverman x-ray technique. These 37 infants were divided into the following six groups:

- *Group 1: Normal fibula growth rate was measured at the end of 3 consecutive control periods.*
- *Group 2: an initial control period was followed by a period of oral administration of tetracycline (25 mg/kg every 6 hours) followed by a post-tetracycline period.*
- *Group 3: an initial period of oral tetracycline administration (25 mg/kg every 6 hours) was followed by 2 consecutive post-tetracycline periods.*
- *Group 4: Tetracycline (25 mg/kg every 6 hours) was administered orally during 3 consecutive periods.*
- *Group 5: Tetracycline (7 mg/kg every 6 hours) was administered orally during 3 consecutive periods.*
- *Group 6: an initial control period was followed by a 10-day period of oral neomycin (25 mg/kg every 6 hours) followed by a post-neomycin period*

The author also reports that the dose of tetracycline administered to Groups 2, 3, and 4 was greater than that previously recommended in clinical practice. These groups received tetracycline 25 mg/kg every 6 hours which the article states is in accordance with Baum's observation (which deals with multiple observation sequences) and that this dose schedule was necessary to insure consistent blood levels in the premature infant since smaller doses result in erratic blood concentrations presumably due to the relative inefficient intestinal absorption of tetracycline in the premature infant.²⁵

Results showed that the infants in Group 2 experienced a decline in fibula growth from control rates of 0.18 and 0.20 to 0.10 and 0.12 mm. per day in the right and left fibula, respectively, during the period after tetracycline administration. However, growth rates in all 6 infants in Group 2 returned to normal levels in the post-tetracycline period. In Group 3 tetracycline was administered during the first period of observation. A similar inhibition of growth was seen with an average fibula growth rate of 0.10 mm. per day reported in both right and left fibula. In the first post-tetracycline period fibula growth rate in 5 of the 7 infants had reportedly returned to normal. Also, in the second post-tetracycline period which followed consecutively, fibula growth rate in all 7 infants had returned to normal. Group 4 study infants were administered tetracycline at 25 mg/kg every 6 hrs. for three consecutive periods and the average growth rate for these infants was 0.11 mm/day compared to the control group average fibula growth rate of 0.19 mm/day. Premature infants in Group 5 received tetracycline at 7 mg/kg every 6 hrs for three consecutive periods and the average growth rate in this group was 0.14mm/day compared to premature infants in the control group who reportedly experienced an average fibula growth rate of 0.19 mm/day. The results of this study show that over the course of approximately a month (roughly the duration of the three consecutive treatment periods of 9-12 days each)

*premature infants who received varying dosing regimens of tetracycline experienced inhibition of their fibula growth rate compared to controls; however when tetracycline was discontinued their fibula growth rate returned to normal.*²⁵

*Overall, tetracycline administered to premature infant produced a 40% depression of normal skeletal growth as measured by the inhibition of fibula growth. However, the fibula growth rate returned to normal after tetracycline was discontinued. This article supports the belief that inhibition of bone growth with administration of tetracycline is transient in nature and the short-term use of tetracycline in the premature infant may not have an effect on these infants' skeletal growth.*²⁵

Case Series

*In one case series, a total of 17 third molars were extracted from 9 patients from 1996 to 2009 that showed brownish discolorations of the crowns and/or root. The extracted teeth were sent to the Institute of Oral Biology for microscopic analyses to determine if the staining could be related to tetracycline exposure.*²⁶ *The teeth had been obtained from five females and four males who ranged in age from 18 years 9 months to 25 years 4 months. These discolored third molars were embedded without being decalcified, ground along the tooth axis, and examined using fluorescence microscopy. A medical history served to determine the start and duration of any administration of tetracyclines. This history confirmed that all but one patient had used minocycline to treat acne. The findings obtained in this study showed that brownish discolorations of third molar crowns can result from minocycline treatment of acne when crown formation occurs between the ages of 9 years to 15 years. The authors concluded that, after completion of crown development, only annular pigmentations of the root seem to occur when minocycline is taken until the age of about 22 years. The authors reported that this pattern conclusively showed that minocycline had been incorporated during third molar development, rather than after termination of tooth formation. These findings are consistent with multiple published reports referenced by the authors describing the occurrence of minocycline-induced tooth discoloration in erupted teeth.*²⁶

Case Reports

Multiple published case reports retrieved by this reviewer described minocycline-associated tooth discoloration in post-eruption molars in adults and adolescents. This reviewer identified four case reports published between 2010 and 2015 describing minocycline-induced discoloration of either the teeth and/or minocycline-induced hyperpigmentation of the tympanic membrane, sclera, teeth and pinna as reported in one case report. The affected patients ranged

²⁶ Antonini, L. G., & Lucrer, H. Y. (2011). Discoloration of teeth from tetracycline - even today. *Schweiz Monatssche*, 414-422.

in age from 7 years to 56 years. The countries from which these cases were reported included the United States, Great Britain, Korea, and Australia.

One case report described a 56-year-old female who had used minocycline for almost seven years for an infective skin condition, and over this period, developed tooth discoloration.²⁷ Upon dental referral for consideration of veneer restorations, she was noted to have not only a yellowish hue to her teeth but also a bluish-gray hue to her sclera, ears, and nail-beds. Her teeth were described as otherwise healthy, so she was conservatively treated by whitening the teeth with 10% peroxide gel in a night-time tray for six months approximately five nights each week. The author reports that treatment resulted in a gradual improvement in teeth color and the final outcome demonstrated this to be an acceptable treatment method for the patient. The author did not report on the outcome of the discoloration of the patient's sclera, ear, and nail-beds.²⁷

Another case report described a 40-year-old woman who was referred by her primary care physician for evaluation at an otolaryngology clinic after a routine physical exam revealed bilateral brownish pigmentation of the tympanic membrane.²⁸ The patient had a history of taking oral minocycline for 14 years as treatment for acne vulgaris and was still taking minocycline at the time of presentation. Her medical history was otherwise unremarkable, and she was taking no other medications. Head and neck examination in the otolaryngology clinic revealed bluish hue of each sclera, teeth, and portions of her pinnae. The author reports that the hyperpigmentation this patient experienced is known to be a rare complication of prolonged minocycline use.²⁸

A case-report described a 16-year-old female who successfully completed 6 months of minocycline treatment at a dosage of 50 mg twice daily for treatment of papulopustular acne and was noted to have visibly discolored third molars when they erupted at age 21 years.²⁹ The rest of her existing dentition was completely unaffected. The third molars were partially impacted and the treating oral surgeon recommended extraction. Upon removal all the third molars had a marked grey-black stain to the crown, a distinct black band at the cemental enamel junction, and sparing of the roots. The author reports that based upon the recognized schedule of development of the crowns for third molars, this patient's crowns should have been formed. However, there is variation in the timing of individual tooth maturation and it may be large for most stages of tooth formation; the timing for tooth maturation also increases with age.²⁹

²⁷ Ashley, M. (2013). *Minocycline Staining*. Manchester: British Dental Journal.

²⁸ Reese, S., & Grundfast, K. (2015). Minocycline - Induced Hyperpigmentation of Tympanic Membrane, Sclera, Teeth and Pinna. *Laryngoscope*, 2601-2603.

²⁹ Raymond, J., & Cook, D. (2015). Still leaving stains on teeth - the legacy of minocycline. *Australian Medical Journal (AMJ)*, 139-142.

A pediatric case report described a 7-year-old female who was referred to the Department of Conservative Dentistry of Gangnam Severance Hospital in Seoul, Korea for an evaluation of the right maxillary central incisor after she sustained a traumatic injury as a result of falling down the stairs 1 day prior.³⁰ She was treated for a fractured tooth but returned 8 months later complaining of spontaneous pain in the treated tooth which was subsequently diagnosed as pulp necrosis with symptomatic apical periodontitis and treated with a mixture of ciprofloxacin, metronidazole, and minocycline as an intracanal medicament in an attempt to disinfect the root canal system. Six weeks after applying the triple antibiotic paste to the root canal of the affected tooth, the tooth developed a dark discoloration. An in vitro experiment with human extracted teeth was performed to determine which of the 3 drugs caused the tooth discoloration. Another experiment was then carried out to examine whether a currently used dentin bonding agent would prevent or reduce such discoloration. The degree of discoloration was assessed by using a colorimeter. Results of the experience showed that among the components of the triple antibiotic paste, only minocycline caused the tooth discoloration. Moreover, the dentin bonding agent reduced the intensity of the discoloration but did not prevent it. The author reports that problems with tooth color should be considered when using minocycline as a canal medication.³⁰

II. DPMH recommendations for Pediatric Use Information in MINOLIRA

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. When substantial evidence does not exist to support a pediatric indication, pediatric information related to the unapproved use should generally be restricted to the Pediatric Use subsection only, to avoid an inference of an approved pediatric indication as required by 21 CFR 201.57(c)(9)(iv). However, if a specific risk has been identified for pediatric patients, this risk information must be described in the Pediatric Use subsection, and if appropriate, be placed in the Contraindications section or Warnings and Precautions section. In such cases, the Pediatric Use subsection must refer to the risk information in the Contraindications or Warnings and Precautions section. 21 CFR 201.57(c)(9)(iv) also describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population (also see the February 2013 draft Guidance for Industry and Review Staff Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling).

This DPMH-Pediatric team labeling review will specifically focus on edits to Sections 1 (Indications and Usage), 2 (Dosage and Administration), 4 (Contraindications), 5 (Warnings and Precautions) and 8.4 (Pediatric Use). Excerpts from the Applicant's proposed labeling are

³⁰ Kim, J.-H., Kim, Y., Shin, S.-J., Park, J.-W., & Jung, I.-Y. (2010). Tooth Discoloration of Immature Permanent Incisor Associated with Triple Antibiotic Therapy - A Case Report. *Journal of Endodontology*, 1086-1091.

followed by the DPMH-Pediatric team’s labeling recommendations below each section. DPMH’s additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text

Applicant’s Proposed Labeling:

1 INDICATIONS AND USAGE

1.1 Indication

MINOLIRA is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years and older.

[Redacted] (b) (4)

To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, MINOLIRA should be used only as indicated [see Warnings and Precautions (5.11)]

Applicant’s Proposed Labeling

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dosage of MINOLIRA is approximately 1 mg/kg once daily for 12 weeks. Higher doses have not shown to be of additional benefit in the treatment of inflammatory lesions of acne, and may be associated with more acute vestibular side effects. [Redacted] (b) (4)

[Redacted] The scored tablets may be split for dosing of patient weight ranges of 45-59 kg and 60-89 kg, respectively.

[Redacted] (b) (4)

Table 1: Dosing Table for MINOLIRA

(b) (4)	Patient’s Weight (kg)	Tablet Strength (mg)	Actual mg/kg Dose
	45 – 59	[Redacted] (b) (4)	1.16 – 0.88
	60 – 89	[Redacted] (b) (4)	1.13 – 0.76
	90 – 125	105	1.17 – 0.84
	126 – 136	135	1.07 – 0.99

DPMH Comments: According to the Draft Guidance for Industry, Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and

Format this section could include a table that shows how to adjust dose based on weight, preferably in kg. Consider adding a column with dosing interval to better inform the prescriber of the daily dosage. Last, we are unsure how the information in the last column (i.e. actual mg/kg dose) is informative for prescribers. DPMH recommends deletion of the actual mg/kg dose column.

DPMH recommends revising Section 2.1 as follows:

Dosing Table for Minolora

<u>Patient's Weight (kg)</u>	<u>Recommended Dose (mg)</u>	<u>Tablet Strength and Size to Administer</u>	<u>Dosing Interval</u>
45 – 59	52.5	Half of the 105 mg tablet	Once daily
60 - 89	67.5	Half of the 135 mg tablet	Once daily
90 - 125	105	One 105 mg tablet	Once daily
126 - 136	135	One 135 mg tablet	Once daily

Applicant's Proposed Labeling

4. CONTRAINDICATIONS

(b) (4) is contraindicated in (b) (4) who have shown hypersensitivity to any of the tetracyclines.

DPMH Comments: DMPH recommends adding the common name of the drug that is contraindicated. DPMH recommends revising Section 4 as follows:

Minocycline HCL is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

Applicant's Proposed Labeling

5 WARNINGS AND PRECAUTIONS

5.1 Tetratogenic Effects

(b) (4)

DPMH Comments: DPMH recommends adding two new Subsections (i.e., 5.2 Tooth Discoloration and 5.3 Inhibition of Bone Growth) to Section 5 Warnings and Precautions

5.2 DMPH Proposed New Subsection: Tooth Discoloration

(b) (4)-The use of drugs of the tetracycline class during tooth development ((b) (4) -second and third trimesters of pregnancy and , infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Unlike tetracycline, minocycline can cause permanent intrinsic tooth discoloration in pediatric patients greater than 8 years of age and in adults, and the discoloration may be green/gray or blue/gray in color The extent of discoloration depends on the dose and duration of treatment and the patient’s age at the time of exposure. Minocycline-induced discoloration occurs most commonly during tooth development up to 8 years of age but can also occur less commonly in adults with long-term exposure to minocycline at doses greater than 100 mg per day. The safety and effectiveness of Minolira have not been established in patients less than 12 years of age.

This adverse reaction is more common during long-term use of the drug (b) (4) Therefore, tetracycline drugs should not be used during tooth development.

5.X DPMH Proposed New Subsection: Inhibition of Bone Growth

(b) (4) All tetracyclines form a stable calcium complex in any bone-forming tissue. Maternal use of oral tetracyclines has been associated with reversible inhibition of growth of the fibula in the fetus and in preterm infants. This effect is reversible and associated with increase in bone growth with discontinuation of tetracycline exposure. The safety and effectiveness of Minolira have not been established in patients less than 12 years of age.

Applicant’s Proposed Labeling
8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

DPMH Comments: In order to comply with labeling regulations (21 CFR 201.57(c)(9)(iv), this subsection must include approved indication(s) in pediatric patients and any limitations on pediatric indication or use and should included approved pediatric age groups. DPMH recommends the additon of approved indication statement in the approved age group of 12 years and older.

DPMH recommends revising Section 8.4 as follows:

The safety and effectiveness of Minolira have been established in pediatric patients 12 years of age and older for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris. [see Pharmacokinetics (12.3) and Clinical Studies (14)]. The safety and effectiveness of Minolira have not been established in pediatric patients less than 12 years of age.

DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant's proposed labeling and participated in the internal meeting with DDDP on February 10, 2017, March 13, 2017 and March 17, 2017. At the March 17, 2017 labeling meeting, the discussion focused on the specific language that DPMH had proposed to be added to subsection 5.2 Tooth Discoloration and subsection 5.3 Inhibition of Bone Growth. For the proposed subsection, Tooth Discoloration, DPMH stated that the label recommendations were based on findings from the medical literature. The review articles generally supported the safety warning regarding tetracycline use and risk of tooth staining in pediatric patients < 8 years of age; however unlike tetracycline, minocycline can cause permanent intrinsic tooth discoloration in pediatric patients greater than 8 years of age and in adults, and the discoloration may be green/gray or blue/gray in color. The extent of discoloration depends on the dose and duration of treatment and the patient's age at the time of exposure. For this proposed subsection, DDDP expressed their intention to keep the Applicant's language regarding tooth discoloration and they also plan to consult the Office of Surveillance and Epidemiology (OSE) to review reports of minocycline usage and tooth staining in pediatric patients > 8 years of age and adults. DPMH has no objection to DDDP's current plan.

For the proposed subsection 5.3, Inhibition of Bone Growth, DDDP expressed their intention to keep the Applicant's language regarding a study conducted in the early 1960's that evaluated the effect of tetracycline on the developing skeleton in the premature infant by measuring fibula growth rates. DDDP stated they wanted the data regarding the dosing of tetracycline to remain in the XYROSA label. DPMH proposed that the language regarding inhibition of bone growth be more general so as not to confuse healthcare practitioners (HCPs) regarding the adequacy of tetracycline dosing administered in the study. The dose of tetracycline (i.e. 25 mg/kg every 6 hrs) that DDDP has proposed remain in the label was administered to one of six study groups and this dose was higher than that previously recommended in clinical practice. DPMH stated their disagreement with DDDP's proposal to retain the Applicant's language regarding study results from a original review article.

Recommended labeling for the pediatric population is based on labeling discussions between DDDP and DPMH and is provided per 21 CFR 201.57(c)(9)(iv). Various comments were also provided for the division's consideration to align MINOLIRA labeling with that of the currently approved SOLDYN label, where applicable. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested in this review.

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/s/

MONA K KHURANA
04/03/2017

JOHN J ALEXANDER
04/03/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: March 29, 2017

To: Belainesh Robnett, RPM
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Silvia Wanis, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 209269**
OPDP labeling comments for MINOLIRA™ (minocycline hydrochloride) extended-release tablets, for oral use

Reference is made to DDDP's July 18, 2016 consult request for OPDP's comments regarding the proposed Package Insert (PI) and Carton and Container Labeling for Minolira.

OPDP's comments on the proposed labeling, which are based on the draft version of the PI and carton/container labeling emailed by Belainesh Robnett on March 22, 2017, are provided below.

OPDP's review and comments on the proposed PPI and IFU was conducted jointly with the Division of Medical Policy Programs (DMPP). This review will be submitted under separate cover at a later date.

If you have any questions, please feel free to contact me:

Silvia Wanis: 301-796-5198; silvia.wanis@fda.hhs.gov

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

SILVIA WANIS
03/29/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: March 29, 2017

To: Kendall Marcus, MD
Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD, BCPS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Silvia Wanis, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI),
Instructions for Use (IFU)

Drug Name (established name): MINOLIRA (minocycline hydrochloride)

Dosage Form and Route: extended-release tablets, for oral use

Application Type/Number: NDA 209269

Applicant: Dr. Reddy's Laboratories LTD

1 INTRODUCTION

On July 8, 2016, Dr. Reddy's Laboratories LTD submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 209269 for MINOLIRA (minocycline hydrochloride) extended-release tablets. The Reference Listed Drug (RLD) is SOLODYN (minocycline HCl) Extended Release Tablets, for oral use. The proposed indication for MINOLIRA (minocycline hydrochloride) extended-release tablets is for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on July 18, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for MINOLIRA (minocycline hydrochloride) extended-release tablets.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and DMEPA deferred to DMPP to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft MINOLIRA (minocycline hydrochloride) extended-release tablets PPI and IFU received on July 8, 2016.
- Draft MINOLIRA (minocycline hydrochloride) extended-release tablets Prescribing Information (PI) received on July 8, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 22, 2017.
- Approved SOLODYN (minocycline HCl) comparator labeling dated October 21, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
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03/29/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Review

Date: February 14, 2017 **Date consulted:** August 2, 2016

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Drug Products (DDDP)

Drug: MINOLIRA (minocycline hydrochloride extended release) tablets

NDA: 209269

Applicant: Dr. Reddy's Laboratories Limited

Subject: Pregnancy and Lactation Labeling

Indication: for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

Materials

Reviewed:

- Applicant's submitted background package and proposed package labeling for minocycline hydrochloride extended release tablets, NDA 209269.
- DPMH consult request dated July 8, 2016; DARRTS Reference ID 3966934.
- Solodyn (minocycline hcl) ER tablets. Drugs@FDA. Accessed 18 Jan 2017.
- Clinical Review. Nikhar, B. NDA 50808. May 8, 2006.
- Clinical Review. Patricia Brown. NDA 50808 June 21, 2011 review of PMC 390-2.
- Nonclinical Review. Norman See, Ph.D. NDA 50808. March 29, 2006.

Consult Question: “Please review the PLLR section of the draft PI labeling.”

INTRODUCTION

The Division of Dermatology and Dental Products consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of MINOLIRA (minocycline hydrochloride) extended release labeling.

REGULATORY HISTORY

On July 8, 2016, Dr. Reddy’s Laboratories Limited submitted a New Drug Application (209269) for minocycline hydrochloride extended release 105 mg and 135 mg tablets for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. NDA 209269 is a 505(b)(2) application relying on the safety and efficacy of the reference listed drug, Solodyn NDA (50808).

- Minocin (minocycline hydrochloride) was originally approved on June 30, 1971
- Dynacin (minocycline hydrochloride) approved on July 31, 1990
- Arestin (minocycline hydrochloride) approved on February 2, 2001 as an adjunct to scaling and root planning procedures for reduction of pocket depth in patients with adult periodontitis
- Solodyn (minocycline hydrochloride) ER approved on May 8, 2006 for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris
- Minocycline hydrochloride is also available as a generic product under more than two dozen ANDAs for the following indications:
 - MINOCIN Pellet-Filled Capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:
 - Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsia pox and tick fevers caused by *rickettsia*
 - Respiratory tract infections caused by *Mycoplasma pneumoniae*
 - Lymphogranuloma venereum caused by *Chlamydia trachomatis*
 - Psittacosis (Ornithosis) due to *Chlamydophila psittaci*
 - Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence
 - Inclusion conjunctivitis caused by *Chlamydia trachomatis*
 - Nongonococcal urethritis, endocervical, or rectal infections in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*
 - Relapsing fever due to *Borrelia recurrentis*
 - Chancroid caused by *Haemophilus ducreyi*
 - Plague due to *Yersinia pestis*
 - Tularemia due to *Francisella tularensis*
 - Cholera caused by *Vibrio cholerae*
 - Campylobacter fetus infections caused by *Campylobacter fetus*
 - Brucellosis due to *Brucella* species (in conjunction with streptomycin)
 - Bartonellosis due to *Bartonella bacilliformis*
 - Granuloma inguinale caused by *Klebsiella granulomatis*

- Minocycline is indicated for the treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
 - *Escherichia coli*, *enterobacter aerogenes*, *shigella* species, *acinetobacter* species
 - Respiratory tract infections caused by *Haemophilus influenzae*
 - Respiratory tract and urinary tract infections caused by *Klebsiella* species
- MINOCIN Pellet-Filled Capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
 - Upper respiratory tract infections caused by *Streptococcus pneumoniae*
 - Skin and skin structure infections caused by *Staphylococcus aureus*
- When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:
 - Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections
 - Infections in women caused by *Neisseria gonorrhoeae*
 - Syphilis caused by *Treponema pallidum* subspecies *pallidum*
 - Yaws caused by *Treponema pallidum* subspecies *pertenue*
 - Listeriosis due to *Listeria monocytogenes*
 - Vincent's infection caused by *Fusobacterium fusiforme*
 - Actinomycosis caused by *Actinomyces israelii*
 - Infections caused by *Clostridium* species
 - In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides
 - In severe acne, minocycline may be useful adjunctive therapy
- Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carriers, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

BACKGROUND

Drug Characteristics^{1,2}

Minocycline hydrochloride extended release is a derivative of tetracycline. The mechanism of action for the treatment of acne is unknown. Minocycline has a molecular weight of 493.95 Daltons, is lipid soluble and has a biological half-life of 11 to 17 hours. Serious adverse events that can occur with the use of minocycline include teratogenic effects, pseudomembranous colitis, hepatotoxicity, metabolic effects, central nervous system effects, benign intracranial hypertension, autoimmune syndromes, photosensitivity, serious skin hypersensitivity reactions, tissue hyperpigmentation, the development of drug-resistant bacteria, and superinfection.

¹ Proposed minocycline HCl ER tablet labeling: Section 11, Description and Section 12, Clinical Pharmacology.

² Approved Solodyn package insert 10/21/2013, submitted by applicant.

Acne Vulgaris and Pregnancy

Acne Vulgaris is the most common skin disease that occurs during adolescence and early adulthood.³ Currently, there are many forms of treatment available for acne vulgaris such as topical therapies, oral antibiotics, hormonal agents and miscellaneous therapies that include chemical peels and laser/photodynamic therapy.⁴ Acne for many improves in early pregnancy and worsens in late pregnancy. This is possibly due to the increase in maternal androgen in later pregnancy. Treating acne during pregnancy can be challenging as many approved acne medications are contraindicated during pregnancy. Topical azelaic acid and benzyl peroxide are first line standard of care recommendations for mild to moderate acne in pregnant women.⁵ Oral erythromycin and cephalexin are recommended for short-term use in more severe cases of acne in pregnant women.⁵

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁶ also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule⁷ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience

Reductions in fetal weight, induced skeletal malformations (bent bone limbs) and skeletal various including reduced skeletal ossification was shown in female rats administered minocycline on gestation days 6-17 at the lowest exposure tested (10 mg/kg/day). In rabbits, dosed on days 7 to 20 of gestation at exposure up to 175 mg/kg/day resulted in induced abortions, reduced maternal weight gain, gravid uterine weight and skeletal malformation including bent limb bones. In pre- and post-natal development toxicology studies, minocycline administered to pregnant female rats from day 6 of gestation through postpartum day 20 resulted in gross external anomalies such as small size, malrotated forelimbs and micromelia. The reader is referred to the full Pharmacology/Toxicology review by Norman See, Ph.D., dated March 29, 2006, for the reference listed drug NDA 50808.

³ American Academy of Dermatology. *AAD Guidelines of Care for Acne Vulgaris Management Technical Report*. 18 Jun 2014.

⁴Zaenglein AL et al. (2016). Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*, 74, 945-973.

⁵ Chien, A., et al. (2016). Treatment of Acne in Pregnancy. *J Am Board Fam Med*, 29, 254-262.

⁶ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁷ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

Current Labeling for Reference Listed Drug⁸

Current labeling for Solodyn (minocycline hydrochloride) ER tablets is not in the PLLR format at this time. Solodyn labeling was last updated October 21, 2013 and does not include a boxed warning; however, there is a Warning and Precautions section describing the potential risk of possible permanent tooth discoloration when given in the last half of pregnancy and the possibility of a decrease in fibula growth rate in premature infants who were given oral tetracycline in doses of 25 mg/kg every 6 hours. Subsection 8.1 Pregnancy states that “There are no adequate and well-controlled studies on the use of minocycline in pregnancy women,” and that “Solodyn should not be used during pregnancy.” According to the clinical review⁹ for the reference listed drug, an AERS¹⁰ (now known as FAERS) search from January 20, 2006 resulted in 4795 adverse reports associated with minocycline use. The following results were found with regard to pregnancy:

- 21 cases of congenital anomalies were associated with minocycline use (regardless of indication). Doses and route of administration were not described.
 - 14 of those cases were reported as using minocycline around the time of conception, 1 during second trimester and 1 case of paternal exposure, time of exposure of remaining cases not reported.
 - Of the congenital anomalies, 15 (one paternal exposure) were reported limb abnormalities and 2 infants died within one week post-delivery.

The following language with regard to these postmarketing reports is in the pregnancy section of the reference listed labeling, “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.”

Review of Literature

Applicant’s Review of Published Literature

The applicant conducted searches of the worldwide medical literature to identify articles published between January 1, 1970 and April 29, 2016 in order to identify published safety information that may be useful for minocycline labeling. No restrictions were used during the search.

The following databases were searched:

- MEDLINE
- Biosis Previews
- EMBASE Alert
- EMBASE
- International Pharmaceutical Abstracts
- SciSearch® Cited Ref Sci

The applicant initially identified 45 citations covering clinical and nonclinical information; however, those citations were narrowed down to 18 publications that describe the effect of

⁸ Solodyn (minocycline hcl) ER tablets. Drugs@FDA. Accessed 18 Jan 2017.

⁹ Nikhar, B. Clinical Review. NDA 50808. May 8, 2006.

¹⁰ FDA’s Adverse Event Reporting System.

minocycline in pregnant women, lactating women and the effect of minocycline on fertility in men, inefficacy of oral contraception during use of minocycline and mycoplasma infection and its treatment with minocycline during pregnancy and the use of minocycline in methicillin-resistant staphylococcus aureus (MRSA) infections in lactating women. Seventeen of these publications were submitted along with the NDA application for review in support of the pregnancy, lactation, and females and males of reproductive potential sections of labeling.

Overall, the applicant submitted four narrative review articles with regard to pregnancy and one general article about minocycline treatment for acne that do not provide new data from the reference listed drug label.¹¹ In addition, the applicant submitted one publication that references data on tetracycline use during pregnancy from the Teratology Information Service (TIS) of the Dutch National Institute of Public Health and Environment that is not adequately cited and the DPMH was unable to determine who the authors are or where this publication originated.¹¹ This publication is a short summary document that does not provide new data from the reference listed drug.

Knothe (1985) is an editorial¹² which consists of a review of published literature describing the tetracycline class as a whole. The side effects described in the editorial with respect to the tetracycline class include discoloration of teeth, disturbances in longitudinal bone growth, the occurrence of congenital limb malformations and “lethal fatty liver degeneration.” The side effect of fatty liver degeneration was cited from two articles, one by Dowling¹³ *et al.* published in 1964 and one by Kunelis *et al.* published in 1965. The Kunelis publication was not located by DPMH. Dowling (1964) describes various case reports of pregnant women who received tetracycline intravenously and orally.¹³ Those cases all resulted in death and are described in the table below:

Table 1. Case Reports

Publication	Number of Patients	Medication and Dose	Comments
Dowling <i>et al.</i> (1964)	6	Tetracycline IV doses between 3.5 and 6 grams	All six patients were treated for acute pyelonephritis. Postmortem findings for each included fatty metamorphosis of the liver. Exact cause of death not stated. No other additional information available.
	1	2 gm of oral tetracycline six time daily for six days (orally days 1-5 and IV on day 6)	Patient died 10 days later. Other medications included aminosalicylic acid, isoniazid and pyridoxine. Postmortem findings included cirrhosis, acute septic endometriosiis, pyelonephritis and necrosis of the liver.
	1	2 gm of tetracycline IV daily for 3 days followed by 2 gm orally for two additional days	Patient died seven days later in hepatic failure. Postmortem findings included fatty metamorphosis of the liver, micro-abscesses in the kidney and fat droplets in the renal tubular epithelium.
	1	3.5 to 6 gm IV	Patient died 2 days after last dose. Unclear

¹¹ 7/8/2016. Applicant submission to NDA 208269. Appendix 1 – Review of the effects of minocycline during pregnancy, lactation and on reproductive potential.

¹² Knothe, et al. (1985). Antibiotics in Pregnancy: Toxicity and Teratogenicity. *Infection*. 13, 49-51.

¹³ Dowling, H., et al. (1964). Hepatic Reactions to Tetracycline. *JAMA*, 188(3), 235-237.

Publication	Number of Patients	Medication and Dose	Comments
		tetracycline and 1.5 gm orally	how many total days received drug. Postmortem findings include fatty metamorphosis of the liver.
	1	3 gm IV tetracycline for 10 days followed by 3 gm daily of oxytetracycline for an addition seven days.	Patient cause of death postoperative bleeding following cesarean section.

Reisner (1993)¹⁴ cites a report by Corcoran (1977) which contains a case report of a 33 year-old female who conceived while taking tetracycline and delivered an infant with multiple abnormalities. Corcoran (1977) is a case report describing a 33 year-old female patient who became pregnant while taking tetracycline and clomocycline.¹⁵ The patient gave birth to a male infant with low set ears, prominent epicanthic folds, micrognathia and mandibular hypoplasia and deformity of both scapulae, arthrogryposis and deficient muscle development. The infant died at 14 days from respiratory complications. Parental and infant chromosome analysis was performed and determined normal.

Additionally, the applicant submitted Nast *et al.* (2010) which contain the Guidelines issued by the German Society of Dermatology (DDG) and the Association of German Dermatologists which the applicant summarizes that the publication states that minocycline is contraindicated in pregnancy or lactating women however the only the abstract is in English and the publication could not be reviewed.

DPMH’s Review of Published Literature

DPMH conducted a literature search in PubMed, EMBASE, and Micromedex¹⁶ using the search terms “minocycline and pregnancy and fetal malformations,” “minocycline and pregnancy and pregnancy and stillbirth,” “minocycline and pregnancy and miscarriage or spontaneous abortion.” In addition to what the applicant reviewed above, DPMH also reviewed the Dowling (1964) and Corcoran (1977) articles that are described in the section above as they are citations found in the literature submitted by the applicant. There is no additional information regarding minocycline and pregnancy.

Micromedex¹⁶ notes the following about minocycline with regard to use in pregnancy: “Due to the risk of teratogenic effects which have been reported with the use of tetracyclines throughout pregnancy, minocycline should not be used during pregnancy. If a patient becomes pregnant while on minocycline, treatment should be discontinued immediately and the patient should be informed of the potential hazard to the fetus. Additionally, due to risk of impaired spermatogenesis, minocycline should not be used in patients, of either gender, who are attempting child conception. Although the use of a tetracycline may be a medical necessity in some cases (such as in cases of plague or in cases of syphilis in true penicillin-allergic patients

¹⁴ Reisner, R. (1993). Antibiotic and Anti-inflammatory Therapy for Acne. *Dermatology Clinics*, 1(3), 385-397.

¹⁵ Corcoran, et al. (1977). Tetracyclines for acne vulgaris and possible teratogenesis. *British Medical Journal*, 807-808.

¹⁶ Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: <http://www.micromedexsolutions.com/> (cited: 01/18/2017).

who cannot be desensitized), in general, penicillins and cephalosporins are considered to be safer for treating susceptible infections in pregnant patients.”

Summary

Overall, neither the applicant nor DPMH found new safety data relevant for inclusion into the minocycline labeling. The applicant’s published literature included a published editorial (Knothe, *et al.* 1985)¹⁷ that makes reference to fatty liver degeneration and congenital limb malformations after use of tetracycline exposure during pregnancy. The fatty liver degeneration language is based on two citations found in the editorial from Dowling¹⁸ et al published in 1964 and one by Kunelis et al published in 1965 that discuss fatty liver degeneration after tetracycline exposure during pregnancy. The Kunelis publication was not located by DPMH. The congenital limb malformation language is passively mentioned in the Knothe editorial and cites an article by Carter et al, titled “Tetracycline and congenital limb abnormalities” from 1962 that the reviewer could not locate. The Dowling publication is a compilation of case reports that include pregnant women who received tetracycline intravenously at higher than approved doses as stated in the publication. Some patients received oral tetracycline and intravenous tetracycline both. The applicant has proposed the following language for the Clinical Considerations, Maternal Adverse Reactions subsection in 8.1 Pregnancy, “Fatty liver degeneration has been reported in pregnant women. In addition, congenital limb malformations in the fetus of pregnant women have also been observed. The incidence of these effects appears to be greatest during the third trimester with minocycline.” It is difficult to make an informed conclusion with regard to the published literature submitted by the applicant and DPMH does not recommend this information go into the Pregnancy section of product labeling at this time. Additionally, this information is not currently available in the labeling for the reference listed drug. Current labeling will be structured in the PLLR format.

LACTATION

Nonclinical Experience

There is no non-clinical information with regard to minocycline and lactation. The reader is referred to the full Pharmacology/Toxicology review by Norman See, Ph.D., dated March 29, 2006 for the reference listed drug NDA 50808.

Current Lactation Labeling for Reference Listed Drug

Current labeling for Solodyn (minocycline hydrochloride) ER tablets is not in the PLLR format at this time. Solodyn labeling was last updated October 21, 2013 and contains a Nursing Mothers subsection that describes the excretion of tetracycline into human milk and the risk of adverse effects on bone and tooth development in nursing infants from tetracycline class of drug products.

Review of Literature

Applicant’s Review of Published Literature

The applicants search parameters of the worldwide medical literature are described in detail above in the pregnancy section review of applicants literature. The applicant reviewed the following published literature with regard to minocycline and lactation.

¹⁷ Knothe, et al. (1985). Antibiotics in Pregnancy: Toxicity and Teratogenicity. *Infection*. 13, 49-51.

¹⁸ Dowling, H., et al. (1964). Hepatic Reactions to Tetracycline. *JAMA*, 188(3), 235-237.

Reisner (1993) cites a case where 200 mg of oral minocycline was administered and concentrations of drug at 0.8 ug per mL were found in breast milk.¹⁹ No other additional information was provided in the review article.

Kohler et al (2005), Hunt (1996) and Basler et al (1985) and Mitrano et al (all report the discoloration of breastmilk.^{20,21,22} The Kohler article is a review of the Hunt and Basler articles. Kohler et al (2005) describes the case of a 25 year-old female who presented to her dermatologist with papulopustular acne, had stopped breastfeeding 18 months prior but had occasions of breast tenderness and breast milk expression. The patient was put on oral minocycline 150 mg daily and topical clindamycin. Four weeks later the patient reported that her breasts were expressing milk that was black in color. Full blood panel including electrolytes, liver function, thyroid function, serum prolactin test displayed normal levels. A mammogram was performed with normal results. Breastmilk samples tested positive for iron concentrations. The author hypothesizes that the dark discoloration is a result of iron chelate of minocycline or a derivative.

Additionally, the article describes a second case (originally reported in Basler et al 1985) involving a 24 year-old female treated with minocycline 200 mg daily for four years as well as phenothiazine compound. Dark pigmented macules were seen around the facial acne and iron concentrations were found in the breast milk. The author stated that the production of milk was most likely due to the patients use of perphenazine or possibly amitriptyline. The author believes that the dark discoloration found in the breast secretion was due to the long-term use of minocycline.

Reviewer comment: These two case reports are repeatedly cited in multiple published literature. In both cases neither patient was actively breastfeeding and it is difficult to determine what stage of breastmilk was present as there are three types of breastmilk when a woman is breastfeeding (colostrum, transitional milk and mature milk). Each stage of breastmilk has different levels of water, fat content and pH levels. Because of this each stage has the potential to differ in the amount of drug delivered during lactation²³. DPMH does not believe that this data should go into minocycline labeling at this time due to the lack of further data.

DPMH's Review of Published Literature

DPMH performed a search of Medications and Mother's Milk²⁴, PubMed, Micromedex¹⁶ and the Drugs and Lactation Database (LactMed)²⁵ using the search terms, "minocycline and lactation" and "minocycline and breastfeeding". DPMH did not find any additional published literature. The findings from Hale (2017) and Micromedex are described below.

¹⁹ Reisner, R. (1993). Antibiotic and Anti-inflammatory Therapy of Acne. *Dermatology Clinics*, 1(3), 385-397.

²⁰ Kohler, S et al. (2005). Discoloration of breast milk. *Research Institute for Child Nutrition*, 46, 77-78.

²¹ Hunt, J et al. (1996). Black breast milk due to minocycline therapy. *British Journal of Dermatology*, 134, 943-944.

²² Basler, R et al (1985). Black Galactorrhea as a Consequence of Minocycline and Phenothiazine Therapy.

²³ Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, FDA Draft Guidance. February 2005.

²⁴ Hale, Thomas, Ph.D. (2017). Medication's and Mother's Milk. New York, NY: Springer Publishing Company

²⁵ LactMed is an online database with information on drugs and lactation and is property of the National Library of Medicine's TOXNET system. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. Accessed 18 Jan 2017.

In *Medications and Mother's Milk*²⁴, Dr. Thomas Hale, a breastfeeding expert, notes the following about minocycline, "It is probably secreted into breastmilk in small but clinically insignificant levels. Because tetracycline's, in general, bind to milk calcium, they would have reduced absorption in the infant, but minocycline may be absorbed to a greater degree than other older tetracyclines." Hale also cites a study where two patients receiving 200 mg orally had breast milk concentrations at peak (6 hours) at 0.8 ug/mL. The average milk level was 0.5 to 0.8 mg/L for a period of 12 hours post dose which would transfer approximately 18 ug to the infant which is approximately 4.2% of the maternal dose that is transferred to the infant, according to Hale.

Micromedex¹⁶ notes the following,

- "The possibility of dental staining and inhibition of bone growth in breast-fed infants appears remote since tetracycline concentrations are undetectable in the breast-fed infant."
- "Breast milk discoloration was reported in a patient receiving minocycline (150 mg daily). Three to 4 weeks after beginning therapy, the breast milk had turned black. Examination of the breast milk revealed pigmented particles that were thought to be an iron chelate of minocycline."
- "From an unpublished report, a single minocycline 200 mg dose resulted in minocycline peak breast milk levels of 800 ng/mL 8 hours after administration; within 12 hours, the concentration was 18 mcg/mL."

No additional information was found in the LactMed search.

Summary

Overall, there are two case reports that describe the discoloration or black coloring of breastmilk described above. In addition, Micromedex references the possible dental staining and effects on bone growth that are already present in the labeling for the reference listed drug. Hale (2017) and Micromedex both reference different publications that show the presence of minocycline at low levels in breastmilk; however, one of these articles is unpublished according to Micromedex and the Hale (2017) cited article is in Japanese. The data are limited for minocycline, there are no reported adverse events in neonates/infants. Therefore, DPMH disagrees with the applicant's recommendation to add the information about black discoloration of breastmilk into the data section of 8.2. Due to the potential for adverse effects on bone and tooth development in breastfed infants and the 12 weeks duration of use for MINOLIRA, DPMH is recommending the following language in section 8.2 Lactation: Tetracycline-class antibiotics including minocycline are present in breast milk. It is not known whether minocycline has an effect on the breastfed infant or on milk production. Because of the potential for serious adverse effects on bone and tooth development in breastfed infants from the tetracycline-class antibiotics, advise a woman that breastfeeding is not recommended with MINOLIRA therapy.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Oral minocycline administered to male rats at doses 15 to 40 times the systemic exposure in humans had an adverse reaction on spermatogenesis such as a reduction in the percentage of motile sperm and morphologically abnormal sperm cells (absent heads, misshapen head and abnormal flagella). The reader is referred to the full Pharmacology/Toxicology review by Norman See, Ph.D., dated March 29, 2006 for the reference listed drug NDA 50808.

Review of Literature

Applicant's Review of Published Literature

The applicants search parameters of the worldwide medical literature are described in detail above in the pregnancy section review of applicants literature. With regard to females and males of reproductive potential, two articles submitted by the applicant discuss factors related to females and males of reproductive potential. One article describes a study conducted at Al Sabah Hospital by the Dermatology and Venereology Department in Kuwait.²⁶ This study looked at twenty-five infertile males and randomly assigned them between two groups. Fourteen in group A that received 100 mg minocycline twice daily for one week and eleven in group B that received 100 mg minocycline twice daily for two weeks. The results between the two groups were not statistically significant however both groups showed a statistically significant increase in sperm count. The beginning of the article discusses the link between infections such as chlamydia and infertility however the study makes no mention of any of the twenty-five men having a diagnosis of any kind.

Additionally, a case report of a 21 year-old female taking oral contraceptives discusses the drug interaction between oral contraceptives and minocycline.²⁷ The 21 year-old female was taking oral contraceptives, oral minocycline and topical clindamycin and became pregnant. The article also discusses other case reports of pregnancy that occurred while taking oral contraceptives and various antibiotics as reported by the English Committee of Safety of Medicines.

Reviewer comment: The reference listed drug label lists a possible drug interaction between tetracycline class products and low dose oral contraceptive based on a multi-center study that demonstrated changes in estradiol, progesterone hormone, FSH and LH plasma levels, breakthrough bleeding. Therefore, DPMH has suggested the following language for section 8.3 Females and Males of Reproductive Potential: MINOLIRA may reduce the effectiveness of low-dose oral contraceptives. Patients of reproductive potential should not rely on low-dose oral contraceptives as an effective contraceptive method, and should use an additional method of contraception during treatment with MINOLIRA [see Drug Interactions (7.5)].

²⁶ Malallah, Y, et al. (1992). Effect of Minocycline on the Sperm Count and Activity in Infertile Men with High Pus Cell Count in Their Seminal Fluid. *Journal of Chemotherapy*, 4(5), 286-289.

²⁷ De Groot, A., et al. (1990). Inefficacy of Oral Contraception During Use of Minocycline.

DPMH's Review of Published Literature

DPMH conducted a search of published literature in PubMed to evaluate the use of minocycline on fertility and contraception and no additional data were found. However, a summary of findings from the clinical review of the reference listed drug is below.

Based on the original clinical review⁹ of the reference listed drug, the applicant conducted a human spermatogenesis study that the clinical reviewer determined may show deleterious effects on male spermatogenesis and it is not stated whether this is a reversible effect. DDDP found that study to be inadequate and recommended that study be repeated through Postmarketing Commitment (PMC 390-2). At the time of initial approval, the following language was put into the Solodyn label under section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility, "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." The applicant submitted a final study report for PMC 390-2 and upon review the division issued a letter fulfilling the PMC on July 6, 2011. Results of that study are not available in the Solodyn labeling. Inclusion of the study results can be incorporated into the MINOLIRA labeling in the future once available in the Solodyn labeling.

Summary

Based on conclusions reached by DDDP in a 2006 review of the reference listed drug application, minocycline appeared to have an adverse effect on spermatogenesis, therefore a statement was added to labeling. The applicant has proposed the following addition to section 8.3 Females and Males of Reproductive Potential, "Although limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis, male patients should be advised of the potential risk for impaired spermatogenesis."

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of MINOLIRA labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
 - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.
- **Lactation, Section 8.2**
 - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," section.
- **Females and Males of Reproductive Potential, Section 8.3**
 - The "Females and Males of Reproductive Potential" section of labeling was formatted in the PLLR format to include: the "Contraception," and "Infertility" sections."
- **Patient Counseling Information, Section 17**

The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 5.1, 8.1, 8.2 and 8.3 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 5.1, 7.5, 8.1, 8.2, 8.3,17 and Highlights of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on February 10, 2017. These recommendations were also discussed with the DPMH – Pediatrics Team and we refer to the final review by J. Spaulding. DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant’s proposed pregnancy and lactation labeling

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- The use of minocycline during the second and third trimesters of pregnancy, infancy and childhood up to the age of 8 years may cause permanent discoloration of the teeth and reversible inhibition of bone growth (5.1, 5.X, 8.1, 8.4).

-----USE IN SPECIFIC POPULATIONS-----

Lactation: Breastfeeding is not recommended. (8.2)

FULL PRESCRIBING INFORMATION

5.1 Fetal Toxicity

Minocycline, like other tetracycline-class antibiotics, may cause permanent discoloration of the teeth and inhibit bone growth when administered during the second and third trimesters of pregnancy. Based on animal data, tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy. If MINOLIRA is used during the second or third trimester of pregnancy advise the patient of the potential risk to the fetus and discontinue treatment [*see Use in Specific Populations (8.1)*].

7 Drug Interactions

7.5 Low Dose Oral Contraceptives

In a multi-center study to evaluate the effect of Minocycline Extended Release Tablets on low dose oral contraceptives, hormone levels over one menstrual cycle with and without Minocycline Extended Release Tablets 1 mg/kg once-daily were measured. Based on the results of this trial, minocycline-related changes in estradiol, progesterin hormone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, cannot be ruled out. To avoid contraceptive failure, patients of reproductive potential should not rely on low-dose oral contraceptives as an effective contraceptive method, female patients are advised and to use a second form of contraceptive during treatment with minocycline.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MINOLIRA, like other drugs of the tetracycline class, may cause permanent discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimesters of pregnancy [*See Warnings and Precautions (5.1), Data, and Use in Specific Populations (8.4)*]. Post-marketing cases of minocycline use in pregnant women report congenital anomalies such as limb reductions. There are no data available on the risk of miscarriage following exposure to minocycline in pregnancy. In animal reproduction studies, minocycline induced skeletal malformations in fetuses when orally administered to pregnant rats and rabbits during the period of organogenesis at systemic exposure of approximately 3 times and 2 times, respectively, the systemic exposure to minocycline observed in patients administered MINOLIRA [*see Data*]. If a patient becomes pregnant while taking this drug, advise the patient of the risk to the fetus and discontinue treatment.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

The use of tetracycline during tooth development (second and third trimester of pregnancy) may cause permanent discoloration of deciduous teeth. This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses.

Animal Data

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development of the developing fetus [*see Warnings and Precautions (5.1)*].

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits during the period of organogenesis at 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 administered MINOLIRA) as a result of use Minocycline Extended Release Tablets. Reduced mean fetal body weight was observed in studies in which when minocycline was administered to pregnant rats during the period of organogenesis 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 administered MINOLIRA) who use Minocycline Extended Release Tablets.

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation 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 administered MINOLIRA) as a result of use of Minocycline Extended Release Tablets. 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).

8.2 Lactation

Risk Summary

Tetracycline-class antibiotics including minocycline are present in breast milk. It is not known whether minocycline has an effect on the breastfed infant or on milk production. Because of the potential for serious adverse effects on bone and tooth development in breastfed infants from the tetracycline-class antibiotics, advise a woman that breastfeeding is not recommended with MINOLIRA therapy. [*see Warnings and Precautions (5.1)*].

8.3 Females and Males of Reproductive Potential

Contraception

MINOLIRA may reduce the effectiveness of low-dose oral contraceptives. Patients of reproductive potential should not rely on low-dose oral contraceptives as an effective contraceptive method, and should use an additional method of contraception during treatment with MINOLIRA [*see Drug Interactions (7.5)*].

Infertility

MINOLIRA may impair fertility in males of reproductive potential. Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis. In a fertility study in rats, minocycline adversely affected spermatogenesis when orally administered to male rats at doses resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients administered MINOLIRA [*see Nonclinical Toxicology (13.1)*].

17 PATIENT COUNSELING INFORMATION

Fetal Toxicity

- Advise pregnant women that MINOLIRA, like other tetracycline-class antibiotics, may cause permanent discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimesters of pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

- Advise a woman that breast feeding is not recommended during MINOLIRA therapy MINOLIRA [*see Use in Specific Populations (8.2)*].

Contraception

- Advise patients of reproductive potential that MINOLIRA may reduce the effectiveness of low-dose oral contraceptives. Advise patients of reproductive potential to not rely on low-dose oral contraceptives as an effective contraceptive method, and to use an additional method of contraception during treatment with MINOLIRA [*see Use in Specific Populations (8.3), Drug Interactions (7.5)*].

Infertility

- Advise males of reproductive potential that MINOLIRA may impair fertility [*see Use in Specific Populations (8.3)*].

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CARRIE M CERESA
02/14/2017

TAMARA N JOHNSON
02/15/2017

LYNNE P YAO
02/22/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: February 13, 2017
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: NDA 209269
Product Name and Strength: Minolira (minocycline hydrochloride) extended release tablets, 105 mg and 135 mg
Product Type: Single ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Dr. Reddy's Laboratories, Inc.
Submission Date: July 8, 2016
OSE RCM #: 2016-1634
DMEPA Primary Reviewer: Madhuri R. Patel, Pharm.D.
DMEPA Associate Director (Acting): Mishale Mistry, Pharm.D., MPH

1 REASON FOR REVIEW

This review evaluates the proposed container labels, Prescribing Information (PI) and Instructions for Breaking Tablets for Minolira (NDA 209269), submitted by Dr. Reddy's Laboratories, Inc. on July 8, 2016. The Division of Dermatology and Dental Products (DDDP) requested that DMEPA review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed product, Minolira, is a 505(b)(2) type NDA with the listed drug product being Solodyn (NDA 050808). Solodyn is available as unscored extended-release tablets in 55 mg, 65 mg, 80 mg, 105 mg, 115 mg strengths. The sponsor for Minolira proposes scored extended-release tablets in 105 mg and 135 mg strengths. DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. DMEPA finds the Prescribing Information and Instructions for Breaking Tablets acceptable from a medication error perspective. However, we note that the container label can be improved to enhance the prominence of the established name and strength. The strengths can also be better differentiated to help avoid wrong strength errors. Additionally, the "Rx" statement is more prominent than other important information on the labels and labeling. Therefore, we provide recommendations in Section 4 for the Applicant to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the Prescribing Information acceptable from a medication error perspective. However, we note that the proposed container label and carton labeling can be improved to

increase the readability and prominence of important information. Please see our letter-ready recommendations in Section 4.1 below for the container labels and carton labeling.

4.1 RECOMMENDATIONS FOR DR. REDDY'S LABORATORIES, INC.

We recommend the following be implemented prior to approval of this NDA:

- A. Container Labels (including Professional Sample)
 - a. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Consider choosing a font that is easy to read, and not lightweight or condensed.
 - b. The strength which is currently stated next to the established name lacks prominence. Increase the prominence (i.e., font size) of the strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6).
 - c. There is inadequate differentiation between the 105 mg and 135 mg strengths, which may lead to wrong strength errors. Therefore, we recommend the use of different colors, boxing, or some other means to provide adequate differentiation between the container labels per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
 - d. Revise "Rx" to read "Rx Only" as the "Rx only" statement is required on the drug label by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Additionally, we recommend decreasing the prominence of the statement "Rx Only" as this information appears to be more prominent than the established name on the principal display panel per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Minolira that Dr. Reddy's Laboratories, Inc. submitted on July 8, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Minolira and the Listed Drug		
Product Name	Minolira	Solodyn
Initial Approval Date	N/A	May 8, 2006
Active Ingredient	Minocycline Hydrochloride	Minocycline Hydrochloride
Indication	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older	Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older
Route of Administration	Oral	Oral
Dosage Form	Extended-release Tablets	Extended-release Tablets
Strength	105 mg, 135 mg	55 mg, 65 mg, 80 mg, 105 mg, 115 mg
Dose and Frequency	Approximately 1 mg/kg once daily for up to 12 weeks	1 mg/kg once daily for 12 weeks
How Supplied	Bottles of 30 (commercial package); Bottles of 10 (physician sample)	30-count bottles
Storage	20°C - 25°C (68°F - 77°F), excursions permitted to 15°C - 30°C (59°F - 86°F)	25°C (77°F); excursions permitted between 15°C– 30°C (59°F – 86°F)
Container Closure	n/a	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 11, 2016, we searched the L:drive and AIMS using the terms, Minolira, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 1 previous proprietary name review that is not relevant to this review.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Minolira labels and labeling submitted by Dr. Reddy's Laboratories, Inc. on July 8, 2016.

- Container label
- Professional Sample Container Label
- Instructions for Use
- Medication Guide

G.2 Label and Labeling Images

Container Labels:



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MADHURI R PATEL
02/13/2017

MISHALE P MISTRY
02/16/2017