# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211913Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

# Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**OFFICE OF DRUG EVALUATION III**
**DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS**

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| **NDA/BLA #s:** | 211913 |
| **Products:** | Absorica LD (isotretinoin) Capsules |
| **APPLICANT:** | Sun Pharma |
| **FROM:** | Tatiana Oussova, MD, MPH<br>Deputy Director for Safety |
| **DATE:** | October 31, 2019 |

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Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity (NME).

A REMS for ABSORICA (isotretinoin) capsules (NDA 21951) was originally approved on May 25, 2012. The REMS uses a shared system called the iPLEDGE Program for the elements to assure safe use and REMS assessments.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe

use is necessary for ABSORICA LD (isotretinoin) capsules (NDA 211913) to ensure that the benefits of the drug outweigh the risks of fetal exposure. In reaching this determination, we considered the following:

A. About 50.2 million people in the USA are affected by acne; 15 to 20% of young people may be affected by moderate to severe acne. This estimate is based on Bickers et al. 2006, and Bhate and Williams, 2013.


1. Bickers DR, Lim HW, Margolis D, Weinstock MA, Goodman C, Faulkner E, Gould C, Gemmen E, Dall T; American Academy of Dermatology Association; Society for Investigative Dermatology. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology, J Am Acad Dermatol. 2006 Sep;55(3):490-500.

2. Bhate K and Williams HC, 2013, Epidemiology of acne vulgaris, Br J Dermatol, 168(3):474-485.


B. Severe nodular acne often shows marked inflammation, erythema and/or hyperpigmentation, nodules, cysts, and pain, and can result in physical and psychological scarring.

C. Use of Isotretinoin for the treatment of severe nodular acne is very effective and has been shown to reduce the total inflammatory lesion count. (Costa et al. 2018)


Costa CS, Bagatin E, Martimbianco ALC, da Silva EMK, Lúcio MM, Magin P, Riera R. Oral isotretinoin for acne. Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD009435.


D. The typical course of isotretinoin treatment lasts 15 to 20 weeks.

E. Isotretinoin is a potent human teratogen and is contraindicated in pregnancy. In addition to embryo-fetal toxicity, isotretinoin has been associated with various other adverse effects that involve serious skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); lipid abnormalities such as hypertriglyceridemia, low HDL, and elevation of cholesterol; hepatotoxicity; and psychiatric disorders such as depression.

F. Absorica LD is not a new molecular entity. This is a 505(b)(2) application and the Applicant submitted a study to assess the bioavailability of a single oral dose of Absorica LD capsules 32 mg, relative to marketed formulation Absorica (Isotretinoin) Capsules 40 mg. The new dose formulation provides comparable exposure. Absorica LD will provide additional strengths of isotretinoin to the currently available products.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Absorica LD. FDA has determined that Absorica LD poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Absorica LD. FDA has determined that Absorica LD is a product for which patient labeling could help prevent serious adverse effects and that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use, Absorica LD.

The elements of the REMS will be a Medication Guide, elements to assure safe use (including that healthcare providers have particular experience or training, or are specially certified; pharmacies, practitioners, or health care settings that dispense the drug are specially certified; the drug is dispensed to patients with evidence or other documentation of safe-use conditions; and patients using the drug are enrolled in a registry), an implementation system, and a timetable for submission of assessments of the REMS.

Sun Pharma is a member company in the Isotretinoin Products Manufacturers' Group (IPMG) and will market Absorica LD under the iPLEDGE REMS, a shared system REMS for isotretinoin. The Applicant's REMS proposal aligns with the currently approved iPLEDGE REMS.

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

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| **Application Type** | NDA |
| **Application Number** | 211913 |
| **PDUFA Goal Date** | September 17, 2019 |
| **OSE RCM #** | 2018-1795 |
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| **Reviewer Name(s)** | Yasmeen Abou-Sayed, PharmD |
| **Team Leader** | Donella Fitzgerald, PharmD |
| **Deputy Division Director** | Jamie Wilkins, PharmD, MPH |
| **Review Completion Date** | August 29, 2019 |
| **Subject** | Evaluation of REMS submission |
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| **Established Name** | isotretinoin |
| **Trade Name** | Absorica LD |
| **Name of Applicant** | Sun Pharmaceuticals |
| **Therapeutic Class** | Retinoid |
| **Formulation(s)** | Micronized oral capsule (8, 16, 20, 24, 28, and 32 mg) |
| **Dosing Regimen** | 0.4 to 0.8 mg/kg/day given in 2 divided doses |

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# EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) documents the evaluation of the proposed risk evaluation and mitigation strategy (REMS) for the drug Absorica LD (isotretinoin). Sun Pharma (Sun) submitted a New Drug Application (NDA) 211913 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Absorica LD with the proposed indication for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. The reference listed drug (RLD) is Absorica, NDA 021951. Sun is a member company in the iPLEDGE shared system (SS) REMS group for isotretinoin and submitted a full REMS proposal that includes the currently approved iPLEDGE REMS, including REMS document, a Medication Guide, a REMS supporting document, and all appended REMS materials.

# 1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) submitted for Absorica LD (isotretinoin). Sun submitted a New Drug Application (NDA) 211913 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, for Absorica LD (isotretinoin) with the proposed indication for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. The reference listed drug (RLD) is Absorica (isotretinoin), NDA 021951. Isotretinoin is approved with a REMS with elements to assure safe use (ETASU) to ensure that the benefits of the drug outweigh its risks. The goals of the REMS are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions. The Applicant is a member company in the Isotretinoin Products Manufacturers' Group (IPMG) and will market their product under the iPLEDGE REMS, a shared system (SS) REMS for isotretinoin. Sun is a member company in the iPLEDGE SS REMS for isotretinoin and submitted a full REMS proposal that includes a REMS document, Medication Guide, REMS supporting document, and all appended REMS materials.[1] This application is under review in the Division of Dermatology and Dental Products (DDDP).

# 2 Background

## 2.1 PRODUCT INFORMATION

Absorica LD (isotretinoin), is a retinoid that inhibits sebaceous gland function and keratinization. Isotretinoin was first approved on May 7, 1982, under NDA 018662 [trade name Accutane (Hoffmann-LaRoche)], for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. The NDA 018662 was voluntarily withdrawn from the U.S. market on November 22, 2010, due to what the Applicant described as business reasons. Generic version s of Accutane have also been approved under various proprietary names. The typical course of isotretinoin treatment lasts 15 to 20 weeks, at a dose of 0.5 to 1 mg/kg daily.[a] Because Absorica LD is a micronized form of the drug and is designed to have a higher bioavailability then regular isotretinoin, the recommended dose for Absorica LD is 0.4 to 0.8 mg/kg/day, it can be dosed regardless of meals, and will provide additional strengths isotretinoin to the currently available products.[2] Isotretinoin is a potent human teratogen and is contraindicated in

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

pregnancy. To minimize fetal exposure, isotretinoin products are required to have a REMS and are approved for marketing only under the REMS, called the iPLEDGE Program. The iPLEDGE Program was originally approved as a RiskMAP. Isotretinoin was one of the products deemed to have a REMS in effect by the Food and Drug Administration Amendments Act (FDAAA). It was approved as a REMS in 2010. The REMS includes six Applicants that market six generic products and one new drug application (NDA), approved under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA). The most recent REMS modification was approved April 23, 2018. All isotretinoin applications share elements of the iPLEDGE REMS as well as the responsibilities of conducting the REMS assessments. The iPLEDGE REMS 12-Year Assessment Report (5-Year Assessment Report for Absorica) was submitted by the Applicants on April 30, 2018. The DRISK review of this assessment was finalized March 18, 2019 and determined that, despite identifying target areas in need of improvement, the REMS is meeting its goals.[3]

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211913 relevant to this review:

- 8/17/2018: New Drug Application (NDA) 211913 for isotretinoin capsules, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, received.
- 5/6/2019: The Applicant submitted a major amendment to the application containing Prescribing Information (PI) conforming to the Pregnancy and Lactation Labeling Rule (PLLR), which extended the PDUFA date to September 17, 2019.

## 3 Benefit Assessment

The efficacy of isotretinoin has been demonstrated, with the approval of NDA 018662 [trade name Accutane (Hoffmann- LaRoche)], on May 7, 1982, for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older.

The Applicant submitted study 11440306 to assess the bioavailability of a single oral dose of Absorica LD capsules 32 mg, relative to RLD Absorica (Isotretinoin) Capsules 40 mg under fed and fasted conditions. The food effect on the bioavailability of Absorica LD was also investigated. This was an open label, multi-center, randomized, single dose, three treatment, three period, six sequence, crossover, bioequivalence study. The study was conducted in healthy adult, male and female subjects. Dosing in each period was separated by a washout period of 21 days. Seventy-one (71) subjects were enrolled into the study; 64 subjects completed at least two periods of the study and 61 subjects completed all three periods of the study. Based on the Applicant's statistical analysis, Absorica LD met the 90% confidence interval criterion for bioequivalence under fed conditions. The new dose formulation provides comparable exposure. The clinical pharmacology reviewer has determined that the clinical bridge between Absorica LD and Absorica is established and that this application is acceptable.[4]

## 4 Risk Assessment & Safe-Use Conditions

Isotretinoin is a known potent human teratogen, and because of the serious risk of life-threatening congenital abnormalities if fetal exposure occurs, isotretinoin products are approved for marketing only

with a REMS known as the iPLEDGE REMS. Isotretinoin must only be prescribed by prescribers who are registered and activated with the iPLEDGE Program. Isotretinoin must only be dispensed by a pharmacy registered and activated with the iPLEDGE Program and must only be dispensed to patients who are registered and meet all the requirements of the iPLEDGE Program.[5] The REMS includes a Medication Guide, Elements to Assure Safe Use (ETASU), and timetable for submission of assessments. The Applicant is a member company in the Isotretinoin Products Manufacturers' Group (IPMG) and will market their product under the iPLEDGE REMS, a shared system (SS) REMS for isotretinoin.

Absorica LD is proposed to be available in strengths of 8, 16, 20, 24, 28, and 32 mg. The 20 mg strength is not bioequivalent or interchangeable with the currently marketed Absorica 20 mg strength, therefore the risk of medication errors is introduced if adequate differentiation is not made between the two products. At the time of this review, DDDP has added language to the combined Absorica and Absorica LD PI indicating[6]:

"ABSORICA and ABSORICA LD have different dosage regimens. Although ABSORICA and ABSORICA LD have a 20 mg strength, these strengths have different bioavailability and are not substitutable."

Additionally, the Office of Prescription Drug Promotion has advised the Applicant to include a warning regarding the lack of interchangeability of other 20 mg isotretinoin products on the Absorica LD 20 mg wallet (carton) and individual blister pack sleeves.[7]

# 5 Risk Management Activities Proposed by the Applicant

## 5.1 Review of Applicant's Proposed REMS

The Applicant submitted a full REMS proposal, including REMS document, Medication Guide, REMS supporting document, and all REMS appended materials. Sun Pharma is a member of the iPLEDGE SS REMS.

***Reviewer's Comments:*** *The Applicant's REMS proposal aligns with the currently approved iPLEDGE REMS. We note that the Medication Guide (MG) is under review in the Office of Medical Policy, Division of Medical Policy Programs and we defer to their review of the MG.*[8]

# 6 Conclusion & Recommendations

DRISK recommends approval of the REMS for Absorica LD (NDA 211913), received on August 17, 2018, and appended to this review, provided that the Patient Labeling Team in the Office of Medical Policy Initiatives determines the Medication Guide is adequate prior to the approval of the application.

If an iPLEDGE REMS Modification is approved between the date of this review and action being taken on this application, this REMS review will no longer be applicable, and the REMS should be considered deficient.

Should DDDP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

# 7 Appendices

## 7.1 REFERENCES


[1] Sun Pharmaceuticals. Risk Evaluation and Mitigation Strategy for Absorica LD, August 17, 2018.

[2] Sun Pharmaceuticals. Clinical Overview for Absorica LD, August 17, 2018.

[3] Cerny, I. Review of the 6-Year Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for Absorica (isotretinoin) and Year 12 for iPLEDGE (March 1, 2017 to February 28, 2018), March 15, 2019.

[4] Division of Dermatology and Dental Products. Draft Unireview for NDA 211913 Absorica LD (isotretinoin). August 29, 2019.

[5] IPMG, REMS Document for iPLEDGE program. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Isotretinoin_2018_04_23_REMS_Document.pdf , accessed on May 8, 2019.

[6] Division of Dermatology and Dental Products. Draft Prescribing Information for Absorica LD, NDA 211913. July 12, 2019.

[7] Buoaccoris, L. Labeling Comments for ABSORICA LD. Office of Prescription Drug Promotion, August 5, 2019.

[8] Mayrosh, R. Review of Patient Labeling: Medication Guide (MG) for Absorica LD NDA 211913. Division of Medical Policy Programs, August 6, 2019.


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