



NDA 021951/S-010

SUPPLEMENT APPROVAL

Ranbaxy Laboratories, Inc.
Attention: Likhitha Konatham, PharmD
Regulatory Affairs Associate
600 College Road East, Suite 2100
Princeton, NJ 08540

Dear Dr. Konatham:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 19, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ABSORICA[®] (isotretinoin) Capsules, 10, 20, 25, 35, and 40 mg.

We also refer to our approval letter dated June 17, 2017 which contained the following error: although you submitted an approvable REMS on June 9, 2017, the incorrect version of certain REMS appended materials were appended to the June 17, 2017 approval letter.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain June 17, 2017, the date of the original approval letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the products for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The iPLEDGE REMS for isotretinoin products, of which ABSORICA (isotretinoin) Capsules is a member, was originally approved on October 22, 2010, and the most recent REMS modification was approved on July 8, 2016. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS provides for implementation of a REMS Pharmacy Network and use of an electronic verification system for iPLEDGE Program certified pharmacies to request and receive a Risk Management Authorization (RMA) directly through the prescription claim adjudication process workflow at the point of dispensing an isotretinoin prescription. It also provides for the changes made to the REMS educational materials to streamline and improve clarity.

Your proposed modified REMS, submitted on December 20, 2016, amended on June 9, 2017, and appended to this letter, is approved.

This REMS uses a shared system for the elements to assure safe use and the REMS assessments. The shared system, known as the iPLEDGE REMS program for isotretinoin products, currently includes the products listed on the FDA REMS website, available at <http://www.fda.gov/rems>. Other products may be added to this REMS in the future if additional isotretinoin NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on May 25, 2012.

The revised REMS assessment plan must include, but is not limited to, the following:

- I. Background
 - i. Program Overview
 - ii. Stakeholder Process and Requirements
 - iii. Non-Compliance Process
 - iv. Post-Isotretinoin Therapy Follow-up
 - v. Isotretinoin Pregnancy Registry with Root Cause Analysis
 - vi. Exemption for Patients With Serious Medical Reasons
 - vii. Program Changes
- II. Methodology
 - i. Pregnancy Categorization
 - ii. Date of Conception
 - iii. Timing of Isotretinoin Exposure Relative to Date of Conception
 - iv. Pregnancy Status
 - v. Study Period
- III. Patient Information
 - i. Patient Statistics
 - ii. Compliance with End of Treatment Pregnancy Testing
 - iii. Lost to Follow-up
- IV. Pregnancies
 - i. iPLEDGE Pregnancies
 - a. Timing of Isotretinoin Exposure Relative to Pregnancy Conception
 - b. Deviations from the iPLEDGE Process and Requirements
 - c. Number of Risk Management Authorizations

- d. Patient Age
- e. Contraceptive Choices
- f. Reasons for Pregnancy as Reported by the Prescriber and Patient
- g. Patient Understanding of the iPLEDGE Program
- h. Contraceptive Counseling
- i. Root Cause Analysis
- j. Pregnancy Outcome
- k. Number of deviations per pregnant patient vs. number of deviations per non-pregnant female of reproductive potential
- ii. Non-iPLEDGE Pregnancies
 - a. Isotretinoin Source
 - b. Reasons for Pregnancy as Reported by the Prescriber and Patient
 - c. Root Cause Analysis
 - d. Pregnancy Outcome
- iii. Pre-iPLEDGE Pregnancies
- V. Exemption for Patients With Serious Medical Reasons
 - i. Number of prescribers who requested an exemption
 - ii. Number of patients per prescriber
 - iii. Age and risk category of each patient
- VI. Operations Assessment
 - i. Wholesalers - to include wholesaler-to-wholesaler shipment compliance
 - ii. Prescribers
 - iii. Pharmacies- to include pharmacy authorizations (RMAs) received by channel
 - iv. Prescriptions
 - v. Summary of iPLEDGE Deviations
 - vi. Call Center
- VII. Compliance Programs
- VIII. Overall Assessment
- IX. Tables
 - Table 1 History of iPLEDGE REMS Modifications
 - Table 2 iPLEDGE Program Sponsors
 - Table 3 Key iPLEDGE Requirements by Stakeholder
 - Table 4 Number of Patients Registered in iPLEDGE by Patient Risk Category through the Reporting Period
 - Table 5 Approved FRP Registration Exceptions
 - Table 6 Patients with at Least One Isotretinoin Prescription Authorized through iPLEDGE by Risk Category and Age
 - Table 7 Disposition of Patients during and at End of Course of Therapy
 - Table 8 Number of Females of Reproductive Potential Who Completed Isotretinoin Treatment
 - Table 9 Number of Females of Reproductive Potential Who Completed Isotretinoin Treatment and Had Supplemental Pregnancy Test Results Reported
 - Table 10 RMAs in a COT by Age and Number of Completed Post-Therapy Pregnancy Tests

- Table 11 Females of Reproductive Potential Who Were Exposed to Isotretinoin and Lost to Follow-up
- Table 12 Average Number of RMAs in a COT by Age for Patients Who Became Lost to Follow-Up
- Table 13 Total Number of Pregnancies Reported to the Pregnancy Registry by iPLEDGE Status
- Table 14 Total Number of Pregnancies: Prior iPLEDGE Years Versus iPLEDGE Current Assessment Year
- Table 15 iPLEDGE Pregnancies by Isotretinoin Exposure
- Table 16 iPLEDGE Pregnancy Rate for FRPs with at Least One RMA
- Table 17 Number of iPLEDGE Pregnancies by Month
- Table 18 Pregnancies Detected by iPLEDGE before Initiation of Isotretinoin Treatment
- Table 19 Timing of Isotretinoin Exposure Relative to Pregnancy Conception
- Table 20 Information Other than Last Menstrual Period that Was Used to Identify the Date of Conception for Women Who Initiated Isotretinoin Treatment While Pregnant
- Table 21 Timing of Isotretinoin Exposure Relative to Pregnancy Conception for Patients Who Took Leftover Medication
- Table 22 Summary of iPLEDGE Pregnancies Fetal Exposure during Current Year
- Table 23 Number of Risk Management Authorizations during the Course of Therapy in Which the Patient Became Pregnant – iPLEDGE Current Year
- Table 24 Average Number of Prescription Windows in a Completed Course of Treatment – iPLEDGE Current Year
- Table 25 Number of Pregnancies by Total Number of Risk Management Authorizations from iPLEDGE Run-In Period through Current Year
- Table 26 Age of Pregnant and Non-Pregnant Females of Reproductive Potential
- Table 27 Most Common Contraceptive Choices for Pregnant and Non- Pregnant Females of Reproductive Potential Based on Monthly Interactions
- Table 28 Top Five Contraception Choices by Age for Pregnant and Non-Pregnant Patients Based on Monthly Interactions
- Table 29 Primary Contraception Changes for Pregnant Patients in Current Year
- Table 30 Reasons Reported by Prescriber and Patient for iPLEDGE Pregnancies
- Table 31 First Month Questions about Avoiding Pregnancy and the Educational Components of iPLEDGE
- Table 32 Monthly Comprehension Testing for Females of Reproductive Potential about the Use of Contraception and the Risk of Birth Defects
- Table 33 Number of Patients Who Passed/Failed Their Monthly Comprehension Test on the First Try of the Month
- Table 34 First Month Questions about Contraceptive Counseling
- Table 35 Pregnancy Outcomes for iPLEDGE Pregnancies
- Table 36 Non-iPLEDGE Pregnancies by Isotretinoin Exposure
- Table 37 Number of Non-iPLEDGE Pregnancies by Month
- Table 38 Isotretinoin Source for Non-iPLEDGE Pregnancies
- Table 39 Reasons Reported by Prescriber and Patient for Non-iPLEDGE Pregnancies

- Table 40 Pregnancy Outcomes for Non-iPLEDGE Pregnancies
- Table 41 Number of Prescribers Who Participated in the Exemption for Patients with Serious Medical Reasons Program by Medical Specialty
- Table 42 Number of Patients Participating in the Exemption for Patients with Serious Medical Reasons per Prescriber
- Table 43 Number of Registered Wholesalers – in most recent 3 years
- Table 44 Number of Registered and Activated Prescribers Who Wrote at Least One Isotretinoin Prescription
- Table 45 Number of Activated Designees
- Table 46 Number of Pharmacies Registered and Activated at the End of the Reporting Period
- Table 47 Number of Pharmacies Registered and Activated in iPLEDGE by Pharmacy Type
- Table 48 Reasons for Pharmacy Deactivations (Not Related to Non-Compliance Events)
- Table 49 Confirmed Incidents and Rate of Dispensing Isotretinoin without an RMA
- Table 50 Missing RMA Summary for iPLEDGE Current Year
- Table 51 Number of Prescriptions Authorized by Risk Category
- Table 52 Number of Prescription Authorization Attempts Denied by Risk Category
- Table 53 Reasons for Prescription Denial
- Table 54 Summary of NCAP Violations in Current Year
- Table 55 Breakdown of Notices of Non-Compliance, Warnings, and Deactivations by Stakeholder in Current Year
- Table 56 Pharmacy Warning-Level Deviations for Current Year

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the

REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 021951 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021951 REMS ASSESSMENT

or

**NEW SUPPLEMENT FOR NDA 021951/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021951/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 021951/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021951/ S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 021951

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We also remind you of your specific reporting obligations regarding serious adverse events in

patients who have received ABSORICA® (isotretinoin) Capsules. In addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80(C)), you will submit a 15-day report for each of the following:

- All pregnancy exposures to ABSORICA® (isotretinoin) Capsules; and
- All psychiatric events including suicides, attempted suicides, and suicidal ideation

In addition, you should continue to provide us with the following reports on an annual basis:

1. Annual Periodic Adverse Drug Experience Report
2. Annual iPLEDGE Report (with contents as described in your approval letter dated April 11, 2003) to be submitted by May 1st each year. Non-compliant distribution events should no longer be submitted as 15-day reports, but, instead, should be included in the Annual iPLEDGE Report.

If you have any questions, call Dawn Williams, Safety Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:

REMS

Annual iPLEDGE Report Contents

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

/s/

TATIANA OUSSOVA
06/17/2017