NDA 021951/S-018

SUPPLEMENT APPROVAL

Sun Pharmaceutical Industries, Inc.
Attention: Praveen Devakadaksham
Director, US Regulatory & Business Continuity
2 Independence Way
Princeton, NJ 08540

Dear Mr. Devakadaksham:

Please refer to your supplemental new drug application (sNDA) dated and received April 14, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Absorica (isotretinoin) capsules, 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved iPledge REMS. This supplement is in response to our June 19, 2018 REMS Modification Notification letter in which we notified you that your REMS must be modified to include gender neutral language so as not to inhibit access to transgender patients who may have not identified with any of the three possible risk categories.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for isotretinoin products, of which Absorica is a member, was originally approved on October 22, 2010, and the most recent REMS modification was approved on December 9, 2020. 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. In order to ensure the benefits of isotretinoin outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated June 19, 2018.

In addition, your proposed modifications to the REMS include the following:

- Removal of the Medication Guide as an element of the Risk Evaluation and Mitigation Strategy (REMS)
- Changes to the REMS document and appended materials to align with labeling changes related to the safety labeling changes approved on August 31, 2018 in prior approval supplement 14 in reference to gender neutral patient risk categories

- Changes to the REMS appended materials to reduce redundancy and streamline the content
- Changes to the pharmacy operations to verify safe use conditions for the REMS risk management authorization
- Addition of an optional quick reference (QR) code for use by patients enrolled in the REMS
- Conversion of the REMS Document to the new, standardized format

Medication Guide: We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of isotretinoin outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted to Drug Master File (DMF) [redacted] (b) (4) on April 9, 2021, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The modification to the approved REMS must be fully implemented within 66 calendar days of the date of this letter.

The REMS uses a shared system for the elements to assure safe use, an implementation system, and a timetable for assessments of the REMS. This shared system, known as iPLEDGE REMS, currently includes products listed on the FDA REMS website, available at:
https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS has been revised. You must submit a REMS Assessment on March 1, 2024, and every other year thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:
Program Outreach and Communication
1) REMS Outreach and Communication *(2-year assessment post-modification only)*

   a) Report on any communication plan activities used to inform stakeholders of the modified iPLEDGE program before, during, and after during the transition phase of the REMS modification
   b) Provide an analysis of the percentage of impacted stakeholders confirmed to have been informed and the modalities used before, during and after the transition stage of modification

Program Implementation and Operations

2) REMS Program Implementation and Operations *(2-year assessment post-modification only)*

   a) Date when the modified iPLEDGE REMS website went live and was fully operational
   b) Date when the REMS Call Center for the iPLEDGE REMS program went live and was fully operational
   c) Date(s) when patients were first able to be enrolled in the modified iPLEDGE REMS via any mechanism (website, IVRS, or the REMS Call Center
   d) Stakeholder Transition
      i) For each stakeholder (prescribers, prescriber designees, pharmacies, patients,) report:

         - *Number certified or enrolled in the iPLEDGE REMS program prior to implementation of the modified iPLEDGE REMS*
         - *Number transitioned into the modified iPLEDGE REMS*

3) REMS Certification and Enrollment Statistics *((provide the (two) previous, current, and cumulative reporting periods beginning with the post-modification 2-year assessment; provide enrollment for the current reporting period in two 12-month intervals).*

   a) Healthcare providers (number and percentage of certified prescribers)
      i) Healthcare providers who are newly certified
      ii) Active prescribers (i.e. who have had an RMA for isotretinoin approved at least once during the reporting period) (number and percent of all certified prescribers)
      iii) Prescribers' specialties
      iv) Number of prescribers who participated in the exemption for patients with Serious Medical Reasons program by medical specialty
      v) Include a summary of reasons certification is incomplete
      vi) Prescribers who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified
   b) Prescriber Designees (number and percentage of enrolled designees)
      i) Newly enrolled
      ii) Active (associated with active prescriber) (number and percent of all certified prescriber designees)
      iii) Include a summary of reasons certification is incomplete
      iv) A summary of the methods of prescriber designee certification
   c) Patients (number and percentage of enrolled patients stratified by patients who can become pregnant and who cannot become pregnant)
      i) Newly enrolled
      ii) Active patients (i.e. received at least one RMA of isotretinoin during the reporting period) by risk category, and total # of RMAs

iii) Appended tables that stratify patients who can become pregnant and who cannot become pregnant should be provided and stratified by age (year) categories of 10-14, 15-19, 20-29, 30-39, 40-49, 50 -53, 54>
iv) Patients enrolled with an exception stratified by exception type and risk category
v) Number of patients participating in the exemption for patients with Serious Medical Reasons per prescriber

d) Pharmacies (number and percentage of certified pharmacies stratified by chain and independent)
   i) Newly certified in the modified iPLEDGE REMS program
   ii) Active pharmacies (i.e., have submitted for an iPLEDGE RMA at least once during the reporting period)
e) Wholesalers/distributors (number and percentage of certified pharmacies)
   i) Newly enrolled
   ii) Active (have shipped isotretinoin at least once during the reporting period)

4) Isotretinoin utilization data *(per previous two reporting periods, current and cumulatively)*
   Provide utilization data for the current reporting period in two 12-month intervals. Utilization data should be stratified by patients who can become pregnant and who cannot become pregnant, pharmacy type and presented as the number and the percent of all RMA's authorized or denied as appropriate.
   a) Number of RMAs authorized
   b) Number of RMAs denied
   c) Number of RMAs submitted using the QR code compared to all submitted RMAs
   d) Number of patients who completed isotretinoin treatment
   e) Disposition of patients during and at end of course of therapy

5) REMS infrastructure and performance
   a) Contact/Call Center report
      i) The number of calls received by the REMS coordinating center, stratified by stakeholder type and reason for the call
      ii) The number of issues/complaints reported to the REMS coordinating center, accompanied by a description of the top five reasons for calls by each stakeholder or 80% of calls by each stakeholder (which ever accounts for the greater number of calls) and the resolution (if applicable)
      iii) A description of each call, including stakeholder type, that may indicate an issue with access, burden, or an adverse even
      iv) A summary of corrective actions resulting from issues identified

6) REMS compliance
   a) Confirmed incidents and rate of dispensing isotretinoin without an RMA *(per previous four reporting periods, current and cumulatively).* Stratify by patients who can become pregnant and patients who cannot become pregnant.

b) Confirmed incidents and rate of dispensing isotretinoin after an RMA was denied (*per previous four reporting periods, current and cumulatively)*. Stratify by patients who can become pregnant and patients who cannot become pregnant.
c) Summary of missing RMA investigations. Stratify by patients who can become pregnant and patients who cannot become pregnant
d) Provide a protocol/process map of the missing RMA investigations*;* include a description of how missing RMAs from first dispenses will be identified.
e) Summary of NCAP violations in current year
f) Root cause analysis of cases of reproductive risk category misclassifications where patients who can become pregnant were initially classified as patients who cannot become pregnant
g) Include the protocol used to conduct the root cause analysis of the risk category misclassifications
h) Report of the sale of any isotretinoin product by a wholesaler to an unregistered and/or unactivated pharmacy or unregistered wholesaler
i) Audits of pharmacies and the REMS program Contact Center will be conducted to ensure that all REMS processes and procedures are in place, functioning, and support the REMS program, and will be submitted with each assessment report

7) Safe use behavior *(per previous two reporting periods, current and cumulatively)*
   a) Number of patients who can become pregnant who completed isotretinoin treatment and had supplemental pregnancy test results reported
   b) Number of completed post-therapy pregnancy tests
   c) Patients patients who can become pregnant who were exposed to isotretinoin and lost to follow-up

Evaluation of Knowledge

8) Knowledge assessment (per previous two reporting periods, current and cumulatively)

   a) Periodic surveys of prescribers and pharmacists to ensure that prescribers and pharmacists informed regarding isotretinoin's serious risks and safe-use conditions *(beginning with the two year REMS Assessment Report and every two years s thereafter)*
   b) Monthly patient knowledge assessment results stratified by patients who became pregnant while on isotretinoin and those that did not become pregnant while on isotretinoin
      i) First month questions about avoiding pregnancy and the educational components of iPLEDGE
      ii) Number and percentage of patients who passed/failed their monthly comprehension test on the first month questions
      iii) Monthly comprehension testing for patients who can become pregnant about the use of contraception and the risk of birth defects

iv) Number and percentage of patients who passed/failed their monthly comprehension test on the first try of the month
v) First month questions about contraceptive counseling

- *Number and percentage of patients who reported being counseled*

Health Outcomes and/or Surrogates of Health Outcomes

9) Safety surveillance (*per previous two reporting periods, current and cumulatively*)
   a) iPLEDGE pregnancies
      i) Total number of iPLEDGE pregnancies reported to the registry
      ii) iPLEDGE pregnancy rate for patients who can become pregnant (patients with at least one RMA)
      iii) Pregnancies detected by iPLEDGE before initiation of isotretinoin therapy
      iv) Timing of isotretinoin exposure relative to pregnancy conception
      v) Summary of iPLEDGE fetal exposure
      vi) Deviations from the iPLEDGE process and requirements
      vii) Number of Risk Management Authorizations
      viii) Patient age
      ix) Contraceptive choices
      x) Reasons for pregnancy as reported by the prescriber and patient
      xi) Patient understanding of the iPLEDGE program
      xii) Contraceptive counseling
      xiii) Root Cause Analysis
      xiv) Pregnancy outcome
      xv) Number of deviations per pregnant patient vs. number of deviations per non-pregnant patients who can become pregnant

   b) Non-iPLEDGE pregnancies
      i) Total number of non-iPLEDGE pregnancies reported to the registry
      ii) Isotretinoin source
      iii) Reasons for pregnancy as reported by the prescriber and patient
      iv) Root Cause Analysis
      v) Pregnancy outcome

10) With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified (Section 505-1(g)(3)).

11) Report on Key Performance Indicators: The key performance indicator(s) (KPI) are the primary measure(s) that are essential to determining if the REMS processes are functioning as designed
    a) The Key Performance Indicator for the iPLEDGE REMS that will demonstrate that the iPLEDGE REMS is functioning as designed to prevent fetal exposure to isotretinoin is:

(i) The number of confirmed incidents of dispensing without an RMA or dispensing after an RMA is denied for patients who can get pregnant with a rate of less than 8 confirmed incidents of dispensing without an RMA per 10,000 dispenses to patients who can become pregnant

b) The Key Performance Indicator for the iPLEDGE REMS that will demonstrate that the iPLEDGE REMS is functioning as designed to inform prescribers about isotretinoin's serious risks and safe use conditions is:
   (i) The KAB survey results for Key Risk Messages 1 – 4, with a minimum threshold to be proposed and agreed to prior to survey implementation for each Key Risk Message
c) The Key Performance Indicators for informing patients about isotretinoin's serious risks and safe use conditions will be:
   (i) The rate of passing monthly comprehension questions on the first try of the month, with a standard threshold of at least 90%
   (ii) The number of confirmed incidents of dispensing without an RMA or dispensing after an RMA is denied with a rate of < 8 confirmed incidents of dispensing without an RMA per 10,000 dispenses
d) The Key Performance Indicator of the iPLEDGE REMS that will demonstrate that the iPLEDGE REMS is functioning as designed to inform pharmacists about isotretinoin's serious risks and safe use conditions is:
   (i) The number of confirmed incidents of dispensing without an RMA or dispensing after an RMA is denied with a rate of < 8 confirmed incidents of dispensing without an RMA per 10,000 dispenses
e) For the initial report, due 2 years after approval of the modification, include a quarterly analysis of the KPI. If the acceptable threshold is not achieved by the final quarter, include a proposal to improve the reliability of the program
f) The assessment report should also include any improvement activities that were implemented during the assessment period, along with the rationale for the improvement and any ongoing monitoring of results

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 ASSESSMENT METHODOLOGY

(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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 LABELING 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 REVISIONS 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.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 product for the claimed indication 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.

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:

- Annual Periodic Adverse Drug Experience 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 Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GORDANA DIGLISIC
10/08/2021 05:05:49 PM
Signing on behalf of Dr. Tatiana Oussova