NDA 021951/S-028
NDA 211913/S-013

SUPPLEMENT APPROVAL

Sun Pharmaceutical Industries, Inc.
Attention: Nitesh Patel
Senior Manager, Regulatory and Business Continuity
2 Independence Way
Princeton, NJ 08540

Dear Nitesh Patel:

Please refer to your supplemental new drug applications (sNDAs) dated and received May 30, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Absorica (isotretinoin) capsules, 10mg, 20mg, 25mg, 30mg, 35mg, 40mg; and Absorica LD (isotretinoin) capsules, 8mg, 16mg, 24mg, 32mg.

These Prior Approval sNDAs provide for the proposed modifications to the approved isotretinoin (iPLEDGE) Shared System Risk Evaluation and Mitigation Strategy (REMS). These supplements are in response to our November 30, 2023, REMS Modification Notification letter.

We have completed our review of these supplemental applications, as amended. They are approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System (SS) REMS for isotretinoin products, of which Absorica and Absorica LD are members, was originally approved on October 22, 2010, and the most recent REMS modification was approved on March 24, 2023. The SS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order 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 November 30, 2023.

In addition, the following modifications were communicated during the course of the review:

- Changes to the REMS goals
- Changes to the REMS educational materials to improve risk messaging, including removal of the Fact Sheet and the Office Staff Designees Activation

Form, and the addition of a new patient material, the Guide for Patients Who Cannot Get Pregnant
- Addition of the following to the list of the REMS materials: The Pregnancy Registry Healthcare Provider Guide and the Pregnancy Registry Patient Guide
- Update to the contraception counseling information, including additional information on emergency contraception, in the REMS educational materials
- Clarification on the required frequency for pharmacy staff training in the REMS Document and Pharmacist Guide
- Change to the information required for the prescription authorization process and removal of the prescription window for patients who cannot get pregnant

Your proposed modified REMS, submitted to Drug Master File (DMF) 032462 on May 28, 2024, amended and appended to this letter, is approved.

This shared system REMS, known as the isotretinoin (iPLEDGE) SS REMS, currently includes products listed on the FDA REMS website[1].

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

The modification to the approved REMS must be fully implemented within 180 calendar days of the date of this letter.

The timetable for submission of assessments must be revised. You must submit a REMS Assessment on March 1, 2026, and annually thereafter.

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

For each metric, provide data for the two previous, current, and cumulative reporting periods (where applicable), unless otherwise noted.

REMS Outreach and Communication

1) REMS Outreach and Communication (March 1, 2027 and March 1, 2028 assessments only)

   a) Provide an assessment to determine if the REMS Communication Materials were disseminated to the target audience within the stated timeframe as required. Include the following in your assessment:

      i) Stratification of results by REMS letter type (e.g. Prescriber Communication Letter)

[1] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

ii) The proportion of each targeted audience of healthcare provider (e.g. healthcare provider certified to prescribe) out of those identified to receive a communication that had an email with the REMS Communication Materials successfully delivered. If this proportion is less than 100%, provide the reason why 100% compliance was not achieved, and any subsequent follow-up actions taken.

b) An assessment to determine if the REMS Website update was published as required. Include in your assessment if the update was published within and for the required timeframes and to the targeted audience. If not published as required, provide the reason why and what actions were taken to remediate.

c) Provide an assessment to determine if the REMS Website Pop-Up Message was published as required.

REMS Implementation and Operations

2) REMS Certification and Enrollment Statistics

a) Healthcare Providers (number and percentage of certified prescribers)

i) Healthcare Providers who are newly certified

ii) Active prescribers (i.e., who have had a Risk Management Authorization (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 by medical specialty

v) Include a summary of reasons certification was 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 was incomplete

iv) A summary of the methods of prescriber designee certification

c) Patients (number and percentage of enrolled patients (stratified by patients who can get pregnant and who cannot get pregnant)

i) Newly enrolled

ii) Active patients (i.e. received at least 1 RMA of isotretinoin during the reporting period) by patient category, and total # of RMAs

iii) Appended tables that stratify patients who can get pregnant and who cannot get pregnant should be provided and stratified by age (year) categories of 0-9,10-14, 15-19, 20-29, 30-39, 40-49, 50 -53, ≥54

iv) Patients enrolled with an exemption stratified by exemption type and patient 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

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 wholesaler/distributors)

i) Newly enrolled

ii) Active (have shipped isotretinoin at least once during the reporting period)

3) Isotretinoin Utilization Data

Provide utilization data for the current reporting period in 2 12-month intervals. Utilization data should be stratified by patients who can get pregnant and who cannot get 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 patients who completed isotretinoin treatment

d) Disposition of patients during and at end of course of therapy

4) 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 event

      iv) A summary of corrective actions resulting from issues identified

5) REMS Compliance

   a) First month questions about pregnancy prevention methods counseling

      i) Number and percentage of patients who reported being counseled

   b) Confirmed incidents and rate of dispensing isotretinoin without an RMA. Stratify by patients who can get pregnant and patients who cannot get pregnant.

   c) 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 get pregnant and patients who cannot get pregnant.

   d) Summary of missing RMA investigations for patients who can get pregnant and patients who cannot get pregnant

   e) Provide a protocol/process map of the missing RMA investigations; include a description of how missing RMAs from first dispenses will be identified.

   f) Summary of Noncompliance Action Policy (NCAP) violations in current year.

   g) Provide an assessment on cases of reproductive patient category misclassifications where patients who can get pregnant were initially classified as patients who cannot get pregnant

      i) If misclassification occurred, provide the reason and actions taken to remediate

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, wholesalers and the REMS Contact Center will be conducted to ensure that all REMS processes and procedures are in place, functioning, and support the REMS, and a report of audit findings are to be submitted with each assessment report.

   i) Include a copy of your audit plan, appended to the assessment report

j) Provide an assessment to determine if those patients who can get pregnant and miss the 7-day prescription window had a repeat pregnancy test as required. Include in the assessment:

   i) Numerators and denominators for all proportions

   ii) Stratification of results by those patients who have not started isotretinoin and those who missed the prescription window during their treatment with isotretinoin

      (1) Of those patients who had not started isotretinoin, the number and proportion of patients that missed the 7-day prescription window out of all active patients who can get pregnant that initiated isotretinoin

      (2) Of those patients who had started isotretinoin and missed the prescription window during their treatment, the number and proportion of patients that missed the 7-day prescription window out of all active patients who can get pregnant

      (3) The number and proportion of patients that had a repeat pregnancy test stratified by setting (in a medical setting or outside of a medical setting)

         (a) Of these patients, the number and proportion of unique patients that had a positive repeat pregnancy test reported to the REMS

            (i) The number and proportion of these patients for whom isotretinoin therapy was discontinued. If < 100% provide the reason why and any follow-up information

         (b) What were the steps taken if repeat pregnancy testing was not completed

         (c) For each instance where the 7-day prescription window was missed, the number and proportion associated with a reversed RMA out of all instances. Include the time between the date of RMA reversal and

repeat pregnancy test and subsequent RMA approval; report as the mean, median, and range (in days)

iii) Include any reported noncompliance that would inform on this assessment (e.g. isotretinoin dispensed to a non-enrolled patient or without an RMA) and the impact on the results.

k) Number and proportion of isotretinoin prescriptions that were dispensed with an RMA compared to total number of isotretinoin prescriptions dispensed with an RMA plus number of confirmed reported dispensed without an RMA.

l) In patients who can get pregnant, provide the number and proportion of confirmed unique incidents of dispensing without an RMA compared to every 10,000 known total dispenses for patients who can get pregnant. The known total dispenses should include dispensed prescriptions with an RMA, plus the number of confirmed reported dispenses without an RMA.

m) In patients who cannot get pregnant, provide the number and proportion of confirmed unique incidents of dispensing without an RMA compared to every 10,000 known total dispenses for patients who cannot get pregnant. The known total dispenses should include dispensed prescriptions with an RMA, plus the number of confirmed reported dispenses without an RMA.

6) Safe Use Behavior

a) Provide an assessment of whether each patient's reproductive status was assessed to determine who can get pregnant. Include in the assessment:

i) Numerators and denominators for all proportions

ii) The number and proportion of patients who had the patient category section fully completed on their Patient Enrollment Form (e.g., no missing data) out of all patients enrolled in the REMS. If <100%, provide the reasoning and actions taken to remediate.

iii) Any reported non-compliance that would inform on this assessment (e.g., isotretinoin dispensed to a non-enrolled patient or without an RMA) and the impact on the results.

b) Provide an assessment on whether patients who can get pregnant agree to use contraception or abstinence. Include in the assessment:

i) Numerators and denominators for all proportions

ii) The number and proportion of patients who can get pregnant that had documentation of their agreement to use contraception or abstinence prior to

initiation of their isotretinoin therapy (first RMA) out of all patients who can get pregnant that initiated isotretinoin therapy (first RMA). If <100%, provide the reasoning and actions taken to remediate.

iii) The number and proportion of RMAs for patients who can get pregnant where documentation of the patient's agreement to use contraception or abstinence was submitted to the REMS out of all RMAs for patients who can get pregnant. If <100%, provide the reasoning and actions taken to remediate.

iv) Include any reported noncompliance that would inform on this assessment (e.g. isotretinoin dispensed to a non-enrolled patient or without an RMA) and the impact on the results

c) Provide an assessment if before treatment initiation (first RMA), patients who can get pregnant had a negative confirmatory pregnancy test. Include in the assessment:

i) Nnumerators and denominators for all proportions

ii) The number and proportion of patients who can get pregnant that had documentation of a negative confirmatory pregnancy test submitted to the REMS prior to their first RMA out of all patients who can get pregnant that initiated treatment (had their first RMA). If <100%, provide the reasoning and actions taken to remediate.

(1) Stratify these results by whether the pregnancy test was completed in a medical setting or completed outside of a medical setting (e.g., at-home pregnancy testing). If <100% of these pregnancy tests were completed in a medical setting provide the reasoning and actions taken to remediate

iii) Include any reported noncompliance that would inform on this assessment (e.g. isotretinoin dispensed to a non-enrolled patient or without an RMA) and the impact on the results

d) Provide an assessment if during treatment (for subsequent RMA after the initial RMA), patients who can get pregnant had documentation of a pregnancy test prior to each dispense. Include in the assessment:

i) Numerators and denominators for all proportions

ii) The number and proportion of subsequent RMAs (all RMAs excluding the initial RMA) for patients who can get pregnant that had documentation of a pregnancy test submitted to the REMS out of all subsequent RMAs for patients who can get pregnant. If <100%, provide the reasoning and actions taken to remediate.

(1) Stratify the results by whether the pregnancy test was completed in a medical setting or completed outside of a medical setting (e.g., at-home pregnancy testing).

iii) Include any reported non-compliance that would inform on this assessment (e.g., isotretinoin dispensed to a non-enrolled patient or without an RMA) and the impact on the results.

e) Provide an assessment on pregnancy test results being falsified or misinterpreted for pregnancy testing done in medical setting or completed outside of a medical setting (e.g., at-home pregnancy testing)

i) Include in your assessment, reasoning for misinterpretation or falsification of the pregnancy test results and actions taken to remediate.

f) Number of patients who can get pregnant who completed isotretinoin treatment and had supplemental pregnancy test results reported

i) Stratify these results by whether the pregnancy test was completed in a medical setting or completed outside of a medical setting (e.g., at-home pregnancy testing).

g) Number of completed post-therapy pregnancy tests

h) Patients who can get pregnant who were exposed to isotretinoin and lost to follow-up

Knowledge

7) Monthly comprehension testing results (stratified by patients who became pregnant while on isotretinoin and those that did not get pregnant while on isotretinoin)

a) First month questions about avoiding pregnancy and the educational components of iPLEDGE

b) Number and percentage of patients who passed/failed their monthly comprehension test on the first month questions

c) Monthly comprehension testing for patients who can get pregnant about the use of pregnancy prevention methods and the risk of birth defects

d) Number and percentage of patients who passed/failed their monthly comprehension test on the first try of the month

Health Outcomes and/or Surrogates of Health Outcomes

8) Safety Surveillance

a) iPLEDGE® Pregnancies

   i) Total number of iPLEDGE® pregnancies reported to the registry

   ii) iPLEDGE® pregnancy rate for patients who can get pregnant (patients with at least 1 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 RMAs

   viii) Patient age

   ix) Chosen pregnancy prevention methods (i.e., contraception or abstinence)

   x) Reasons for pregnancy as reported by the prescriber and patient

   xi) Patient understanding of the iPLEDGE® REMS

   xii) Chosen pregnancy prevention methods (i.e., contraception or abstinence) counseling

   xiii) Root Cause Analysis

   xiv) Number of deviations per pregnant patient vs. number of deviations per non-pregnant Patients Who Can Get Pregnant

b) Provide a descriptive trend analysis covering the current and the two previous reporting periods that includes the iPLEDGE pregnancy rate for patients who can get pregnant (patients with at least 1 RMA). If findings indicate an increase in the iPLEDGE pregnancy rate, include in the analysis any actions taken to remediate.

c) 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

Overall Assessment of REMS Effectiveness

9) The requirements for assessments of an approved REMS under section 505-1(g)(3) include, 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.

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 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

REMS modifications, provide a rationale for why the REMS does not need to be modified.

Additionally, we recommend that you submit your pregnancy root cause analysis protocol for FDA review within 30 days of this letter. 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: **"REQUEST FOR REMS ASSESSMENT METHODOLOGY PROTOCOL REVIEW/ PREGNANCY ROOT CAUSE ANALYSIS"**.

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 021951/211913 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, AUDIT PLAN)

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 021951/211913 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 021951/211913/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021951/211913/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021951/211913/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 021951/211913/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 021951/211913

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

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

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

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

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 supplemental applications, you are exempt from this requirement.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for isotretinoin capsules you submit all instances of pregnancy exposure and serious and non-serious, domestic and/or foreign cases of psychiatric events including suicides, attempted suicides, and suicidal ideation as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) until December 31, 2030.

We request that you provide a narrative summary including analyses of 1.) all pregnancy exposures and 2.) all psychiatric events including suicides, attempted suicides, and suicidal ideation as part of your required periodic safety reports (e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)), annually, through December 31, 2030.

Your analyses should include interval and cumulative data from January 1, 2022. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

If you have any questions, contact Sascha Randolph, Regulatory Project Manager, at Sascha.Randolph@fda.hhs.gov.

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: 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/

JILL A LINDSTROM
02/09/2026 08:08:32 PM
Signed on behalf of Dr. Tatiana Oussova