NDA 211913

NDA APPROVAL

Sun Pharmaceutical Industries Limited
c/o Sun Pharmaceuticals Industries Ltd.
Research & Development Centre
Attention: Ronak Patel
2 Independence Way
Princeton, NJ 08450

Dear Mr. Patel:

Please refer to your new drug application (NDA) dated and received August 17, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ABSORICA LD (isotretinoin) capsules, 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, and 32 mg.

We acknowledge receipt of your major amendment dated May 06, 2019, which extended the goal date by three months.

This new drug application provides for the use of ABSORICA LD (isotretinoin) capsules for the treatment of severe recalcitrant nodular acne in patients 12 years and older.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211913**." Approval of this submission by FDA is not required before the labeling is used.

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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for ABSORICA LD to ensure the benefits of the drug outweigh the risk of fetal exposure.

Your proposed REMS must also include the following:

Medication Guide:
In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, 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. Under section 505-1 of the FDCA, FDA has determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risk of fetal exposure.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed ABSORICA LD.

Elements to assure safe use:
Pursuant to 505-1(f)(1), we have also determined that ABSORICA LD can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of fetal exposure listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- 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
- Patients using the drug are enrolled in a registry

Implementation System:
The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

Your proposed REMS, submitted on August 17, 2018, amended and appended to this letter, is approved.

The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments.

Your REMS must be fully operational before you introduce ABSORICA LD into interstate commerce.

There is an established shared system REMS for products containing isotretinoin called the iPLEDGE REMS. This REMS Program uses a shared system for elements to assure safe use and REMS assessments. This shared system includes, in addition to

NDA 211913, the products listed as part of the isotretinoin iPLEDGE REMS on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added to the iPLEDGE REMS in the future if additional NDAs or ANDAs are approved.

The 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
      a. Report cumulative data as well as data for patients that newly register per reporting period.

IV. Prescriber Information
   i. Specialties that prescribe isotretinoin

V. Pharmacy Information
   i. Number of prescriptions from practice settings such as Chain and Independent Pharmacies

VI. 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

VII. 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

VIII. 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

IX. Compliance Programs – including reproductive risk category classification and changes as well as end of isotretinoin pregnancy testing
i. Root cause analysis of cases of reproductive risk category misclassifications where females of reproductive potential were initially classified as females of non-reproductive potential
ii. Include the protocol used to conduct the root cause analysis.

X. Prescriber Survey

XI. Pharmacist Survey

XII. Overall Assessment

IIIX. Tables

- Table 1 History of iPLEDGE REMS Modifications
- Table 2 iPLEDGE Program IPMG
- 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

XIV. 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). 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 the 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 211913 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 211913 REMS ASSESSMENT

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

or

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

or

NEW SUPPLEMENT FOR NDA 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 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 REVISION FOR NDA 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

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

If you have any questions, call Barbara Gould, Chief, Project Management Staff, at 301 796-4224.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- REMS

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

---

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
11/05/2019 08:24:17 AM