NDA ######

REMS MODIFICATION NOTIFICATION

APPLICANT NAME
ADDRESS

Dear CONTACT:[1]

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PROPRIETARY NAME (ESTABLISHED NAME).

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

The REMS for isotretinoin was originally approved on October 22, 2010, and the most recent REMS modification was approved on March 24, 2023. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for isotretinoin must be modified to minimize the burden on the healthcare delivery system of complying with the REMS.

This determination is based on an analysis of potential changes to the current REMS requirements that could reduce burden on the healthcare delivery system while maintaining a comparable level of safe use. This analysis considered the advice, presentations, and discussion from the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee held on March 28-29, 2023; stakeholder feedback from prescribers, pharmacists, and patients; review of the literature; experience during the COVID-19 Public Health Emergency; review of postmarketing data and REMS assessment reports covering years 12 through 16 of the REMS along with additional supplemental REMS data provided by the applicants.

Your approved REMS must be modified as follows:

- Remove the requirement that pregnancy tests must be performed in a CLIA-certified laboratory; however, all pregnancy testing before isotretinoin treatment

[1]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.

initiation must be completed in a medical setting (e.g., prescriber's office, clinic, laboratory).

- Allow prescribers the option of using home pregnancy testing for their patients during and after isotretinoin treatment in conjunction with measures to minimize falsification of pregnancy tests.
- Remove the waiting period requirement (also referred to as the "19-day lockout") for patients if they do not obtain isotretinoin within the first 7-day prescription window. Before isotretinoin treatment initiation, a repeat confirmatory test must be completed in a medical setting (as described above) without any required waiting period.
- Revise the registry requirement to remove the objective to document the outcome (and associated data collection) for each pregnancy.
- Revise the requirement for prescribers to document patient counseling in patients who cannot become pregnant from monthly to only at enrollment. Before dispensing each prescription, the authorization to dispense must verify patient enrollment and prescriber certification.

The timetable for submission of assessments of the proposed modified REMS may remain the same as that approved on October 8, 2021.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements, proposed changes to the REMS assessment plan, and proposed changes to the pregnancy registry protocol and associated data collection forms. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, you must submit a proposed REMS modification within 180 days of the date of this letter.

The Isotretinoin Product Manufacturer Group (IPMG) should submit the proposed modified REMS to DMF 032462. Submit your cross-reference submission as a Prior Approval Supplement (PAS) to your NDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA ######
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA ######/S-000
PROPOSED REMS MODIFICATION-AMENDMENT

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

In addition to submitting the proposed modified REMS as described above, submit the REMS document in Structured Product Labeling (SPL) format as described 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.