

ANDA 200652/S-007

**CHANGES BEING EFFECTED  
APPROVAL**

Hikma Pharmaceuticals USA Inc.  
1809 Wilson Rd.  
Columbus, OH 43228  
Attention: Suzanne McLeod for James Connell  
Associate Director, Drug Regulatory Affairs

Dear Sir or Madam:

This is in reference to your supplemental abbreviated new drug application (sANDA) received for review on August 20, 2021, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for alosetron hydrochloride tablets.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The sANDA, submitted as “Changes Being Effected in 30 Days,” provides for proposed modifications to the approved Alosetron REMS Program.

We have completed the review of this sANDA and it is **approved**.

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

Your proposed modifications to the REMS consists of:

- Updates to the REMS Letter to Healthcare Providers to remove information related to program changes that were made in 2016, as that information is no longer relevant to prescribers becoming newly trained
- Changes to the REMS call center hours
- Removing the option for prescribers to mail the Prescriber Completion of Training Form

Your REMS, received on August 20, 2021, is approved and will be posted on the FDA REMS website: <http://www.fda.gov/remis>.

The modified REMS for **alosetron** consists of a elements to assure safe use.

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

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether

the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

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:

**ANDA 200652 REMS CORRESPONDENCE**  
(insert concise description of content in bold capital letters, e.g.,  
**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY**

We remind you that 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 FD&C Act.

We remind you that section 505-1(f)(8) of the FD&C Act 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) of the FD&C Act. A violation of this provision in 505-1(f) of the FD&C Act 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:

**ANDA 200652 REMS ASSESSMENT**  
  
**NEW SUPPLEMENT FOR ANDA 200652/S-000/  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR ANDA 200652/S-000/  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR ANDA 200652/S-000/  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

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 ANDA 200652**

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 REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email [REMSWebsite@fda.hhs.gov](mailto:REMSWebsite@fda.hhs.gov).

**REPORTING REQUIREMENTS**

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

If your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts, we remind you that you must comply with the postmarketing safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>.

## **ANNUAL FACILITY FEES**

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions<sup>1</sup> with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

If you have any questions, call CAPT Stacy Barley, REMS Coordinator, at (301) 796-2137.

Sincerely,

*{See appended electronic signature page}*

Howard Chazin, MD MBA  
Director  
Division of Clinical Safety and Surveillance  
Office of Safety and Clinical Evaluation  
Office of Generic Drugs  
Center for Drug Evaluation and Research

## APPENDIX 1

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<sup>1</sup> Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).  
U.S. Food & Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20903  
[www.fda.gov](http://www.fda.gov)

## Dates for submission of waiver-granted REMS assessments

The Alosetron Sponsors will submit REMS Assessments to FDA 18 months following the REMS modification approval on January 7, 2016, and every 12 months thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. The Alosetron Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

## Alosetron REMS Assessment Plan

The purpose of the Alosetron REMS Program assessments is to evaluate the effectiveness of the mitigation strategies associated with meeting the goals of the REMS. Findings from these evaluations will be used to improve program processes over time as needed.

1. Results of an evaluation of whether patients received counseling from the prescriber, the patients' understanding of the serious risks of ischemic colitis and serious complications of constipation associated with alosetron, and the actions patients need to take should they experience early warning signs and symptoms of these risks.
2. Results of an evaluation of prescriber understanding of the appropriate patient population, the risks of ischemic colitis and serious complications of constipation associated with alosetron, and the importance of counseling patients about these risks. The evaluation will include a comparison of prescribers who completed training and prescribers who have not reported completion of training.
3. The number of prescribers and the medical specialty of prescribers who reported that they completed training in the Alosetron REMS Program, including the number and medical specialty of prescribers contacted by the Alosetron Sponsors to become trained after prescribing alosetron, during the reporting period and cumulative.
4. The number of prescribers who have not completed training and are writing prescriptions for an alosetron product.
5. Numbers of prescriptions dispensed by year for the last five years and annually thereafter.
6. Number of cases of the following events reported (from any source) during the reporting period and cumulative:
  - All reports of ischemic colitis
  - All reports involving ischemic changes, ischemia, or necrosis of the colon
  - All reports involving constipation requiring hospitalization or emergency room visit
  - All reports involving possible complications of constipation such as obstruction, perforation, intestinal ulceration, toxic megacolon, ileus, or impaction resulting in hospitalization or emergency room visit
  - All reports of death, regardless of causality

## APPENDIX 1

7. Summary and discussion of the above cases (received during the reporting period) and the clinical significance of these events
8. An assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified

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**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.**  
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/s/  
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HOWARD D CHAZIN  
10/18/2021 09:19:35 AM