



NDA 204684/S-006

**SUPPLEMENT APPROVAL  
FULFILLMENT OF POSTMARKETING  
REQUIREMENTS**

Knight Therapeutics (USA) Inc.  
c/o Fast-Track Drugs and Biologics, LLC  
Attention: Bernadette Tock, MS  
Applicant Representative  
20010 Fisher Avenue, Suite G  
Poolesville, MD 20837

Dear Ms. Tock:

Please refer to your supplemental new drug application (sNDA) dated June 28, 2019, received June 28, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for IMPAVIDO (miltefosine) capsule, 50 mg.

This Prior Approval supplemental new drug application provides for updates to the prescribing information (PI) to be in compliance with the requirements of the Pregnancy and Lactation Labeling Rule (PLLR). Additionally, this supplement provides for revisions to the PI based on the results of postmarketing requirements (PMRs) #2127-2 and #2127-3, listed in the NDA approval letter dated March 19, 2014. The PMRs evaluated the effects of IMPAVIDO on spermatogenesis and male hormones [#2127-2] and the effects of IMPAVIDO on the QT interval [#2127-3].

Specifically, revisions have been made to the following sections of the PI: **HIGHLIGHTS, BOXED WARNING, DOSAGE AND ADMINISTRATION (2), CONTRAINDICATIONS (4), Pregnancy (4.1) subsection, WARNINGS AND PRECAUTIONS (5), Embryo and Fetal Toxicity (5.1), Impaired Semen Quality and Impaired Spermatogenesis (5.2), Female Reproductive Effects (5.3), and Absorption of Oral Contraceptives (5.4) subsections, ADVERSE REACTIONS (6), Clinical Trials Experience (6.1) subsection, USE IN SPECIFIC POPULATIONS (8), Pregnancy (8.1), Lactation (8.2) and Females and Males of Reproductive Potential (8.3) subsections, CLINICAL PHARMACOLOGY (12), Pharmacodynamics/Cardiac Electrophysiology (12.2) subsection, NONCLINICAL TOXICOLOGY (13), Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1) subsection, and PATIENT COUNSELING INFORMATION (17).**

Additionally, the Medication Guide has been updated to reflect the revisions in the PI and minor editorial changes have been made throughout the labeling.

## **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](http://FDA.gov).<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, 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*.<sup>2</sup>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **FULFILLMENT OF POSTMARKETING REQUIREMENTS**

We have received your submissions dated March 11 and 19, 2019, containing the final reports for the following PMRs listed in the March 19, 2014, approval letter.

2127-2      Conduct a study to evaluate the effects of Impavido (miltefosine) on spermatogenesis and male hormones in patients with leishmaniasis receiving Impavido (miltefosine) treatment. Evaluations will include semen volume, sperm count, sperm concentration and motility as well as evaluation of total testosterone and FSH.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> 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>.

2127-3 Conduct a dedicated QT study in leishmaniasis patients receiving Impavido (miltefosine) treatment to evaluate the effects of Impavido (miltefosine) on the QT interval. ECGs and PK samples will be obtained to identify potential effects of Impavido (Miltefosine) on the QT interval or other ECG parameters.

We have reviewed your submissions and conclude that the above requirements were fulfilled.

We remind you that there is a postmarketing requirement and postmarketing commitments listed in the March 19, 2014, approval letter that are still open.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.<sup>3</sup>

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at [FDA.gov](http://FDA.gov).<sup>4</sup> Information and Instructions for completing the form can be found at [FDA.gov](http://FDA.gov).<sup>5</sup>

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

### **REPORTING REQUIREMENTS**

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

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<sup>3</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

<sup>4</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

*{See appended electronic signature page}*

Sumathi Nambiar, MD, MPH  
Director  
Division of Anti-Infectives  
Office of Infectious Diseases  
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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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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