



NDA 018907/S-007

SUPPLEMENT APPROVAL

Hikma Pharmaceuticals USA Inc.
Attention: Karen D. Deuter
Senior Specialist, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, NJ 08003

Dear Ms. Deuter:

Please refer to your supplemental new drug application (sNDA) dated and received September 24, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Metronidazole Injection, 5 mg/mL.

We also refer to our letter dated September 01, 2021, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for nitroimidazole products. This information pertains to the risk of irreversible hepatotoxicity/acute liver failure with fatal outcomes in patients with Cockayne syndrome.

This supplemental new drug application provides for revisions to the labeling for Metronidazole Injection consistent with our September 01, 2021, safety labeling change notification letter.

The **CONTRAINDICATIONS** section was revised to state that Metronidazole Injection is contraindicated in patients with Cockayne syndrome. Additionally, the **Hepatic** subsection of the **ADVERSE REACTIONS** section was updated to reflect this change.

Additionally, other requested changes not required under section 505(o)(4) added to the prescribing information to make it consistent with other metronidazole labeling are listed below:

CONTRAINDICATIONS section was revised to add:

Psychotic Reaction with Disulfiram

Use of oral metronidazole is associated with psychotic reactions in alcoholic patients who were using disulfiram concurrently. Do not administer metronidazole to patients who have taken disulfiram within the last two weeks (see PRECAUTIONS-Drug Interactions).

Interaction with Alcohol

Use of oral metronidazole is associated with a disulfiram-like reaction to alcohol, including abdominal cramps, nausea, vomiting, headaches, and flushing. Discontinue consumption of alcohol or products containing propylene glycol during and for at least three days after therapy with metronidazole (see PRECAUTIONS-Drug Interactions).

Also, the **PRECAUTIONS** section was revised to add the following under **Drug Interactions**.

Disulfiram

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks (see CONTRAINDICATIONS).

Alcoholic Beverages

Abdominal cramps, nausea, vomiting, headaches and flushing may occur if alcoholic beverages or products containing propylene glycol are consumed during or following metronidazole therapy (see CONTRAINDICATIONS).

APPROVAL & LABELING

We have completed our review of this application. 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), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. If the content of labeling in SPL format initially submitted with this CBE-0 labeling supplement is identical to the attached approved labeling, an additional submission of content of labeling in SPL format is not required.

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

The SPL will be accessible from publicly available labeling repositories.

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>.

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).

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).

If you have questions, call Maureen Dillon-Parker, MS, RAC, Chief, Regulatory Project Management Staff, at (301) 796-0706.

Sincerely,

{See appended electronic signature page}

Dmitri Iarikov, MD, PhD
Deputy Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
 - Prescribing Information

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/

DMITRI IARIKOV
12/15/2021 08:55:23 AM