NDA 214429/S-003
NDA 214429/S-004

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
c/o Sanofi US Services Inc.
Attention: Stephen Canning
Manager, Global Regulatory Affairs, North America and Global Regulatory Affairs
450 Water Street
Cambridge, MA 02141

Dear Stephen Canning:

Please refer to your supplemental new drug applications (sNDAs) dated and received March 22, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fexinidazole tablets.

These Prior Approval sNDAs propose to update Prescribing Information (PI) for Fexinidazole tablets based on results of studies from Postmarketing Requirements (PMRs) 3952-2 [S-004] and 3952-3 [S-003]. The updates made to the PI were as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION

a. **RECENT MAJOR CHANGES:** Listed the Contraindications heading, because substantive changes were made to this section in the **FULL PRESCRIBING INFORMATION**.
b. **CONTRAINDICATIONS:** Added the word "severe" to the previous contraindication for hepatic impairment text.

FULL PRESCRIBING INFORMATION:

1) **CONTRAINDICATIONS (4)** section: Revised the contraindication for patients with hepatic impairment text to apply to "severe" hepatic impairment only.
2) **DRUG INTERACTIONS (7)** section, **Pharmacokinetic Drug Interactions (7.2)** subsection, **Table 3: Effect of Fexinidazole on other Drugs**
   a. **Drugs Metabolized by Cytochrome P450 (CYP) 3A4/5:** Under the *Clinical Impact* heading**,** added the statement "Fexinidazole is considered a moderate CYP3A4/5 inducer." Revised the risk statement to indicate a risk of reduced efficacy associated with decreased systemic exposures of the CYP3A4/5 substrate drug (s) when co-administered with Fexinidazole Tablets, due to induction of CYP3A4/5. Under the *Prevention or Management* heading, updated and added recommendations regarding concomitant use of Fexinidazole Tablets with CYP3A4/5 substrates and contraceptives, respectively.

b. **Drugs Metabolized by uridine 5'-diphospho – glucuronosyl transferase (UGT):** Added a new "Drugs Metabolized by uridine 5'-diphospho – glucuronosyl transferase (UGT)" section to Table 3.

3) **USE IN SPECIFIC POPULATIONS (8)** section, **Hepatic Impairment (8.7)** subsection: Updated with clinical recommendations for each hepatic impairment group.

4) **CLINICAL PHARMACOLOGY (12)** section, **Pharmacokinetics (12.3)** subsection:

a. Specific Populations:
Hepatic Impairment**:** Revised section to include information regarding hepatic impairment study, changed "patients" to "subjects", and added cross-reference to section 4 Contraindications.

b. Drug Interaction Studies**:**

- *In vitro* studies*: Cytochrome P450 (CYYP450) and UDP-glucuronosyl transferase (UGT) Enzymes:* Revised subsection heading to include "UDP-glucuronosyl transferase (UGT) Enzymes." Revised paragraph to clarify the induction potential for fexinidazole, and its metabolites M1 and M2.
- Clinical studies: Added paragraph detailing findings from a clinical drug-drug interaction study with midazolam. Moved statement regarding moderate induction of CYP3A4/5 to subsection 7.2. Added parenthentical statement, "not an approved dosing regimen" for clarification of the fexinidazole tablet dose administered in the study.

Additionally, minor editorial updates were made throughout the PI.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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.

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.

Also within 14 days, amend all pending supplemental applications that include labeling changes for these sNDAs, 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 these supplemental applications, 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).

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.*[3]

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.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the

[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.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

important new safety-related 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).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, contact Alison Rodgers, Senior Regulatory Project Manager, at 301-796-0797 or alison rodgers@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE(S):

- 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
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