NDA 50797/S-026

**SUPPLEMENT APPROVAL**

Pfizer, Inc.
Attention: Sushma Hirani
Senior Director, Pfizer Global Regulatory Affairs
235 East 42nd Street (MS 219/9/21)
New York, NY 10017-5755

Dear Ms. Hirani:

Please refer to your supplemental new drug application (sNDA) dated and received July 09, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for for Zmax (azithromycin extended release) for oral suspension, 2 g.

We also refer to our letter dated June 10, 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 azithromycin products. This information pertains to the risk of cardiovascular death.

The agreed upon changes to the language included in our June 10, 2021, letter are as follows. New additions are noted by underline and deletion are noted by ~~strikethrough~~.

**Prescribing Information**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**Recent Major Changes**

Warnings and Precautions, Cardiovascular Death (5.5) 11/2021

**WARNINGS AND PRECAUTIONS**

(b) (4)

Cardiovascular Death: Some observational studies have shown an approximately two-fold increased short-term potential risk of acute cardiovascular death in adults exposed

to azithromycin relative to other antibacterial drugs, including amoxicillin. Consider balancing this potential risk with treatment benefits when prescribing Zmax. (5.5)

**FULL PRESCRIBING INFORMATION-CONTENTS**

**5.5** Cardiovascular Death

**FULL PRESCRIBING INFORMATION**

**5. WARNINGS AND PRECAUTIONS**

**5.5 Cardiovascular Death**

(b) (4)

Some observational studies have shown an approximately two-fold increased short-term potential risk of acute cardiovascular death in adults exposed to azithromycin relative to other antibacterial drugs, including amoxicillin. The five-day cardiovascular mortality observed in these studies ranged from 20 to 400 per million azithromycin treatment courses. This potential risk was noted to be greater during the first five days of azithromycin use and does not appear to be limited to those patients with preexisting cardiovascular diseases. The data in these observational studies are insufficient to establish or exclude a causal relationship between acute cardiovascular death and azithromycin use. Consider balancing this potential risk with treatment benefits when prescribing Zmax.

**6 ADVERSE REACTIONS**

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Infantile Hypertrophic Pyloric Stenosis (IHPS) *[see Warnings and Precautions (5.3)]*
- QT Prolongation *[see Warnings and Precautions (5.4)]*
- Cardiovascular Death *[see Warnings and Precautions (5.5)]*
- *Clostridioides difficile*-Associated Diarrhea (CDAD) *[see Warnings and Precautions (5.6)]*
- Exacerbation of Myasthenia Gravis *[see Warnings and Precautions (5.7)]*

### 6.2 Postmarketing Experience with Other Azithromycin Products

*Cardiovascular:* Arrhythmias including ventricular tachycardia and hypotension. There have been reports of QT prolongation, (b) (4) *torsades de pointes,* and cardiovascular death.

**Patient Information**

**What are the possible side effects of ZITHROMAX?**

(b) (4)

**Serious heart rhythm changes that can be life-threatening, including heart stopping (cardiac arrest), QT prolongation, torsades de pointes, feeling that your heart is pounding or racing (palpitations), chest discomfort, or irregular heartbeat.**

Tell your healthcare provider right away if you or your child feel a fast or irregular heartbeat, get dizzy or faint.

**Other labeling changes unrelated to the FDAAA SLC**

**ADVERSE REACTION (6)** section **, Postmarketing Experience with Other Azithromycin Products (6.2)** subsection was revised to harmonize the prescribing information (PI) with other azithromycin labeling

**PATIENT COUNSELING INFORMATION (17)** and **Patient Information** was revised to substitute the word “doctor “ with the “healthcare provider”.

**Patient Information** section was revised to add the following to harmonize the Patient Information with other azithromycin labeling .

Zmax may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:

- who are elderly
- with a family history of prolonged QT interval
- with low blood potassium
- who take certain medicines to control heart rhythm (antiarrhythmics)

In addition, *Clostridium difficile* was replaced with *Clostridioides difficile* in the PI. Minor editorial revisions were also 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.

## 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, Patient Package Insert), 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 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).

## REPORTING REQUIREMENTS

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

[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.

If you have any questions, call Jacquelyn Rosenberger, PharmD, RAC, Regulatory Project Manager, at (301) 796-9179.

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(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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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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