NDA 50095/S-078

SUPPLEMENT APPROVAL

Akorn Operating Company LLC
Jean Poulos, MS, MBA
Head of Regulatory Affairs
5605 Centerpoint Court, Suite A
Gurnee, IL 60031

Dear Ms. Poulos:

Please refer to your supplemental new drug application (sNDA) dated and received November 14, 2022, and your amendment, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Capastat Sulfate (capreomycin for injection), 1 gram per vial.

We also refer to our letter dated November 03, 2022, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for Capastat Sulfate. This information pertains to the risk that Capastat Sulfate may be associated with worse clinical outcomes, i.e., decreased effectiveness and increased mortality, compared with other parenteral therapy for pulmonary multidrug-resistant tuberculosis (MDR-TB).

This supplemental new drug application provides for revisions to the labeling for Capastat Sulfate, consistent with our November 03, 2022, letter.

Specifically, the **BOXED WARNINGS, WARNINGS, ADVERSE REACTIONS** and **REFERENCES,** of **PRESCRIBING INFORMATION (PI)** were revised to add the following.

Addition = Double underline
Deletion = Strikeout

PRESCRIBING INFORMATION

BOXED WARNINGS
The use of Capastat® Sulfate may be associated with worse clinical outcomes, i.e., decreased effectiveness and increased mortality, compared with other parenteral therapy for pulmonary multidrug-resistant tuberculosis (MDR-TB) (see WARNINGS and ADVERSE REACTIONS). In patients who require parenteral treatment for pulmonary MDR-TB, reserve Capastat Sulfate for those with resistance to injectable aminoglycosides and limited treatment options.

WARNINGS
The use of Capastat Sulfate may be associated with worse clinical outcomes, i.e., decreased effectiveness and increased mortality, compared with other parenteral therapy for pulmonary multidrug-resistant tuberculosis (MDR-TB) (see ADVERSE REACTIONS). In patients who require parenteral treatment for pulmonary MDR-TB, reserve Capastat Sulfate for those with resistance to injectable aminoglycosides and limited treatment options.

ADVERSE REACTIONS
Increased Mortality and Decreased Effectiveness: The results of a meta-analysis of patient-level data from 12030 patients from 25 countries that included but was not limited to an evaluation of capreomycin (N=2401) for the treatment of pulmonary MDR-TB suggested that capreomycin may be associated with worse clinical outcomes, i.e., decreased effectiveness and increased mortality, compared with other parenteral therapy for pulmonary MDR-TB[3] (see WARNINGS AND REFERENCES).

REFERENCES
3.Cegielski JP, Chan PC, Lan Z, Udwadia ZF, Viiklepp P, Yim JJ, Menzies D. Aminoglycosides and Capreomycin in the Treatment of Multidrug-resistant Tuberculosis: Individual Patient Data Meta-analysis of 12 030 Patients From 25 Countries, 2009-2016. Clin Infect Dis. 2021 Dec 6;73(11):e3929-e3936.

Additionally, other requested changes not required under section 505(o)(4) of the FDCA have been made to the PI to revise the following:

BOXED WARNINGS
Use with ~~non-antituberculosis~~ other drugs (polymyxin A sulfate, colistin sulfate, amikacin, gentamicin, tobramycin, vancomycin, kanamycin, and neomycin) having ototoxic or nephrotoxic potential should be undertaken only with great caution.

~~**Usage in Pregnancy**: The safety of the use of Capastat Sulfate in pregnancy has not been determined.~~

~~**Pediatric Usage:** Safety and effectiveness in pediatric patients have not been established.~~

PRECAUTIONS
Usage in Pregnancy ~~— Pregnancy Category C~~
Safety in pregnancy has not been determined.

Capastat Sulfate has been shown to be teratogenic in rats when given in doses 3 1/2 times the human dose. There are no adequate and well-controlled studies in pregnant women. Capastat Sulfate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (*see ~~boxed~~* WARNINGS *~~and~~* ANIMAL PHARMACOLOGY).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established ~~(*see boxed WARNINGS*)~~

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), 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).

[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.

PROMOTIONAL MATERIALS

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 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 questions, call Sheel Shah, PharmD, Regulatory Project Manager, at 240-402-3968

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

- 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/

PETER W KIM
01/17/2023 08:49:05 AM