CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213645Orig1s000

OTHER ACTION LETTERS

NDA 213645

COMPLETE RESPONSE

Baxter Healthcare Corporation
Attention: Hiren Gadhiya, RAC
Manager, Global Regulatory Affairs
1 Baxter Parkway
Deerfield, IL 60015

Dear Mr. Gadhiya:

Please refer to your new drug application (NDA) dated June 30, 2020, received June 30, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for DAPZURA RT (daptomycin) for Injection.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

NON-CLINICAL

You have not adequately qualified the safety (i.e., general toxicity) of several of the leachables detected with your drug product.

The following are specific deficiencies and recommendations to address our concerns regarding several leachables detected with your drug product:

In your submission dated March 31, 2021, in response to an information request, you have not provided adequate safety information to support the qualification of the following leachables:

(b) (4)

Therefore, [redacted] (b) (4) we have insufficient data to conduct an independent safety review of these 5 leachable compounds identified in your leachables assessment (Study Report BXU562758).

Information needed to resolve the deficiency

- In the absence of adequate information in the published literature or public toxicological databases to support the safety of the identified leachables at the levels detected in your drug product, additional nonclinical qualification studies including repeated-dose toxicology studies are recommended for any leachable that exceeds the qualification threshold of 5 mcg/day. For example, you may consider conducting a toxicology study in one relevant animal species of 28-day duration using the API enriched with the identified leachables, administered in a clinically relevant manner at leachable levels equivalent or greater than what patients would be administered. Plan to include a justification for the species selected for this nonclinical study.
- If an additional nonclinical study is planned, we recommend that you submit a draft study protocol for the Agency to review prior to initiating any additional nonclinical studies. By providing a draft protocol for comment, the Agency will be better able to work with you on designing a study that can best inform the safety of the identified leachables when administered at clinically relevant exposures.
- A justification indicating that the leachables in the drug product to be administered to the animals is qualitatively and quantitatively similar to the identified leachables described in Study Report BXU562758.
- Plan to conduct additional (Q)SAR evaluation(s) for bacterial mutagenicity for any new leachables detected in any follow-up leachables testing that exceeds the 20 mcg/day qualification threshold. A follow-up Ames test (bacterial reverse mutation assay) is recommended to qualify leachables with any identified structural alerts for genotoxic potential.

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on our proposed revisions dated February 22, 2021.

PROPRIETARY NAME

Please refer to correspondence dated, December 9, 2020, which addresses the proposed proprietary name, DAPZURA RT. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial

response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Carmen DeBellas, Chief Regulatory Project Management Staff, at 301-796-1203.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:

- Content of Labeling
  - Prescribing Information

44 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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.

/s/

SUMATHI NAMBIAR
04/29/2021 06:16:24 PM