CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213895Orig1s000

OTHER ACTION LETTERS

NDA 213895

COMPLETE RESPONSE

Xellia Pharmaceuticals, ApS
c/o Xellia Pharmaceuticals USA, LLC
Attention: Edward Eichmann
Director, Regulatory Affairs
8841 Wadford Drive
Raleigh, NC 27616

Dear Mr. Eichmann:

Please refer to your new drug application (NDA) dated September 20, 2019, received September 20, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Vancomycin Injection, 5 g/100 mL.

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.

PRODUCT QUALITY and NONCLINICAL TOXICOLOGY

(1) Qualify all applicable leachables for the proposed vancomycin drug product. The acceptability of the proposed stopper cannot be determined until the identity and the safety profile of the leachables are considered acceptable from a nonclinical perspective. The data from the leachables study have not been submitted to the NDA.

(2) Provide a comprehensive toxicological risk assessment (e.g., local toxicity, systemic toxicity, mutagenicity, carcinogenicity, reproductive toxicity) for any leachable that exceeds 5 mcg/day. From a genetic toxicology perspective, 120 mcg/day is considered an acceptable daily intake of any leachable that contains a structural alert for mutagenicity for an acute indication (≤ 1 month). The risk assessment should be based on the levels of leachables detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Additional nonclinical studies may be required to qualify any leachables identified that exceed the safety thresholds. Refer to the publication “The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and

Ophthalmic Drug Product (PODP)"[1], and the ICH M7 Guideline on Genotoxic Impurities[2] for guidance on the evaluation of impurities relative to their genotoxic potential.

ADDITIONAL COMMENT

We have the following comment that is not an approvability issue:

We note that orally administered vancomycin products are associated with adverse reactions such as nausea, abdominal pain, and hypokalemia. When submitting a safety update for your NDA, provide a review of the safety of vancomycin administered intravenously and orally.

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. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include

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[1] http://journal.pda.org/content/67/5/430.full
[2] https://www.fda.gov/media/85885/download
[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[5]

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 Christopher L. Smith, PharmD, MPH, Regulatory Project Manager, at (301) 796-4851.

Sincerely,

{See appended electronic signature page}

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

[5] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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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
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