CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213593Orig1s000

OTHER ACTION LETTERS

NDA 213593

COMPLETE RESPONSE

Azurity Pharmaceuticals, Inc.
Attention: Michael C. Beckloff
Chief Development Officer
7300 W. 110th St, Ste 950
Overland Park, KS 66210

Dear Mr. Beckloff:

Please refer to your new drug application (NDA) dated March 30, 2020, received March 30, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for omeprazole and sodium bicarbonate for oral suspension.

We also acknowledge receipt of your amendments dated December 15, 2020 and January 8, 2021, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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

Based on our review of the chemistry, manufacturing, and controls information provided in the original submission and reviewed amendments, we find that the proposed control strategy is insufficient to assure the identity, strength, purity, quality, and bioavailability of the drug product as required by 21 CFR 314.50. Specifically, the submission lacks sufficient information to demonstrate that the proposed control strategy for the omeprazole and sodium bicarbonate active ingredients of this combination product meets the regulatory standard. The following deficiencies are noted:

(1) The strength of the active ingredient, sodium bicarbonate, in the drug product throughout the product shelf-life and during the in-use period is not adequately assured.

a. The suitability of proposed assay method for the active ingredient sodium bicarbonate (b) (4) has not been fully demonstrated. Specifically, (b) (4)

(b) (4) Thus, the method may be underestimating the amount of sodium bicarbonate at the high end and, more importantly, may be overestimating the amount of sodium bicarbonate at the low end.

b. There are no data demonstrating that the diluent and constituted suspension will consistently meet the requisite sodium bicarbonate assay acceptance criterion of 90.0% to 110.0% of the label claim (LC) at release and throughout the shelf-life. Similarly, there are no data to demonstrate that the constituted suspension will meet the 90.0% to 110.0% of the LC and throughout the 30-day in-use period.

(2) The strength and uniformity of the active ingredient omeprazole in the constituted suspension at release and on stability are not assured. Analytical procedure MET-CDM-000025 for omeprazole identification, assay, and within bottle uniformity, submitted on October 16, 2020 (SN 0027), differs from the assay procedure (b) (4) submitted in SN 0001)) used for analyzing the constituted suspension in the registration stability studies. Furthermore, the Analytical Method Validation Report (04-R-MV-18-026.01) submitted in SN0001 does not cover Method (b) (4). Additionally, the comparability of MET-CDM-000025 to (b) (4) has not been demonstrated.

(3) You have not established an in-process control for the (b) (4) (b) (4)

To Address These Deficiencies,

(1) Revise the specifications for the diluent and the constituted oral suspension to include the tests, analytical procedures, and acceptance criteria for the identification and assay of the active ingredient (API) sodium bicarbonate. Update Diluent section 3.2.P.5.1 and Kit (Constituted Suspension) section 3.2.P.5.1 accordingly.

(2) Provide evidence that analytical procedure (b) (4) is suitable for the intended use by demonstrating that the range of recoveries does not significantly overestimate or underestimate the bicarbonate measurement. Alternatively, revise the method to minimize the wide range in percent recovery.

(3) Provide method validation reports for omeprazole assay procedures (b) (4) MET-CDM-000025, and provide evidence of the comparability of the results obtained using each test.

(4) Submit batch release data and a minimum of 6 months of long-term and accelerated stability data from at least one batch of each filling configuration (90 mL, 150 mL and 300 mL) of the diluent and the constituted suspension. Testing should be performed per the revised specifications that include the identification and assay of sodium bicarbonate. The drug product batches should be packaged in the to-be-marketed container closure systems and manufactured at no less than 1/10th of the intended commercial scale. Submit in-use stability data for suspensions prepared from each of these stability batches.

(5) The above-mentioned diluent batches should be manufactured per the manufacturing process and the revised control strategy including (b) (4) Submit representative batch record in 3.2.R and update the corresponding sections of 3.2.P.3.3 if there is any change made (See Item #6 below).

(6) To address Deficiency #3, provide the sampling plan (sampling number and the locations) and the acceptance criteria supported by batch data and in line with the acceptance criteria at the product release. Update 3.3.P.3.4 accordingly and include the in-process testing results.

CLINICAL

(b) (4)

(2) The information provided in this NDA and reviewed amendments is not adequate to support the proposed indication of “reduction of risk of upper gastrointestinal bleeding in critically ill patients”. Data to support administration of omeprazole and sodium bicarbonate for oral suspension via nasogastric and orogastric tube is necessary to support this indication.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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 updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3] Please refer to the initial comments sent December 22, 2020.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on our proposed revisions dated January 8, 2021.

PROPRIETARY NAME

Please refer to correspondence dated November 25, 2020, which addresses the proposed proprietary name, Konvomep. 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 product 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:

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

- 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 product. Include an updated estimate of use for product marketed in other countries.

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

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

(1) With regard to the test for particle size distribution of the constituted suspension (Proc. No. 20-12-SP-2972), address the following comments.

a. Provide a copy of Method Development Report No. 19-012-80800-R01 "Method Optimization Report for Particle Size Distribution of Omeprazole Oral Suspension, 2 mg/ml."

b. [redacted] (b) (4) Provide evidence that the proposed conditions do not result in particle size reduction.

c. Provide particle size distribution data for the constituted suspension [redacted] (b) (4)

(2) Confirm the omeprazole bottle target fill weights and the diluent bottle target fill volumes required to prepare constituted suspensions meeting the label claim of 2 mg/mL omeprazole and 84 mg/mL sodium bicarbonate and the requisite deliverable volumes of 90, 150 and 300 mL, and provide clarification on how the target fill weights and volumes were determined.

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 Andrew Kelleher, PhD, Regulatory Project Manager, at (301) 796-9330 or email andrew.kelleher@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

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/

JESSICA J LEE
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