CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202049Orig1s000

OTHER ACTION LETTERS

NDA 202049

COMPLETE RESPONSE

Chiesi USA, Inc.
175 Regency Woods Place, Suite 600
Cary, NC 27518

Attention: Vicki Gunto, PhD
US Head of Regulatory Affairs, R&D-Pipeline

Dear Dr. Gunto:

Please refer to your new drug application (NDA) dated May 17, 2012, received May 18, 2012, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for mannitol inhalation powder, 40 mg.

We acknowledge receipt of your amendment dated December 19, 2018, which constituted a complete response to our March 18, 2013, action 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.

Clinical-Human Factor Studies

The submitted data from the human factors (HF) validation studies do not provide sufficient evidence to demonstrate that healthcare providers can reliably and accurately perform the Mannitol Tolerance Test (MTT) to correctly identify the intended target patient population. HF study results demonstrated several use errors and use difficulties with critical tasks in administering the MTT, which could result in healthcare providers prescribing the medication to patients who cannot tolerate mannitol inhalation powder. As inhaled mannitol is known to cause severe bronchospasm in susceptible individuals, this could result in patient harm (e.g. bronchospasm, hypoxia, pulmonary compromise) and is a significant safety concern.

To address this deficiency: (1) revise the product user interface to address the errors and use difficulties seen in your HF validation studies and (2) then conduct a supplemental HF validation study to demonstrate the effectiveness of the additional risk mitigations and to ensure that they address user interface concerns and do not introduce new risks.

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]

PROPRIETARY NAME

Please refer to correspondence dated, March 19, 2019, which addresses the proposed proprietary name, Bronchitol. 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:

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

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[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 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.

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 Ngoc-Linh Do, Regulatory Project Manager, at 301-348-1896.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Acting Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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/

SALLY M SEYMOUR
06/19/2019 12:18:05 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202049

COMPLETE RESPONSE

Pharmaxis Ltd.
1 E. Uwchlan Avenue, Suite 405
Exton, PA 19341

Attention: Ronald Dundore, Ph.D.
Vice President, US Regulatory Affairs

Dear Dr. Dundore:

Please refer to your New Drug Application (NDA) dated May 17, 2012, received May 18, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bronchitol (mannitol) Inhalation Powder.

We acknowledge receipt of your amendments dated, May 31, June 6, 15, 22, and 29, July 13, August 2, 17, and 24, September 6, 19, and 27, October 12, November 14, 27, and 29, and December 19, 2012, and February 8, 2013.

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.

CLINICAL

The submitted data do not provide a favorable benefit-risk balance to support the use of inhaled mannitol in patients with cystic fibrosis 6 years of age and older. The determination of efficacy based on the two submitted trials are not adequate because of the treatment-related frequent early dropouts in trial 301 for which the primary statistical analyses did not account and the lack of statistical significance in trial 302 for the primary endpoint. Sensitivity analyses conducted on data from study 301 either fail to confirm a treatment effect on the primary efficacy or are problematic in that they attribute a good outcome to some patients who discontinue treatment or they impute a single score without accounting properly for variability. In addition, there was lack of support for efficacy from secondary endpoints in both the studies. Assessment of safety findings show that, compared to control, subjects treated with mannitol 400 mg had a high occurrence of hemoptysis, particularly in pediatric patients, which is concerning and does not balance favorably with the submitted efficacy data, especially in the pediatric population.

To support approval of inhaled mannitol for the treatment of cystic fibrosis, conduct a clinical program including at least one adequate clinical trial to show substantial evidence of efficacy in patients with cystic fibrosis and balancing safety findings. In order to better balance benefit to

risk, consider:1) changing the threshold for passing for the mannitol tolerance test to make it more conservative, 2) including a lower dose of mannitol in addition to the dose that was studied, and 3) testing efficacy and safety initially in adults and later in children informed by data from adults. In the clinical trial include specified criteria that address the specific safety concern of hemoptysis.

PRODUCT QUALITY

During an inspection on (b) (4), of the (b) (4) packaging and labeling facility for this application, our field investigator conveyed current Good Manufacturing Practices (cGMP) deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

6. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

FACILITY INSPECTIONS

During an inspection on (b) (4), of the (b) (4) packaging and labeling facility for this application, our field investigator conveyed current Good Manufacturing Practices (cGMP) deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

ADDITIONAL COMMENTS

We have the following additional comments and recommendations.

PRODUCT QUALITY

1. Revise the specifications for drug product delivered dose uniformity (DDU) to comply with the recommendations of the FDA guidance document for metered dose inhalers (MDI) and dry powder inhalers (DPI), e.g., 9 of 10 within 85-115% of labeled claim and 10 of 10 to be within 75-115% of labeled claim, with the average of all values within 85-115% of labeled claim.

2. We recommend that you explore the possibility of revising the drug product manufacturing process (b) (4) (b) (4) (b) (4) The results of stability data (refer to report RN-09-021-04 submitted in amendment dated November 29, 2012) indicate physicochemical changes occurring in the drug product (b) (4) (b) (4) (b) (4)

(b) (4)

3. We recommend tightening the processing and holding times for the drug product, with the minimum and maximum time defined for each manufacturing step, to minimize the (b) (4) In particular, substantially tighten the hold/processing time (b) (4) (b) (4)

4. We recommend that you perform a study and submit data demonstrating the through-life (e.g., beginning and end of use life) ruggedness of the to-be-marketed HR device. Include results of drug product tested with repeatedly dropped devices to investigate potential changes in the delivered dose uniformity (DDU) and APSD (b) (4) .

5. Critically evaluate the number of inhalers supplied for the delivery of (b) (4) capsules ((b) (4) (b) (4) in view of the results of the ruggedness study (refer to comment #3 above), and intermittent high drug delivery occurring due to powder accumulation in the device. We note a significant difference in the drug quantity delivered by the individual capsules over the course of (b) (4) doses (refer to Figure 3.2.P.2c). The intermittent high drug delivery is about six times more likely for doses # (b) (4) in comparison to doses # (b) (4) (b) (4) and by itself supports the use of more than one inhaler for the delivery of (b) (4) capsules. Provide data analysis and propose an adequate supply of inhalers to reliably deliver consecutive (b) (4) doses of medication to the patients. Your conclusions need to be supported by the dose performance data, including APSD and be adequately addressed in the labeling, especially in the instructions for patients.

6. We do not recommend extension of the (b) (4) months expiry period *via* the annual report, (b) (4) Until these changes are adequately addressed (refer to comment #1, above) and subsequent manufacturing experience is gained we recommend that the drug product expiry be limited to NMT (b) (4) months with (b) (4)

7. Revise the post-approval stability protocol to include testing for the assay and the (b) (4)

content for the 3 months time point, since the submitted stability data indicate (b) (4)
(b) (4)

8. We acknowledge your statement provided in the NDA amendment dated November 29, 2012, to submit a validated improved method for the foreign particulate matter and data-based acceptance criteria.

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 the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA 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 NDA 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. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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 FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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 Angela Ramsey, Senior Program Management Officer, at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Division of Pulmonary, Allergy, Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
03/18/2013