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APPLICATION NUMBER:

203629Orig1s000

OTHER ACTION LETTERS



NDA 203629

COMPLETE RESPONSE

Fresenius Kabi USA, LLC
1501 E. Woodfield Road, Suite 300 East
Schaumburg, IL 60173

Attention: Dale Carlson
Senior Director, Regulatory Affairs

Dear Mr. Carlson:

Please refer to your New Drug Application (NDA) dated December 28, 2011, received December 29, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Neostigmine Methylsulfate Injection, USP.

We acknowledge receipt of your amendments dated January 13 and 20, March 7 and 21, April 11, June 4 and 15, July 31, August 29, September 12, 14 and 27, and November 30, 2012.

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.

FACILITY INSPECTIONS

During a recent inspection of the Grand Island, New York, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

LABELING

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>.

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.

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 203629 for neostigmine methylsulfate injection is approved, you will be required to conduct the following:

1. An in vitro or in vivo assay using mammalian cells for chromosomal damage for neostigmine methylsulfate
2. If you conducted an in vivo assay to address Number 1 above, conduct a second different in vivo assay for chromosomal damage for neostigmine methylsulfate. Otherwise

conduct an in vivo assay for chromosomal damage for neostigmine methylsulfate. Note that, in order to address PMRs 1 and 2, you may refer to the options outlined in ICH S2(R1) titled “Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use” and propose an adequate battery of genetic toxicology studies.

3. A fertility and early embryonic development toxicology study in the rat model for neostigmine methylsulfate
4. An embryo-fetal developmental toxicology study using the rat model for neostigmine methylsulfate
5. An embryo-fetal developmental toxicology study using the rabbit model for neostigmine methylsulfate
6. A peri-and post-natal developmental toxicology study in the rat model for neostigmine methylsulfate
7. An adequate extractable/leachable safety assessment for the [REDACTED] (b) (4) [REDACTED] gray [REDACTED] (b) (4) rubber stopper used in your container closure system – This assessment must include controlled extraction studies to qualitatively and quantitatively determine the chemical species which may migrate into the dosage form, using appropriate solvents that adequately represent the chemical characteristics of the drug product formulation, and leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified/specified extractables also leach into the drug product over time, and a toxicological risk assessment justifying the safety of the extractables and leachables taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed 1.5 mcg/day total daily exposure or it will need to be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds 5 mcg/day.

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>.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction 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/

BOB A RAPPAPORT
01/29/2013