



NDA 203629

NDA APPROVAL

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 (FDCA) for Neostigmine Methylsulfate Injection, 0.5mg/mL and 1 mg/mL.

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, and January 31, April 26, and October 14, 2013, and January 27, February 28, March 12, July 11, August 29, October 29, and December 12, 19, and 22, 2014.

The July 11, 2014, submission constituted a complete response to our January 29, 2013, action letter.

Reference is also made to your email dated January 8, 2015, which included the final agreed upon labeling.

This new drug application provides for the use of Neostigmine Methylsulfate Injection for reversal of the effect of nondepolarizing neuromuscular blocking agents (NMBA) after surgery.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your December 22, 2014, submission containing final printed carton and container labels.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Allison Meyer
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3176
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in all relevant pediatric populations. Therefore, no additional pediatric studies are needed at this time.

POSTMARKETING REQUIREMENTS UNDER 505(o)

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.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of reproductive/developmental and/or genetic toxicity associated with potential extractables and leachables into the Neostigmine Methylsulfate Injection drug product.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to identify an unexpected serious risk of reproductive/developmental and/or genetic toxicity.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2855-1 Conduct an adequate extractable/leachable safety assessment for the (b) (4) [redacted] gray (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 that may migrate into the dosage form, using appropriate solvents that adequately represent the chemical characteristics of the drug product formulation. Additionally, leachable data from long-term stability studies (taking into consideration the proposed shelf-life) should be used to determine if the identified/specified extractables also leach into the drug product over time. Using this information, conduct 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 (b) (4) mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day.

The timetable you submitted on December 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2015
Study Completion:	01/2015
Final Report Submission:	01/2015

Submit the protocol(s) to your IND 106574, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under Section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA Section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

EXPIRATION DATING PERIOD:

A 24-month expiry dating period is granted for Neostigmine Methylsulfate Injection 0.5mg/mL and 1 mg/mL, when stored at 20° to 25°C (68° to 77°F) [see USP].

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

RIGOBERTO A ROCA
01/08/2015