CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203629Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	January 8, 2015
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	203629/S-000
Applicant Name	Fresenius Kabe, USA
Date of Original Submission	December 28, 2012 Complete Response letter issued January 29, 2013 (included a 3-month clock extension)
Date of Complete Response Submission	July 11, 2014
PDUFA Goal Date	January 11, 2015
Proprietary Name / Established (USAN) Name	Neostigmine Methylsulfate Injection, USP
Dosage Forms / Strength	10 mL multiple dose vials / 0.5 mg/mL and 1 mg/mL
Proposed Indication(s)	Reversal of non-depolarizing neuromuscular blockade after surgery.
Action	Approval

Material Reviewed/ Consulted OND Action Package, including:	
Medical Officer Review	Arthur Simone, MD, PhD
Pharmacology Toxicology Review	Huiqing Hao, PhD; R. Daniel Mellon, PhD
ONDQA Review	Julia Pinto, PhD
ONDQA Biopharmaceutics Review	Minerva Hughes, PhD; Okponanabofa Eradiri, PhD
Clinical Pharmacology Review	David Lee, PhD; Yun Xu, PhD
Project Management Staff	Allison Meyer; Parinda Jani
OMP/OPDP	Jessica Fox, PharmD
OSE/DMEPA	Vicky Borders-Hemphill, PharmD; Millie Brahmbhatt, PharmD

DMEPA = Division of Medication Error Prevention and Analysis
OMP = Office of Medical Policy
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assessment
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, Fresenius Kabe, has submitted a complete response to the action letter issued on January 29, 2013. Although several issues had been identified during the course of the review, at the end of the first review cycle all had been satisfactorily resolved except for one: product quality. As noted in Dr. Rappaport's Division Summary of January 29, 2013, the routine inspection had identified systemic problems at the manufacturing plan, and the final decision was that the NDA could not be approved at that time.

The Applicant is utilizing the 505(b)(2) regulatory pathway, as the support for the application is largely based on published literature of nonclinical and clinical data (including clinical pharmacology).

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

Neostigmine was first synthesized over 80 years ago. The following scientific and clinical background information is reproduced from Dr. Rappaport's review, which in turn has incorporated information from Dr. Simone's first cycle review:

> **Scientific Background**
>
> Neostigmine, an anticholinesterase agent first synthesized in 1931, competes with acetylcholine for binding to acetylcholinesterase and thereby inhibits the hydrolysis of acetylcholine at sites of cholinergic transmission. At neuromuscular junctions, the neostigmine-induced reduction in the breakdown of acetylcholine facilitates neuromuscular transmission. Clinically, this effect of neostigmine has been used for the treatment or prevention of post-operative non-obstructive abdominal distention, i.e., adynamic ileus, the symptomatic treatment of myasthenia gravis and the reversal of nondepolarizing neuromuscular blocking agents (NMBAs).
>
> The proposed clinical use of neostigmine, i.e., reversal of neuromuscular blockade due to the administration of nondepolarizing blocking agents, is predicated on its pharmacological action. Specifically, nondepolarizing NMBAs induce paralysis by competing with acetylcholine at the postjunctional nicotinic receptors where they prevent changes in ion permeability of the skeletal muscle endplate and thereby prevent depolarization and subsequent contraction. Neostigmine, by inhibition of acetylcholinesterase, increases the amount of acetylcholine at the junction, which can compete with the NMBA and ultimately restore impulse transmission and skeletal muscle function.
>
> Neostigmine is associated with direct postsynaptic cholinomimetic effects that may be severe enough to warrant treatment with an anticholinergic agent such as atropine or glycopyrrolate. As the neostigmine-induced inhibition of acetylcholinesterase is fully reversible, in contrast to organophosphates, its cholinomimetic effects have limited duration.
>
> **Clinical Background**
>
> In general, the goal in reversing an NMBA is to expedite and assure the return of neuromuscular function to the extent that a patient is capable of maintaining a patent airway and an adequate level

of ventilation so that mechanical ventilation can be discontinued and the trachea extubated. In the clinical practice of anesthesia, a number of assessments are typically made to evaluate a patient's ability to carry out both of these functions. These assessments include:

- Mechanical responses of muscles to electrical stimulation of the motor nerves supplying them,
- Grip strength, which requires a level of consciousness that permits the patient to follow commands,
- Sustained head lift, for 5 or more seconds, which requires a level of consciousness that either allows the patient to follow commands or is associated with a return of the gag reflex,
- Spontaneous ventilation parameters, such as
    - Negative inspiratory force > -20 cm H2O
    - Tidal volume > 5 mL/kg
    - Vital capacity > 10 mL/kg
    - Respiratory rate < 30 breaths/min
    - Appropriate oxygen saturation and end-tidal CO2 levels

The clinical benefit of neostigmine lies in its ability to substantially reduce the recovery time from NMBAs. No clinical studies have been reported in the literature demonstrating a meaningful benefit for the reductions in recovery times observed with neostigmine. However, several potential benefits can be postulated and may be reasonably incorporated into the benefit risk analysis. These include reducing the risks associated with:

- Patient movement during the final stages of the surgical procedure including wound closure because the ability to reverse an NMBA permits maintaining paralysis through the end of surgery.
- Exposure to anesthetic agents required to maintain unconsciousness as they may be discontinued once paralysis has been reversed.
- Mechanical ventilation and the presence of an endotracheal tube as well as other airway management devices as they can be discontinued with return of spontaneous ventilation and maintenance of a patent airway.
- Delays in evaluation of neurological function, i.e., assess a patient's ability to move extremities, peripheral sensation, speech or cognitive function, following certain surgical procedures that can affect the nervous system, e.g., spine surgery, carotid endarterectomy.

At the end of the first review cycle, there were no nonclinical issues that would have precluded approval of the application. However, several nonclinical studies were identified as potential postmarketing requirements and included in the letter issued on January 29, 2013. These are reproduced below:

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 (b) (4) 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 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.

The Applicant has conducted studies in the interim between the issuance of the Complete Response letter and their resubmission to address six of these requirements, and included that information in the resubmission. This will be further discussed below, in Section 4 of this review.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The product is formulated as a sterile, (b) (4) solution. The following summary of the drug substance and drug product are reproduced from Dr. Jao's review from the first review cycle.

Drug Substance

The drug substance is neostigmine methylsulfate, USP. It is not a NME. The characterization of this compound has been well documented in the literature, and the manufacturer has adequately confirmed the structure of the drug substance they produced. While it contains structural alert moieties ((b) (4) and (b) (4)), it is not genotoxic based on non-clinical data (see pharmtox team review). Neostigmine Methylsulfate, USP is manufactured by (b) (4) The establishment received "Acceptable" recommendation from the Office of Compliance on 1/22/2012. This compound is prepared through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF (b) (4) which is considered adequate to support

this NDA. The proposed drug substance specification meets and exceeds that required by the USP monograph for neostigmine methylsulfate. The quality and stability of the registration batches of the drug substance Neostigmine Methylsulfate, USP are adequately demonstrated by release and stability data. The drug substance is packaged (b) (4). There are no safety concerns for the container/closure system. The proposed retest period of (4) months is supported by real time stability data.

Drug Product

The drug product is Neostigmine Methylsulfate Injection, USP, 0.5 mg/mL and 1.0 mg/mL, (b) (4) in 10 ml Type I USP glass vials, with rubber stopper and aluminum seal. Neostigmine Methylsulfate injection has been approved only for animal use (21CFR 522.1503), but not for human. Neostigmine Methylsulfate OPHTHALMIC SOLUTION was approved on 5/4/1939 (NDA 000654), but was withdrawn on 4/12/1996. Currently there are three companies marketing Neostigmine Methylsulfate injection (American Reagent, APP, and West-Ward Pharmaceuticals), and none of them have an approved NDA. Neostigmine Methylsulfate injection is on the drug shortage list. There is a current USP monograph for neostigmine methylsulfate injection. The excipients used in the formulation are liquefied phenol, sodium acetate, and water for injection. All the excipients are compendial. Liquefied Phenol (used as preservative) has been approved for IV drug product for up to 0.5% based on Inactive Ingredients database. There is no safety issue from CMC perspective.

Specific Issues Identified in the Course of the First Cycle Review

As noted above in the Introduction section, approval of the application during the first review cycle was precluded by the findings of the routine inspection of the manufacturing facilities. The following is reproduced from Dr. Rappaport's review of January 29, 2013:

Observations cited in Form 483 were related to various deficiencies observed in the (b) (4) insects and arachnids in the building, procedures not followed for cleaning and maintenance, etc. Although these observations were not specific to neostigmine, they suggest that there is no assurance that the neostigmine manufacturing area or line will be clean or without (b) (4) contamination, or that the product will be manufactured under GMP regulations having high quality standard. Based on these findings, the Compliance review team recommended a "Withhold" for this application. I concur with the review team that this product's quality has not been adequately established and, indeed, may be of sufficient concern to block distribution of the unapproved product.

Facilities Review/Inspections

The manufacturing facilities in Grand Island, New York, were re-inspected by the Office of Compliance. The deficiencies identified during the inspection conducted during the first review cycle were resolved, and the facilities were given an overall satisfactory recommendation on December 22, 2014.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Dr. Pinto regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding product issues at this time that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

As noted above, there were no nonclinical issues that precluded approval during the first review cycle. However, there were several nonclinical studies that would become post-marketing requirements (PMRs) if and when the application was to be approved, and these were conveyed

to the Applicant in the Complete Response letter of January 29, 2013. These studies, which are enumerated above, included genotoxicity studies, reproductive and developmental toxicology studies, and an extractable/leachable safety assessment of the rubber stopper used in the closure container system.

The Applicant has submitted the results from nonclinical studies to address the first six requests. The assessments of the data by the review team are reproduced below:

> Genotoxicity:
> The two submitted genotoxicity studies, an in vitro chromo aberration assay in human peripheral blood lymphocytes and an in vivo rat bone marrow micronucleus assay, were reviewed and the results suggest that neostigmine did not demonstrate genotoxic potential under the conditions of the studies.
>
> Based on these negative findings and negative finding in the Ames test that was previously reviewed (9/18/2013), neostigmine methylsulfate is not mutagenic or clastogenic.
>
> Reproductive and Developmental Toxicology:
> A standard battery of reproductive and developmental toxicology studies were submitted. All studies used the intravenous route to administer neostigmine methylsulfate as a daily bolus dose. The dose levels were 0, 10, 25, and 50 mcg/kg in rats; 0, 10, 25, and 40 mcg/kg in rabbits. The high dose tested, 50 mcg/kg in rats, 40 mcg/kg in rabbits were considered acceptable based on the treatment-related clinical finding of tremor/twitch following dose administration. There were no treatment-related adverse findings in the fertility and early embryonic development study in rats, embryonic fetal development study in rats and rabbits, or the pre- and post-natal development study in rats. NOAELs for reproductive toxicity were defined as 50 mcg/kg for the rat studies and 40 mcg/kg for the rabbit study. These NOAELs represent human equivalent doses (on a mg/m^2 basis) of 8.06 mcg/kg (rat data) and 12.9 mcg/kg (rabbit data).
>
> Compared to the maximum recommended human dose of 5 mg (83 mcg/kg for a 60 kg human body), these animal NOAELs are 6.5-10.3 times lower than the MRHD based on mg/m^2 basis. Therefore, these negative findings in reproductive toxicology studies are of limited clinical relevance.

The Applicant did not submit any data to address the extractable/leachable safety assessment of the rubber stopper used in the container closure system. This will be included in the action letter as a PMR.

Outstanding or Unresolved Issues
I concur with the conclusions reached by Drs. Hao and Mellon that there are no pharmacology/toxicology issues that would preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology data submitted with this submission. The clinical pharmacology review team had deemed the information submitted in the application acceptable during the first review cycle.

Outstanding or Unresolved Issues
I concur with the conclusions reached by Drs. Lee and Xu that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Neostigmine is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical – Efficacy

The Applicant did not submit any new data to address the efficacy of their product. Dr. Rappaport's review of January 29, 2013, clearly summarized the review team's assessment of the data that were reviewed during the first cycle. Dr. Rappaport concluded that the Applicant had provided sufficient evidence to support the conclusion that the product is effective for the proposed indicated use.

Outstanding or Unresolved Issues

I concur with the review team that the Applicant has provided sufficient evidence to support the conclusion that neostigmine is effective for the proposed indicated use: reversal of non-depolarizing neuromuscular blockade after surgery. There are no unresolved efficacy issues that would preclude approval.

8. Safety

The conclusion of the review team's assessment of the data submitted by the Applicant in the original submission was that the safety profile of neostigmine was well defined and that there were well-established clinical procedures to address the potential adverse events associated with the drug.

The Applicant was required, as per 21 CFR 314.50(d)(5)(vi)(b), to submit a safety update. The safety update consisted of a literature search to identify any new information since the last literature-based update conducted on October 21, 2013. The results of this literature search, and the assessment of the data contained in the articles, are well-summarized in Dr. Simone's review of December 16, 2014.

Dr. Simone's conclusions were that the articles did not provide any new information that significantly affected the previous determinations that the proposed doses were safe and effective when used for the proposed indication.

Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding or unresolved safety concerns that would preclude approval.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this NDA, as it is a product that has been used clinically for decades and there were no specific efficacy or new safety concerns noted at the time of filing or during the course of the review of the NDA.

10. Pediatrics

As noted in Dr. Breder's review conducted during the first review cycle, the Division presented the NDA to the Pediatric Review Committee (PeRC) on December 5, 2012, with the conclusion that the NDA contained sufficient information to permit pediatric labeling and that further studies would not likely result in any further refinement of the dosing guidance, or additional safety findings. This was based on the following rationale, which is reproduced from Dr. Breder's review:

> Pediatric efficacy
> The efficacy studies were similar in design to the studies conducted in adult patients and had similar limitations for deriving a uniform method of using neostigmine to reverse the effects of NMBs. Nonetheless, the findings for pediatric patients were similar to those for adults as they relate to when the drug should be given relative to the extent of spontaneous recovery, the range of dosing (by body weight) that should be administered, and the recovery times of the ToF ratios. The data indicate that neostigmine is equally efficacious across pediatric age groups when adult dosing paradigms are applied. Furthermore, the efficacy results were similar for the NMBs more commonly used in the pediatric patient population.
>
> Pediatric pharmacokinetics
> The available pharmacokinetic data indicate that PK parameters are similar across pediatric age groups and are also similar to those measured in adults.
>
> Pediatric Safety
> The safety findings reported in the published literature were limited and were supplemented by a review of available safety data in the literature and the AERS database by conducted by the Division of Pharmacovigilance 2. There were three key findings:
>
> 1. The reported adverse events for pediatric patients were similar to those observed in the adult population and were neither severe nor life-threatening.
>
> 2. No unexpected adverse events occurred in pediatric patients that raised a safety concern.
>
> 3. The use of anticholinergic agents (atropine and glycopyrrolate) counteracted the well-known and predictable effects of neostigmine at the sites of muscarinic cholinergic transmission occurring in the parasympathetic, postganglionic receptors of the autonomic nervous system (most notably bradycardia and bronchoconstriction). The timing of administration and dosing (by weight) of these agents in pediatric patients was the same as for adults;
>
> In light of this data, the Division had the following summary findings upon which it derived its recommendation to the PeRC:
>
> 1. The evidence supporting the use of 30 to 70 mcg/kg in the pediatric population is adequate. Dosing in the youngest group (0 to 3 months) seems to be similar to that of older pediatric age groups and adults.
>
> 2. Given the influence of confounding factors (different PK of different NMBs, different concomitant adjunctive medications used in anesthesia), further studies of

dosing for neostigmine in the pediatric population are not likely to result in a more refined dosing guidance than that which is proposed by the Sponsor.

3. Given the extensive monitoring of patients after neostigmine administration, which is detailed in the proposed labeling, further study in the pediatric population is not likely to result in the description of a safer paradigm of clinical use of neostigmine.

The PeRC concurred with the Division's assessment.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The review team had not engaged the Applicant in labeling discussions during the first review cycle.

As noted above, representatives from the Office of Surveillance and Epidemiology, and the Office of Prescription Drug Promotion, were consulted and their recommendations were incorporated during the discussion of the label during this review cycle.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval.

Risk:Benefit Assessment

I concur with the review team that the Applicant has submitted sufficient evidence to demonstrate the safety effectiveness of neostigmine when used as described in the approved labeling.

As noted in the review team's assessment during the first review cycle, the clinical utility of neostigmine is based on its ability to substantially reduce the recovery time from non-depolarizing neuromuscular blocking agents. Even though there are no clinical studies in the published literature that demonstrate a meaningful clinical benefit from such a reduction, there are several potential benefits that can be postulated. These include a reduction in the risks associated with the following:

1. Patient movement during the final stages of the surgical procedure including wound closure because the ability to reverse an NMB permits maintaining paralysis through the end of surgery.

2. Exposure to anesthetic agents required to maintain unconsciousness as they may be discontinued once paralysis has been reversed.

3. Mechanical ventilation and the presence of an endotracheal tube as well as other airway management devices as they can be discontinued with return of spontaneous ventilation and maintenance of a patent airway.

4. Delays in evaluation of neurological function, i.e., assess a patient's ability to move extremities, peripheral sensation, speech or cognitive function, following certain surgical procedures that can affect the nervous system, e.g., spine surgery, carotid endarterectomy.

Recommendation for Postmarketing Risk Management Activities

As noted above, based on the data submitted to date, the following study is to be completed as post-marketing requirement (PMR):

1. An extractable/leachable safety assessment of the rubber stopper used in the container closure system.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
01/08/2015