CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204078Orig1s000

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	May 31, 2013
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	204078/S-000
Applicant Name	Éclat Pharmaceuticals
Date of Submission	July 31, 2013
PDUFA Goal Date	May 31, 2013
Proprietary Name / Established (USAN) Name	Bloxiverz/ (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, M.D., Ph.D.
CDTL Review	Christopher D. Breder, M.D., PhD.
Pharmacology Toxicology Review	Huiqing Hao, Ph.D.; R. Daniel Mellon, Ph.D.
ONDQA Review	Arthur B. Shaw, Ph.D.; Prasad Peri, Ph.D.
ONDQA Biopharmaceutics Review	Elsbeth Chikhale, Ph.D.; Angelica Dorantes, Ph.D.
OPS/NDMS Microbiology Review	Erika Pfeiler, Ph.D.; Stephen Langille, Ph.D.
Clinical Pharmacology Review	Suresh Babu Naraharisetti, Ph.D.; Yun Xu, Ph.D.
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SEALD	Abimbola Adebowale, Ph.D.; Laurie Burke, R.Ph.

CDTL = Cross-Discipline Team Leader
DMEPA = Division of Medication Error Prevention and Analysis
DPV = Division of Pharmacovigilance
NDMS = New Drug Microbiology Staff
OMP = Office of Medical Policy
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assessment
OPS = Office of Pharmaceutical Sciences
OPSP = Office of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology
SEALD = Study Endpoints and Labeling Development

1. Introduction

The Applicant, Éclat Pharmaceuticals, has submitted a new drug application (NDA) for neostigmine for the following indication: reversal of neuromuscular blocking agents after surgery. 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). Neostigmine is a marketed unapproved product and, although the Applicant has never marketed the product, neostigmine has been marketed by other manufacturers for decades.

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. Breder's review, which in turn has incorporated information from Dr. Simone's 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.
>
> 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. Historically, most of the adverse events that are observed with this drug are a result of unopposed cholinomimetic effects.
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> **Clinical Background**
> Clinically, neostigmine has been used for the treatment or prevention of postoperative non-obstructive abdominal distention, i.e., adynamic ileus, the symptomatic treatment of myasthenia gravis, and the reversal of nondepolarizing neuromuscular blockers agents (NMBs).
>
> In general, the goal in reversing an NMB 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:
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> - 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 NMBs.

As noted in Dr. Breder's review, there are no reports in the medical literature of clinical studies demonstrating a meaningful benefit for the reductions in recovery times observed with neostigmine. Nevertheless, several potential benefits can be postulated, including 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.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

Bloxiverz is formulated as a sterile, non-pyrogenic solution. The following summary of the drug substance and drug product are reproduced from Dr. Shaw's review.

1. Drug Substance

The drug substance is a white, crystalline powder, freely soluble in water. It is covered by USP and EP monographs. It is a parasympathomimetic agent that acts as a reversible anticholinesterase inhibitor. Complete CMC information is included in DMF (b) (4), which was found acceptable in a review dated December 21, 2012 by Dr. Edwin Jao. The applicant performs their own testing for the receipt of the drug substance and the methods have been validated. The applicant has provided the synthetic procedure from the DMF holder, (b) (4), which shows that a known (b) (4) We recommend that the applicant commit to submit a Prior Approval Supplement if the DMF holder (b) (4) The DMF holder controls this compound at a level of (b) (4) in the finished drug substance and includes the amounts in their COA. This has been found acceptable by the pharm/tox team. All other impurities are well-controlled and present no safety issues. The drug substance is stable.

2. Drug Product

The drug product is a sterile, non-pyrogenic solution. There is a USP monograph for neostigmine methylsulfate injection and the product has been marketed without an NDA for many years. However there was an NDA for the same drug substance (NDA 654, Prostigmine Ophthalmic Solution) which was approved in 1939 and withdrawn in 1996. Therefore this has the Chemical Classification of 7 and 5. It is intended as a multi-use vial containing 10 mL of drug product at either 0.5 mg/mL or 1.0 mg/mL. The proposed dosing is 30 µg/kg. Additional doses, up to a total dose of 70 µg/kg (or 5 mg, whichever is less), may be given. Since this is a multi-use vial, phenol is added as a preservative (b) (4). In the Pharmaceutical Development (PD) report the applicant provided data to justify the choice of this preservative compared with others, (b) (4) The PD report also contains a study showing that (b) (4) causes degradation of the drug product and therefore the product is (b) (4). The entire Microbiology package, including the preservative effectiveness testing and the (b) (4) procedure, were found adequate in the Microbiologist's review dated 1/25/2013.

The solution is (b) (4) which are supplied (b) (4) The stoppers are covered in DMF (b) (4) which was found adequate.

The applicant evaluated extractables and potential leachables in the PD report and found one potential leachable, (b) (4), whose structure was confirmed by mass spectrometry. The applicant developed an assay to be used in stability studies for the compound, with an acceptance criterion of NMT (b) (4), which is the limit of quantitation. This level was found acceptable by the pharm/tox review team.

The drug product specifications are adequate to control the potency, impurities and microbiological quality. The applicant has provided sufficient stability data to support a 24 month expiration date.

The drug is stable when stored at (b) (4) for up to 12 months, which permits an expiration date of 24 months.

The product will be available in two strengths, 0.5 mg/mL and 1 mg/mL, and supplied in 10 mL vials in packages of 10.

Specific Issues Identified in the Course of the Review

There were three issues identified by ONDQA during the course of the review: the use of (b) (4); a potential leachable, (b) (4) and the osmolality of the solution. Below is a summary of the three issues and their resolution, as noted in Dr. Breder's review.

1. The applicant provided the synthetic procedure from the DMF holder, (b) (4) (b) (4) which showed that a (b) (4) The DMF holder controls this compound at a level of (b) (4) in the finished drug substance and includes the amounts in their COA. This was been found acceptable by the P/T team. They recommend that the applicant commit to submit a Prior Approval Supplement if the DMF holder (b) (4) (b) (4).

2. The applicant evaluated extractables and potential leachables in the PD report and found one potential leachable, (b) (4), whose structure was confirmed by mass spectrometry. The applicant developed an assay to be used in stability studies for the compound, with an acceptance criterion of not more than (b) (4) which is the limit of quantitation. This level was found acceptable by the P/T team.

3. Dr. Shaw noted that infusion of neostigmine at a maximum dose of 5 mg would result in administration of 5 mL of a 55 mOsmol/L solution. Dr. Simone (Clinical Primary Reviewer) indicated that plasma tonicity is about 285 mOsm/kg, and so the intended formulation of neostigmine would be, comparatively, very hypotonic Dr. Shaw also noted that a 70 kg adult would typically be given 3.5 mL of neostigmine for reversal as opposed to the (b) (4) claimed by the Applicant. However, Dr. Simone noted that 3.5 mL of neostigmine injected in an IV line with a more isotonic solution flowing through it (the usual situation in the perioperative setting) will mix rapidly with the carrier solution raising the tonicity of the injectate. Similarly, the solution emanating from the intravenous line rapidly mixes with blood when administered. Therefore, no tissue damage or hemolysis is expected. Dr Simone also reported that his review of the literature and the AERS database did not identify any evidence of either local tissue toxicity or hemolysis related to neostigmine administration.

Facilities Review/Inspections

Facilities inspections were completed by the Office of Compliance and by ONDQA and deemed to be acceptable.

Outstanding or Unresolved Issues

There are no outstanding issues and I concur with the conclusions reached by the ONDQA review team regarding the acceptability of the manufacturing of the drug product and drug substance.

4. Nonclinical Pharmacology/Toxicology

General Considerations

The Applicant was informed during the pre-IND/pre-NDA meeting of June 30, 2011, that no new nonclinical pharmacology or toxicology studies of the drug substance would be require for the NDA due to the long history of clinical use of neostigmine. They were also informed that the standard battery of genetic toxicology studies and reproductive and developmental toxicology studies would be required to be completed in the post-approval period if adequate data could not be identified in the published literature to appropriately inform the labeling.

No new pharmacology/toxicology information was submitted with this supplement. Nevertheless, Dr. Hao was able to identify some basic toxicology information from the published literature, and the summary from her review is reproduced below.

> The toxicity of neostigmine in animals as reported in the literature is consistent with excessive nicotinic and muscarinic receptor activation. The toxic effects include skeletal muscle weakness and fasciculations, pupillary constriction, increased lacrimation, salivation and airway secretions, rise in colonic pressure, colonic spasms, defecation, flatulence, diarrhea, and, at higher doses, convulsions, dyspnea, bradycardia, and death. Death is usually caused by respiratory failure due to constriction of the bronchiolar musculature and excess bronchiolar secretions. The main toxicities are observed shortly after dosing (e.g., 2-4 minutes after a single subcutaneous dose of 0.1 mg in rats) and decrease in intensity as neostigmine is cleared from the circulation (Aeschlimann and Reinert, 1931). Toxicities after repeated doses were similar to the acute toxicities but tolerance develops after a few doses.

The pharmacology toxicology review of the NDA was primarily focused on the safety of the drug substance impurities and drug product degradants, the container closure system, and the drug product excipients.

The pharmacology toxicology team had no safety concerns with respect to the drug substance impurity specifications, the drug product degradant specifications, or the container closure system. It was noted that, with respect to the excipient safety qualifications, the total daily dose of the preservative used, phenol, exceeded that of currently FDA-approved drug products that are administered as single-bolus injection.

The summary of how this safety concern was evaluated by the review team is noted below, reproduced from Dr. Breder's review.

Phenol Content

In terms of excipient safety qualification, the total daily dose of the preservative phenol via this drug product formulation exceeds that of currently FDA-approved drug products that are administered as a single bolus injection; however, the P/T team recognizes that previous clinical experience exists with the marketed unapproved drug products that may justify the safety in the phenol exposure via this product. The current product contains 4.5 mg/mL phenol as a preservative, with the same concentration employed in both the 0.5 mg/mL and 1.0 mg/mL strengths of neostigmine. Based on the maximal clinical dose of 5 mg neostigmine, the total dose of phenol is expected to be 45 mg if the 0.5 mg/mL neostigmine is used or 22.5 mg if the 1.0 mg/mL neostigmine drug product is employed. The Agency's risk assessment must be based on the potential that up to 45 mg of phenol could be administered via this product as labeled. Currently, numerous FDA-approved IV drug products contain up to 5 mg/mL phenol, therefore, the concentration of phenol in this drug product is less than other FDA-approved intravenous drug products and the total daily dose of intravenous phenol is also less than other FDA-approved intravenous drug products. From these perspectives, phenol is not novel. However, in all other identified FDA-approved drug products, the total dosage of the drugs is administered several times a day rather than as a single bolus injection. Therefore, the use of phenol in this drug product is novel in the sense that it likely results in a higher Cmax than any other identified FDA-approved drug product to date based on current labeling.

The Sponsor did find historical data to indicate that the drug Anzemet (dolasetron mesylate), which contains phenol, was originally labeled for dosing up to 100 mg (20 mg/mL solutions) for the treatment of prevention of chemotherapy-induced nausea of vomiting, as outlined in the table below and reproduced from the submission:

Table: Comparison of Phenol Exposures from Neostigmine and Anzemet

	Neostigmine Methylsulfate (Éclat Pharmaceuticals)	Anzemet (sanofi-aventis)
Indication	*Reversal of effects of non-depolarizing blocking agents*	Prevention of chemotherapy-induced nausea and vomiting
Concentration of drug in drug product	1 mg/mL	20 mg/mL
Dose of drug	5 mg (maximum dose)	100 mg (standard dose)
Volume of drug administered at the above dose	5 mL	5 mL
Concentration of phenol in the drug product	4.5 mg/mL	5 mg/mL
Maximum daily dose of phenol	22.5 mg	25 mg
Route of administration	Intravenous	Intravenous
Rate of administration	Slow intravenous injection*	Can be safely infused intravenously as rapidly as 100 mg/30 seconds
Reference	Formulation and dosing recommendations based on current marketed unapproved products (e.g., Neostigmine methylsulfate package insert 04/2008)	Anzemet package insert 01/2008

*Over at least 1 minute

The Applicant acknowledges that the indication and dosing regimen cited in the table above are not longer in the approved product labeling. This indication was removed in 2010 based on concerns that the drug product resulted in QTc prolongation. As discussed with the Applicant at the time of the preNDA meeting, the challenge faced by the Agency is that the removal of this indication was based on data obtained after administration of the drug product, and the adverse effect of QTc prolongation may have been due to the drug substance dolastetron or the formulation which contained phenol. That being said, there are data in the published literature that suggests that dolasetron and other 5HT3 antagonist drugs can interact with cardiac ion channels (Kuryshev et al., 2000). However, we cannot definitively rule out the possibility that the phenol in this formulation contributed to the AEs.

In response to the Division's concern, Éclat provided the following rationale for the safety of phenol in this formulation:

- The vasculature exposure to phenol is expected to be less than 0.1% (1:4 dilution from the concentration of 4.5 mg/mL) due to the blood flow through the cephalic and basilic veins in the upper arms (40-95 mL/min) and the 10 mL of maximal dosing volume of neostigmine. With mixing in the blood beyond the injection site, the effective concentration of phenol in the blood would be further diluted.

- Studies of the effects of phenol on the nervous system indicate that injection of 5% phenol or greater directly onto neuronal tissue is required to produce neurolytic effect (Wood, 1978). Degenerative effects on downstream organs are not expected at a concentration of 0.1% phenol should blood flow deliver this concentration to a tissue.

- Phenol at a concentration of 0.1% is only marginally hemolytic (<2% of blood cells were lysed by 1 hour of incubation) in vitro (Bukowska and Kowalska, 2004).

The above information, although generally supportive of the safety for the local tissue effects of phenol, do not provide definitive safety justification. There are no adequate intravenous toxicology studies for either phenol or this specific neostigmine drug product formulation that can define a NOAEL for phenol; therefore, there are technically inadequate nonclinical data to justify the safety of the proposed bolus dose of phenol.

However, the Division recognizes that this formulation has been marketed by other companies in the U.S. and overseas for over 20 years, and considerable human experience appears to exist which may be deemed adequate upon review to justify the safety of the phenol in this drug product formulation. Assuming adequate clinical experience exists to justify the safety of the phenol in this product, The P/Team felt there was no further nonclinical studies will be required to support approval of this NDA.

Dr Simone noted that Neostigmine methylsulfate is currently marketed, without FDA approval, in the United States by APP Pharmaceuticals/Fresenius Kabi. In their label, dated April 2008 and the Material Safety Data Sheet (MSDS) both concentrations of the product (0.5 mg/mL and 1 mg/mL) are listed as containing 4.5 mg/mL of phenol. This formulation has been marketed for > 20 years. In contrast, two other marketers of the product in the United States, West-Ward Pharmaceuticals (formerly Baxter Healthcare Corporation's US Multi Source Injectables) and American Regent, sell formulations that do not contain phenol. The Drug Utilization Data Analysis Team in the Division of Epidemiology II within the Office of Surveillance and Epidemiology provided U.S. sales data for each of these manufacturers from 2008 through 2012. During that time period, the APP formulation (b) (4) however, during that period, a total of (b) (4) were sold in this country with each unit containing 10 multidose vials. Over a 20 year period, this would translate to more than (b) (4) vials in the U.S. alone. Based on this information, if any safety issues exist, related to the bolus administration of the amounts of phenol in the product, they would likely have been apparent by this point in time. It should also be noted that the safety concern is related to the bolus administration of phenol as the same dose is

contained in approved products that are administered intravenously but by infusion rather than as a bolus.

Therefore, adequate clinical experience does exist to justify the safety of the phenol levels in this neostigmine product.

The Applicant also submitted the results of an in vitro bacterial reverse mutation assay for neostigmine, which indicated no concern for mutagenic potential. However, adequate data regarding the complete characterization of the genotoxic potential based on current standards, or reproductive and developmental toxicology studies are not available in the published literature. Therefore, the pharmacology toxicology recommendation is that the product be labeled as Pregnancy Category C due to the lack of adequate nonclinical data, and that the studies be completed as post-marketing requirements. Since the product is not intended for chronic use, carcinogenicity data are not required for this NDA.

The following summary of the pharmacology/toxicology team's recommendations has been reproduced from Drs. Hao and Mellon's review.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 204078 may be approved, pending agreement on the drug product labeling and with the recommended post-marketing requirements (PMRs) as listed below.

1.3.2 Additional Non Clinical Recommendations

There are no adequate reproductive and developmental toxicity data available in the published literature and only one of the standard battery of genotoxicity studies has been completed to date. To allow adequate drug product labeling, post-approval requirements for the full standard batteries of reproductive and developmental toxicology and genetic toxicology studies (excluding the completed Ames test) are recommended.

Based on the data submitted to date, the following studies are recommended as post- marketing requirements (PMRs) should this NDA be approved:

1. Conduct 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 Item 1 above, conduct a second in vivo assay for chromosomal damage for neostigmine methylsulfate; otherwise conduct an in vivo assay for chromosomal damage for neostigmine methylsulfate. NOTE: To address PMRs 1-2, 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. Conduct a fertility and early embryonic development toxicology study in the rat model for neostigmine methylsulfate.

4. Conduct an embryo-fetal developmental toxicology study using the rat model for neostigmine methylsulfate.

5. Conduct an embryo-fetal developmental toxicology study using the rabbit model for neostigmine methylsulfate.

6. Conduct a peri- and post-natal developmental toxicology study in the rat model for neostigmine methylsulfate.

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 supplement.

5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology studies submitted with the NDA. All the clinical pharmacology information was based on 8 clinical pharmacology studies and 5 neostigmine bioanalytical publications. The submitted publications were reviewed comprehensively based on the current review practice. Attention was focused on the study design, dosage administration, blood sampling scheme, and analytical methodology information.

Below is the summary of the adequacy of the information, reproduced from Dr. Naraharisetti's review.

Adequacy of the neostigmine clinical pharmacology information from the publications:

It was determined that all of the publications submitted in the application do not have adequate analytical information (e.g., QCs, recovery, stability, validations, etc.). Based on the current clinical pharmacology standards, none of the publications are adequate and are not optimal in constructing the information for the Labeling purpose. However, it appears that the following information is consistent through out the publication regardless which analytical methods used.

Single dose half-life:
Neostigmine half life ranged from 24 to 113 minutes after a single intravenous administration.

Metabolism:
Nonclinical information suggested that neostigmine is eliminated in the urine and feces (unabsorbed material given by routes other than IV) unchanged and undergoes hepatic metabolism in the liver microsomes. 3-Hydroxyphenytrimethyl ammonium (PTMA) is the primary metabolite, which then becomes glucuronide conjugated PTMA.

Pediatric
Fisher et al. determined the pharmacokinetics of neostigmine, five subjects per group, in infants (2-10 months), children (1-6 years) and adults (29-48 years). Neostigmine was administered as a 2-min intravenous infusion. Infants' dose was 100 μg/kg; children and adults doses were 70 μg/kg. Atropine was also administered as 30 μg/kg. The plasma conc vs. time data were fitted to a three-compartment pharmacokinetic model. Elimination half-life for infants, children and adults were 39 ± 5 min, 48 ± 16 min, and 67 ± 8 min (mean ± SD), respectively. Clearance for infants, children and adults were 13.6 ± 2.8, 11.1 ± 2.7 and 9.6 ± 2.3 mL/min/kg (mean ± SD), respectively.

Hepatic
The pharmacokinetics of neostigmine in patients with hepatic impairment has not been studied. Neostigmine is metabolized by microsomal enzymes in the liver. Use with caution in patients with impaired hepatic function.

Renal
Cronnelly et al, determined the pharmacokinetics of neostigmine in patients with normal renal function (n = 8), undergoing renal transplantation (n = 6) or bilateral nephrectomy (n = 4). Neostigmine, 0.07 mg/kg, and atropine, 0.03 mg/kg, were given by infusion over a 2·min period.

Blood samples were obtained at pre-, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min following neostigmine administration. Plasma conc vs time data was fitted to a two-compartment pharmacokinetic model. Elimination half life for normal, transplant and anephric patients were 79.8 ± 48.6, 104.7 ± 64 and 181 ± 54 min (mean ± SD), respectively. Clearances for normal, transplant and anephric patients were 16.7 ± 5.4, 18.8 ± 5.8 and 7.8 ± 2.6 mL/min/kg (mean ± SD), respectively. The clearance in patients with impaired renal function is lower compared to patients with normal renal function. Use with caution in patients with impaired renal function.

Elderly
Considering the elderly patients will have decreased renal function which will lead to decreased neostigmine clearance, neostigmine should be used with caution in elderly patients.

Drug Interaction Stuides (sic)
The pharmacokinetic interaction between neostigmine and other drugs has not been studied. Neostigmine is metabolized by microsomal enzymes in the liver. Use with caution when using neostigmine with other drugs which may alter the activity of metabolizing enzymes or transporters.

Gender, Race
No information was submitted.

Analytical Methodology
As stated above, the Applicant submitted 5 publications under the biopharmaceutics section, for an analytical method assessment. Of the submitted publications, two publications, Chan et al. (1976) and De Ruyter et al. (1980), were mostly used by the publications submitted under the clinical pharmacology section. Chan et al., and De Ruyter et al., developed gas-liquid chromatography with nitrogen detection followed by mass spectroscopy and a reverse phase liquid chromatography, respectively, to analyze neostigmine in plasma. The concentration ranges were 50-1000 and 0-1000 ng/mL, respectively. As stated above, both publications did not contain the optimal information (e.g., quality control samples), and, thus, the data obtained using these analytical methods should be carefully interpreted.

The Applicant did not submit any information to characterize neostigmine's effect on the QT interval. The review team evaluated the literature and the Adverse Event Reporting System (AERS) to determine whether there was any information that should be incorporated into the Applicant's proposed label, including with respect to prolongation of the QT interval. There were no safety risks identified from AERS or the literature that merited modification of the proposed label.

Outstanding or Unresolved Issues
I concur with the conclusions reached by Drs. Naraharisetti 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 was advised during the pre-submission meetings that, in order to have a published study support the NDA, it would have to, at a minimum, be a prospective randomized study that also met the following criteria:

1. It would need to use a control group (e.g., spontaneous recovery or a placebo group).

2. It would need to statistically analyze the effects of neostigmine compared to the control group.

3. It would need to use an endpoint of the time to a train-of-four (TOF) ratio of 0.7 to 0.9, as determined by objective monitoring (i.e., acceleromyography, electromyography, or mechanomyography.

The Applicant identified 5 such studies. These studies had a common primary endpoint – a return of the train-of-four twitch ratio to 90% ($TOF_{0.9}$). The studies evaluated a range of neostigmine doses; neostigmine's ability to reverse different neuromuscular blockers (rocuronium, vecuronium, atracurium, cisatracurium, and mivacurium), and neostigmine's efficacy when administered at varying points of spontaneous recovery. The salient features of the studies are summarized in the table below, adapted from Dr. Simone's and Dr. Breder's reviews.

Summary of the Principal Studies Supporting Efficacy

Study Author, Year	NMBA Reversed	Timing of Administration	Neostigmine Dose (mcg/kg)	Comparator	Number of Subjects Treated with Neostigmine
Fuchs-Buder, 2010	Atracurium	$TOF_{0.4}$ or $TOF_{0.6}$	10, 20, or 30	Saline	90
Lederer, 2010	Rocuronium	5 min after NMBA	50	Spontaneous Recovery	40
Adamus, 2006	Cisatracurium and Rocuronium	T1 = 25%	40	Spontaneous Recovery	60
Bevan, 1999	Vecuronium and Rocuronium	5 min after NMBA or at T1 = 1, 10, or 25%	70	Spontaneous Recovery	68
Baurain, 1994	Mivacurium	T1 = 25% (~ $TOF_{0.1}$)	40	Spontaneous Recovery	12

Subject Demographics

The Applicant provided summaries of the demographic information in their review of the individual studies, but did not integrate these data as the efficacy and demographic information for the individual subject or groups of subjects were not available, except for the age ranges. Nevertheless, Dr. Simone concluded that there was no evidence to suggest that efficacy would be affected by gender or racial backgrounds, due to neostigmine's mechanism of action and its widespread clinical use in patients.

Subject Disposition

The Applicant did not perform an analysis of efficacy based on subject disposition. However, given that the studies reported in the literature generally involved an administration of a single dose of neostigmine, nearly all the subjects completed the study. Therefore, Dr. Simone concluded that it was unlikely that an analysis by subject disposition would have a clinically relevant impact on the evaluation of efficacy or safety.

Primary Efficacy Analysis

Based on the findings in the five studies, the Applicant drew the following conclusions:

- The Applicant recommended a dosing range from 30 µg/kg to 70 µg/kg. They noted that this is consistent with the dosing recommendations in standard anesthesia texts.
- The Applicant believes that reversal time may be longer when neostigmine is administered at the time of deep residual block, suggesting that additional neostigmine dosing may be considered. However, there isn't enough data to recommend any adjustment to the standard initial dose of neostigmine base on the depth of the block.
- A comparison of the data in pediatric, non-elderly adults, and elderly adult populations suggest that spontaneous and neostigmine-assisted recovery is more rapid in pediatric patients and slightly slower in elderly adults. However, the data do not support a modification of the standard dosing recommendation for either of these two subpopulations.

The review team's conclusions regarding the efficacy demonstrated in the published studies are summarized below, reproduced from Dr. Breder's review:

> Dr Simone felt that the findings were consistent across studies and robust. However, using the data generated by these studies to develop precise dosing guidelines (i.e., a single dose vs. a dose range) is limited by a number of confounding factors:
>
> 1. The timing of neostigmine administration, based on factors such as the time after last dose of the NMB or the level of spontaneous recovery, varied substantially across studies.
> 2. The dose of neostigmine needed to reverse the blockade depended on the extent of recovery that had occurred at the time neostigmine was to be administered.
> 3. The extent of neuromuscular blockade was influenced by other medications commonly used in the perioperative period, most notably, volatile anesthetic agents and certain antibiotics.
> 4. The twitch monitoring devices used to assess neuromuscular function in the research setting are much more sensitive and reliable than the devices used in clinical practice. This can impact timing of neostigmine administration, and therefore, the dose required, as well as the ability to determine the extent to which neuromuscular blockade has been reversed.
> 5. None of the studies correlated twitch monitoring findings to clinically meaningful outcomes related to reversing NMB activity, e.g., ability to discontinue artificial ventilation and extubate the patient, or ability of the patient to maintain a patent airway and ventilate adequately.
> 6. The studies selected by the Applicant serve the purpose of supporting the claimed effect but with some limitations, most notably that there is no one dose that has been identified as optimal for administration at any specific time point during spontaneous recovery. The data suggest that a range of doses will work for any particular level of spontaneous recovery, but lower doses will not hasten recovery as much as higher doses.
>
> Furthermore, the ability to hasten recovery from neuromuscular blockade has not been demonstrated to have a clinical benefit.

Based on the data and recommendations presented by the applicant, Dr Simone made the following recommendations for the use of neostigmine to reverse paralysis induced by nondepolarizing NMBs to be incorporated in the labeling:

1. A peripheral nerve stimulator should be used throughout the surgical procedure to monitor the patient's twitch response following NMB administration in order to:
    a. assess the need for additional doses of the NMB
    b. determine if sufficient spontaneous recovery from the NMB has occurred to assure the block is reversible
    c. estimate the dose of neostigmine required to reverse the block
    d. monitor the reversal of the block after neostigmine administration
    e. evaluate the need for additional doses of neostigmine

2. Using train-of-four (TOF) stimuli, preferably applied to the ulnar nerve at the level of the wrist, neostigmine should only be administered if there is a detectable twitch response to the first impulse of the TOF, i.e., if the first twitch, T1, is present.

3. The dose of neostigmine should be determined based on the responses to the TOF stimuli with lower doses administered if more twitches are present and higher doses administered if only T1 is detected.

4. The recommended dose range is 30 mcg/kg to 70 mcg/kg.
    a. Although there is evidence that weight-based dosing < 30 mcg/kg is efficacious, the amount of data is limited to support such a recommendation.
    b. The recommendation of 70 mcg/kg as the upper limit of dosing is based on the lack of data to support higher weight-based dosing and some evidence in the literature that excessive doses of neostigmine, based on the level of neuromuscular blockade at the time of its administration and possibly the NMB being reversed, may result in prolonged blockade or paradoxical weakness.

5. Recovery times vary depending on the degree of neuromuscular blockade at the time neostigmine is administered, the dose of neostigmine administered, and other factors, e.g., the types of anesthetic agents in use at the time of reversal, the patient's body temperature. Generally, recovery to the point where the ratio of the contractile strength of the fourth twitch to the first twitch, T4/T1, is 90% (TOF0.9) occurs over a period of about 10 minutes.

6. Adequacy of the reversal of the neuromuscular block needs to be based on a clinical assessment of the patient and not TOF responses alone.

7. Patients should be monitored for clinical signs of residual blockade (e.g., difficulty maintaining a patent airway, generalized weakness, inadequate ventilatory effort) following cessation of the anesthetic and extubation. The duration of monitoring should take into account the duration of action of the NMB used and of neostigmine, which is estimated to be 20–30 minutes.

There was no analysis of secondary endpoints, either by the Applicant or the review team, as these endpoints were not as clinically relevant (e.g., $TOF_{0.7}$ or $TOF_{0.8}$).

Pediatric Patients

Five studies were identified by the Applicant as being adequate and well controlled. The neuromuscular blocking agent used, the neostigmine doses, the timing of the neostigmine

administration, and the TOF ratio endpoints are summarized in the table below, adapted from Dr. Simone's review.

	Residual Block at time of Neostigmine Dose Administration				TOF ratio	Study Author [Number of Neostigmine Exposures]
	Profound T1 = 0	Deep 0 < T1 ≤ 10%	Moderate 10%<T1≤25%	Light T1 > 25%		
Rocuronium						
Neostigmine Dose	70 µg/kg	70 µg/kg	70 µg/kg		0.9, 0.7	Bevan [11]
			40 µg/kg		0.7	Motsch [13]
		5 µg/kg 10 µg/kg 20 µg/kg 50 µg/kg			0.73 0.89 0.98 0.99	Abdulatif [15]
Vecuronium						
Neostigmine Dose	70 µg/kg	70 µg/kg	70 µg/kg	70 µg/kg	0.9	Bevan [11]
	70 µg/kg	70 µg/kg		70 µg/kg	0.7	
Mivacurium						
Neostigmine Dose		50 µg/kg			0.97	Bevan [16]

As noted in Dr. Breder's review, Dr. Simone concluded the following:

> Dr. Simone felt that adequate evidence supporting the efficacy and informing the dosing requirements for pediatric patients >1 year old had been presented. He noted that although relatively few neonates and infants have been evaluated for efficacy, the available data strongly suggest:
>
> 1. Their recovery from NMBs is faster than their older pediatric counterparts and adults;
> 2. Their neostigmine dosing requirements are probably less than the other patient groups;
> 3. They tolerate a 70 mcg/kg dose of neostigmine as well as the other patient groups.
>
> Therefore, there does not appear to be a need for further study of any segment of the pediatric patient population.

Geriatric Patients

The review team noted that several studies indicated that the action of neostigmine is prolonged in the elderly; however, elderly subjects also experience slower spontaneous recovery from neuromuscular blocking agents. Therefore, no modifications to the dosing recommendations for this patient subpopulation are warranted, although elderly patients should be monitored more closely.

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

As noted by Dr. Breder the safety data submitted in the NDA was derived from the following literature:

1. Five prospective, controlled trials with quantitative presentation of adverse events.
2. Ten studies with qualitative information.
3. Controlled trials presented at the FDA Advisory Committee meeting held on March 11, 2008, for sugammadex, another neuromuscular blocking reversal agent.
4. Two meta-analyses and a systematic review on gastrointestinal events.
5. One randomized controlled trial evaluating the effects of neostigmine on heart rate.
6. Twenty-seven case reports.
7. Three studies with additional pediatric information.

In the 120 safety-update submitted on November 30, 2012, the Applicant identified 5 additional articles, which included three prospective clinical trials and 2 case reports.

The combined total of patients exposed to neostigmine described in the publications was approximately 3,600 adult and 60 pediatric patients who were exposed to neostigmine. The details as to how many patients were discussed in each publication are described in Dr. Simone's and Dr. Breder's reviews.

As noted in Dr. Breder's review, the Applicant had the following observations about the safety data reported in the literature.

1. The patients were not highly selected.
2. Most patients were undergoing elective surgery.
3. The majority of the patients in clinical trials were adults (age range 18-74); however, children aged 2-14 years old were also studied.
4. The age range for safety data derived from case reports was 13 months to 82 years.
5. Both genders were equally represented.
6. The majority of the patients were ASA 1-3.
7. Many papers did not identify the racial or ethnic groups of the patients; those that did list racial groups indicated that the subjects were predominantly Caucasian.

Dr. Simone noted that, although the safety database did not contain the usual amount of demographic information that is reported in full study reports of clinical trials, there was still a sufficient amount of information to permit a characterization of the overall risk of neostigmine for the proposed indication in the intended patient populations.

The following summary on the number of deaths, serious adverse events, and discontinuation due to adverse events is reproduced from Dr. Breder's review.

Deaths

The Applicant found no reports of deaths attributable to neostigmine in the studies in which neostigmine was given intravenously to reverse neuromuscular blockade. They did find a report by Briggs et al. (Reference 78 from Dr. Simone's review) on the death of a girl who was diagnosed with megacolon at 6 months of age and treated with 3.75 mg to 7.5 mg of neostigmine daily. The dose was increased to 15 mg daily at 7 years age. At age 9 years old, she presented with constipation and required disimpaction. One hour later, she was unable to move her legs and

experienced shortness of breath that progressed to apnea and death. Neostigmine overdose was suspected and was confirmed via determination of serum cholinesterase levels.

A review of the literature, conducted by Dr. Simone, revealed three reports of acute cardiac arrest leading to death in anesthetized patients following intravenous administration of neostigmine. The etiologies of these deaths were attributed to the rapid administration of neostigmine or inappropriate timing of administration of atropine leading to bradycardia and cardiac arrest. These events emphasize the need for careful monitoring and the timely use of an anticholinergic agent – both of which have been incorporated into the proposed product labeling.

Serious Adverse Events
The Applicant did not report on nonfatal serious adverse events. In the review of the literature, potentially life-threatening adverse events were reported; however, the articles generally did not specify whether these events met the regulatory criteria for being serious adverse events. These events included anaphylaxis and cardiac arrhythmias. The arrhythmias were consistent with the known effects of neostigmine at the muscarinic receptors.

Discontinuations due to Adverse Events
The Applicant did not report on or conduct an analysis of the dropouts and discontinuations in the reported studies. This is expected given the acute use of neostigmine in the surgical setting and the short duration of follow-up, which was generally limited to the time in the operating room and post-anesthesia care unit following surgery.

Common Adverse Events

In order to provide a list of the most common adverse events for the label, the Applicant utilized publically available information regarding clinical trials for the sugammadex clinical development program that included neostigmine as a comparator, and published literature.

The review team's assessment and conclusions of the Applicant's proposal is described below, reproduced from Dr. Breder's review.

The Applicant made no assessment of the potential for drug-demographic interactions. The literature did not provide sufficient information for such an assessment or analysis to be performed.

Dr Simone noted that the Applicant did not conduct an exploration for dose responses of adverse events. Although such an exploration may be possible, he felt that the data to do so are limited and confounded by a number of factors, most notably, the use of varying doses of anticholinergic agents to mitigate or prevent excessive acetylcholine related adverse events and the concurrent use of anesthetic agents each with its own adverse event profile.

Dr. Simone and I concur with the Sponsor's labeling of common adverse events. The Applicant was consistent in their classification of the adverse events by SOC and preferred terms. They were also appropriate in their classifications, i.e., there was no evidence that the Applicant attempted to understate an adverse event in the selection of the preferred terms.

The table below, reproduced from Dr. Breder's review, summarizes the most common adverse reactions which the review team concluded should be included in the label.

Adverse reactions associated with neostigmine methylsulfate occurring with a frequency of ≥ 1% as reported for controlled clinical trials

System Organ Class	Adverse Reaction
Cardiovascular	bradycardia hypotension tachycardia/heart rate increase
Gastrointestinal	nausea vomiting postprocedural nausea dry mouth
General and Administration Site Reactions	procedural pain incision site complication pharyngolaryngeal pain procedural complication C-reactive protein increased
Nervous System	dizziness headache postoperative shivering prolonged neuromuscular blockade
Psychiatric	insomnia
Respiratory, Thoracic and Mediastinal	dyspnea oxygen desaturation <90%
Skin and Subcutaneous Tissue	pruritus

Adverse Events of Special Interest

Dr. Simone noted that the literature did not contain any significant amount of information on the effects of neostigmine administration on common clinical laboratory investigations (i.e., electrolytes, glucose, acid-base balance, renal or hepatic function, hematology and coagulation parameters, or urine composition). Nevertheless, Dr. Simone concluded that, given the long history of clinical use for the proposed indication, any effect on these parameters are likely to not be clinically relevant, as any clinically significant effect would have likely been identified and characterized by now.

With regard to neostigmine's effects on the cardiac conduction, Dr. Simone created a list of ECG-related adverse events based on the safety findings reported in the published studies. These included:

1. Bradycardia A-V dissociation
2. Premature ventricular contraction
3. First degree heart block
4. Ventricular extrasystoles
5. T-wave inversion
6. Cardiac arrest
7. Sinus arrhythmia
8. Tachycardia

Since continuous electrocardiographic monitoring is the standard of care in the operating room, post-anesthesia care unit, and intensive care unit, it is unlikely that these conduction abnormalities will go undetected, and medical personnel will most likely be available for rapid intervention.

Search of FDA's Adverse Event Reporting System (AERS)

The Applicant conducted a search of the AERS database for cases of adverse events where neostigmine methylsulfate was used intravenously for the purposes of neuromuscular blockade reversal and was identified as a suspect medication. The details of the Applicant's analyses are described in Dr. Simone's and Dr. Breder's reviews; the Applicant's conclusions were that there was no evidence to suggest any particular event of interest not already identified in the published literature, and the review team concurred.

Dr. Pollock and his colleagues from the Division of Pharmacovigilance II evaluated also conducted an evaluation of the AERS database, as well as literature search, and did not find any new safety issue that needed to be added to the proposed label, or which required modification. They, therefore, also concurred with the Applicant's assessment.

Outstanding or Unresolved Issues

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

8. 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, 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

Financial Disclosure
The Applicant submitted a table which listed the studies which were included in support of the NDA. The Applicant certified that it did not sponsor any of the trials referenced in the published studies, nor did it engage in any financial arrangement with any of the investigators in the listed studies.

Proprietary Name Request
The Applicant's request for the proprietary name (b) (4) had had originally been deemed acceptable by the Division of Medication Error and Analysis; therefore, several of the reviews by the review team also refer to the product by that name. However, upon its re-review prior to the action, the names was found to be unacceptable because of its similarity to (b) (4)

The Applicant subsequently submitted the name Bloxiverz for consideration, and it was found acceptable by DMEPA.

Outstanding or Unresolved Issues
There are no other unresolved relevant regulatory issues.

12. Labeling

The Applicant has submitted enough information to support their proposed labeling.

As noted above, representatives from the Office of Surveillance and Epidemiology, the Study Endpoints and Labeling Development team, and the Office of Prescription Drug Promotion, were consulted and their recommendations were incorporated during the discussion of the label.

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 Bloxiverz when used as described in the approved labeling.

As noted in Dr. Breder's review, the clinical utility of Bloxiverz 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 studies are to be completed as post-marketing requirements (PMRs):

1. An in vitro or in vivo assay using mammalian cells for chromosomal damage for neostigmine methylsulfate.

2. If the Applicant conducts an in vivo assay to address Item 1 above, they must also conduct a second in vivo assay for chromosomal damage for neostigmine methylsulfate; otherwise, the Applicant can conduct an in vivo assay for chromosomal damage for neostigmine methylsulfate. NOTE: To address PMRs 1-2, the Applicant 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.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
05/31/2013