

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204078Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 10, 2013
From	Christopher D. Breder, MD PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	204078
Supplement#	
Applicant	Eclat
Date of Submission	July 31, 2012
PDUFA Goal Date	May 31, 2013
Proprietary Name / Established (USAN) names	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 neuromuscular blocking agents after surgery
Recommended:	Approval

1. Introduction

Neostigmine methylsulfate injection is a cholinesterase inhibitor that has been marketed as an unapproved product and used for reversal of neuromuscular blockers for decades. The Sponsor has submitted a New Drug Application (NDA) under 505(b)(2) based largely on published literature of nonclinical and clinical (including clinical pharmacology) data supporting its safety and efficacy, with CMC information specific to the drug product and limited original toxicology information. The CMC, Pharmacology / Toxicology (P/T), Clinical Pharmacology, and Clinical reviewers have all recommended approval with relatively minor alterations in the proposed labeling. The CMC and P/T teams have communicated Postmarketing Commitments (CMC) and Requirements (P/T; PMR) to the Sponsor. The Division of Medication Error Prevention and Analysis recently informed the Sponsor that their proposal for a proprietary name was unacceptable.

2. Background

Adapted from the primary clinical review of Dr. Simone, MD PhD

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.

Clinical Background

Clinically, 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 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:

- 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.

3. CMC/Device

• Review Strategy

The CMC primary review was performed by Dr. Arthur Shaw, PhD and signed off without comment by Dr. Prasad Peri, PhD.

• General product quality considerations

Three issues were identified and found to be acceptably resolved by Dr. Shaw.

1. The applicant provided the synthetic procedure from the DMF holder, (b) (4) which showed that a known (b) (4) 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).
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/inspection

Facilities inspections have been completed and whether Offices of Compliance and New Drug Quality Assessment have determined these facilities to be acceptable (**Table 1**).

Table 1 Inspection of Manufacturing Facilities

Responsibility	Facility	Inspection Status
Manufacture, control, packaging, testing and labeling of Neostigmine Methylsulfate, USP Stability Testing	(b) (4)	Acceptable 17-Jan-2013
USP testing Visual Appearance Melting Range, ID by FTIR Purity by HPLC (Related Substances) Release of Drug Substance for drug product manufacture	(b) (4)	Inspection request cancelled
USP testing: Identification Tests B & C LOD ROI Sulfate Ion Assay	(b) (4)	Acceptable 31-Dec-2012

ACCEPTABLE

Dr Prasad Peri clarified¹ the entry in this table that the inspection of the (b) (4) had been cancelled in the following passage:

An inspection of the (b) (4) facility (drug product manufacturing and testing facility) was initially scheduled by the District Office in (b) (4). However, upon evaluation of the establishment status, the Office of Compliance noted that an earlier inspection of the same facility was performed in (b) (4). This inspection resulted in no significant concerns from a GMP perspective and hence on December 31, 2012 the District Office recommended an acceptable status for the (b) (4) facility for the responsibilities of manufacturing and testing the drug product. The final overall acceptable recommendation from the Office of Compliance was issued on Jan. 31, 2013 for all manufacturing and testing facilities.

It should be noted that because of a recent policy within the Office of Compliance, the assessment of the (b) (4) facility as a control testing lab for the drug product was cancelled. The Office of Compliance indicates that if the drug product is manufactured at a certain facility, it is assumed that the site is also responsible for release testing of that drug product and hence a separate request for the assessment of that site for the responsibilities of being a testing site need not be submitted in the CDER Establishment Evaluation System. Hence the assessment of

¹ Personal communication, electronic mail on May 07, 2013

(b) (4) site as a control testing site (CTL Profile) within the CDER Establishment Evaluation System was cancelled.

• Other notable issues (resolved or outstanding)

1. All other impurities are well-controlled and present no safety issues.
2. The drug product specifications were found to be adequate to control the potency, impurities and microbiological quality². The applicant has provided sufficient stability data to support a 24 month expiration date.
3. The stoppers are covered in DMF (b) (4) which was found adequate.
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.
5. **Recommendation and Conclusion on Approvability** The application may be approved from a CMC point of view.
6. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.**
 - a. We remind you that you must submit a PAS if the drug substance supplier (b) (4)
 - b. We recommend making (b) (4) a Critical Process Parameter.
 - c. We recommend amending the manufacturing directions in the master batch record to do the following:
 - i. Include (b) (4)
 - ii. Include (b) (4)

7. Nonclinical Pharmacology/Toxicology

• Review Strategy

The P/T review was performed by Drs. Huiqing Hao, PhD and Dr. R. Daniel Mellon, PhD. Unless otherwise stated, the materials in this section were derived from their review.

Given the long clinical history of neostigmine use, no new pre-approval nonclinical pharmacology or toxicology studies for the drug substance were required to support approval of this NDA. The pharmacology toxicology review therefore focused on the safety of the drug substance impurities and drug product degradants, the container closure system, and the drug product excipients.

Upon review of the published data on these topics, the P/T team concluded that there were no safety concerns with respect to the container closure system, the drug substance impurity specifications, or the drug product degradant specifications. The remainder of the P/T review focused largely on two remaining issues, excipient safety qualification of phenol and the genetic toxicology and reproductive and developmental studies.

² As determined in the Product Quality Microbiology Review by Dr. Erika Pfeiler, PhD., January 25, 2013.

- **General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise)**

Neostigmine methylsulfate is a cholinesterase inhibitor. The P/T review noted that 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. Toxicities after repeated doses were similar to the acute toxicities but tolerance develops after a few doses.

- **Carcinogenicity**

Carcinogenicity studies are not required for the proposed acute use. There are no adequate carcinogenicity data in the published literature.

For assessment of genotoxicity, only an Ames Assay (In Vitro Reverse Mutation Assay in Bacterial Cells) was submitted with the NDA. No dose-related cytotoxicity was observed with any of the strains tested in the presence or absence of S9. There were no increases in the mean number of revertants/plate observed with any of the tester strains in the presence or absence of S9 mix.

No adequate in vitro mammalian genotoxicity assays or in vivo clastogenicity assays were identified. As noted in the preIND/preNDA meetings, the P/T team recommends that these studies be required to be completed as post-marketing requirements if there were no data to inform the labeling at the time of NDA submission.

- **Reproductive toxicology**

There are no adequate reproductive and developmental toxicology studies reported in literature. As noted in the preIND/preNDA meetings, as there were no adequate data to inform labeling, the P/T team recommended that relevant studies be required as post-marketing requirements.

- **Other notable issues (resolved or outstanding)**

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 C_{max} 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 2: Comparison of Phenol Exposures from Neostigmine and Anzemet

	Neostigmine Methylsulfate (Éclat Pharmaceuticals)	Anzemet (sanofi-aventis)
Indication	<i>Reversal of effects of non-depolarizing blocking agents</i>	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 dolasetron 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 (Kuryshv 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/T

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) (b) (4) 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.

• Recommendation

- From a nonclinical pharmacology toxicology perspective, NDA 204078 may be approved pending agreement on labeling and with the recommended post-marketing requirements (PMRs).
- The drug will be considered a Pregnancy Category C drug at this time. Based on the long history of human use, the Division has informed the Sponsor that such studies were not required for approval but they would be required as Post-Marketing Requirements (meeting minutes for pre (b) (4) meeting dated 12/22/2009).

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.

8. Clinical Pharmacology/Biopharmaceutics

• Review Strategy

Dr. Suresh Babu Naraharisetti, PhD conducted the primary Clinical Pharmacology (CP) review and the Team Leader, Dr. Yun Xu, PhD signed off without comment. The CP review was substantially based on The Sponsor's review of 8 papers summarized in **Table 3** below. Dr. Naraharisetti determined that the literature which formed the basis of the CP review did not have adequate analytical information (e.g., QCs, recovery, stability, validations, etc.); however, the information was consistent throughout the publication regardless which analytical methods used.

Table 3 Published Studies used in the Clinical Pharmacology Review

Author	Study objectives	# of patients	Treatment		Bioanalytical Assay information presented			Reviewer's Comments
			Neo	Other meds	Stand. curve	Q.C.	Assay Validation	
Fisher, 1983 Anesth.	Neo PK in infants, children and adults after NM block	Infant: n=5 2-10mon; Children: n=5 1-6 y Adults: n=5 29-48 y	Infant: 100 µg/kg iv; Children and adults: 70 µg/kg iv	Atropine 30 µg/kg iv	No	No	No	1. Refers to De Ruyter et al, 1980 2. No within analytical methods presented in the paper
Calvey 1979 Brit.J. Clin. Pharm.	Neo PK after NM block with tubocurarine	Female: n=6 Age not reported;	68.9-103 µg/kg iv	Atropine sulfate (1.2 mg iv)	No	No	No	1. Refers to Chan et al. 1976 2. No within analytical methods presented in the paper 3. Not useful to overall PK information due to missing assay information
Morris, 1981; Anesth.	Neo PK after NM block with tubocurarine	Male: 6 Age not reported	0.07 mg/kg iv	Atropine sulfate (1 mg iv)	No	No	No	1. Refers to De Ruyter et al, 1980 2. No within analytical methods presented in the paper
Broggini 1991; Meth Find Exp Clinical Pharm.	Neo Single-dose PK intranasal and IV, healthy	Male: 3 Female: 3 Age: 25.5 y (23-28y)	0.5 mg	Not reported	No	No	No	1. Authors have their own HPLC method 2. However, no assay information presented in the paper 3. Not useful to overall PK information due to missing assay information
Cronnelly 1979, Anesth.	Neo PK in healthy, transplant and anephric patients	Healthy: n=8 patients Anephric: 4 patients Transplant: 6 patients Age: 23-52 y range	0.07 mg/kg iv	Atropine (0.03 mg/kg iv)	No	No	No	1. Refers to Chan et al. 1976 2. No within analytical methods presented in the paper 3. Not useful to overall PK information due to missing assay information
Willams, Br.J. Anaesth. (1978) 50, 1065	Neo PK after neuromuscular (NM) block	Healthy Female: 5 Age: 22- 62 range WT: 63.1 – 72.6 kg	5 mg iv	Atropine sulfate 1.2 mg iv	No	No	No	1. Refers to Chan et al. 1976 2. No within analytical methods presented in the paper 3. Not useful to overall PK information due to missing assay information
Chan, 1976 J. of Chrom. (also in Biopharm section)	Neo bioassay human plasma after NM block	1 (sex not reported) Not reported	5 mg iv	Not reported	50- 1000 ng/mL; no data provid ed	No	No	1. Used neostigmine bromide as analyte 2. Not optimal, the information presented in the paper is good enough to accept the analytical methodology 3. Not useful to overall PK information due to missing assay information
De Ruyter, 1980 J.of Chrom. (also in Biopharm section)	Neo bioassay human plasma after NM block	Not reported	0.05 mg/kg iv	Not reported	0-1000 ng/mL; no data provid ed	No	No	1. Not optimal, the information presented in the paper is good enough to accept the analytical methodology 2. Not useful to overall PK information due to missing assay information

• **ADME**

ADME parameters were obtained from the studies in **Table 4** below.

Table 4 ADME Parameters from the Published Literature

Study	No. of Subjects	Neostigmine Dose	Atropine Sulphate dose	C _{max} , T _{max} , AUC	T _{1/2} β (min) Mean ± SD	V _{dss} (L/kg) Mean ± SD	Cl (mL/kg/min) Mean ± SD
Morris et al. 1981 (De Ruyter method)	6 adults (6 M)	70 µg/kg	1.0 mg iv		77 ± 47	0.74 ± 0.2	9.2 ± 2.6
Broggini et al. 1991 (Authors' own HPLC method)	6 adults (3M, 3F)	500 µg		C _{max} 83 ± 9 ng/ml T _{max} 5 min AUC 127 ± 16 (ng.h/mL)	113 ± 34	0.18 ± 0.05	1.14 ± 0.44 a
Young et al. 1984 (abstract only)	7 adults	70 µg/kg			18.5 ± 7 b	0.549 ± 0.12 b	33.5 ± 4 b
	5 elderly	70 µg/kg			16.7 ± 0.8 b	0.566 ± 0.013 b	23.4 ± 5 b
Fisher et al. 1983 (De Ruyter method)	5 infants	100 µg/kg	30 µg/kg iv	Conc. profile	39 ± 5	0.54 ± 0.17	13.6 ± 2.8
	5 children	70 µg/kg	30 µg/kg iv	Conc. profile	48 ± 16	0.49 ± 0.25	11.1 ± 2.7
	5 adults	70 µg/kg	30 µg/kg iv	Conc. profile	67 ± 8	0.52 ± 0.15	9.6 ± 2.3
Cronnelly et al. 1979 (Chan method)	8 healthy adults	70 µg/kg	30 µg/kg iv		79.8 ± 48.6	1.4 ± 0.5	16.7 ± 5.4
	4 anephric adults	70 µg/kg	30 µg/kg iv		181.1 ± 54.4	1.6 ± 0.2	7.8 ± 2.6
	6 renal transplant	70 µg/kg	30 µg/kg iv		104.7 ± 64.0	2.1 ± 1.0	18.8 ± 5.8
Hester et al. 2002 (De Ruyter method)	7 adults (6M, 1F)	70 µg/kg					10.2 ± 2.3 c
Williams 1978 (Chan method)	5 adults (5 F)	5 mg iv	1.2 mg iv	Conc. profile	24.2 ± 6.6	6.2 ± 5.4 d	
Calvey 1979 (Chan method)	6 adults (6 F)	68.9-103 µg/kg	1.2 mg iv	Conc. profile	25.4 ± 6.4	0.12 ± 0.10	3.15 ± 2.1

Atr Sul- Atropine Sulphate
a Converted from L/kg
b mean ± SE
c Based on median weight
d- Vd in litres
M- male; F-female

Neostigmine's half life ranged from 24 to 113 minutes after a single intravenous administration.

Nonclinical information suggested that neostigmine is eliminated in the urine and feces unchanged and undergoes hepatic metabolism in the liver microsomes.

• Drug-Drug Interactions

Dr. Naraharisetti noted that the pharmacokinetic interactions between neostigmine and other drugs have not been studied. Neostigmine is metabolized by microsomal enzymes in the liver. 3-Hydroxyphenytrimethyl ammonium (PTMA) is the primary metabolite, which then becomes a glucuronide conjugated PTMA.

• Demographic Based Interactions

Pediatrics

Dr. Naraharisetti noted from the paper by Fisher et al. (See **Table 4**) that the distribution half-lives and distribution volumes were similar for infants, children, and adults. He therefore recommends, in addition to relating specific PK details in Section 12 of the labeling (Clinical Pharmacology), that pediatric patients respond similar to adults be noted in Section 8 (Use in Special Populations).

Hepatic

Dr. Naraharisetti notes that neostigmine methylsulfate is metabolized by microsomal enzymes in the liver but has not been studied in patients with liver failure. He plans to place a cautionary statement in the labeling.

Renal

Dr. Naraharisetti notes that the clearance in patients with impaired renal function is lower compared to patients with normal renal function. He plans to place a cautionary statement in the labeling to use with caution in patients with impaired renal function.

Elderly

Elderly patients may have decreased renal function which could lead to decreased neostigmine clearance. Dr. Naraharisetti plans to place a cautionary statement in the labeling neostigmine that NM should be used with caution in elderly patients. The issue of dosing neostigmine methylsulfate in the Elderly is discussed in Dr. Simone's Clinical Review.

- **Biopharmaceutics**

Dr. Elsbeth Chikhale, PhD, the primary ONDQA Biopharmaceutics reviewer, noted that the acceptability of the human PK data from the literature was to be determined by the Clinical Pharmacology Reviewer from OCP and so the ONDQA Biopharmaceutics review team evaluation of this NDA was not needed.

- **Thorough QT Assessment**

No information was submitted to characterize neostigmine's effect on QT. There did not seem to be a signal from the postmarketing surveillance investigation or from the literature reviewed by Dr. Simone or Martin Pollock (**see Section VIII**). Inasmuch as the Clinical Pharmacology group did not believe this to be a deficiency requiring further study before or after approval, I concur with this position considering the long clinical use without a known, related safety signal.

- **Other notable Issues**

Dr. Naraharisetti noted that the information submitted in the NDA is acceptable for approval, pending agreement on the labeling language.

9. Clinical Microbiology

There is no need for data pertaining to clinical microbiology for this application.

10. Clinical/Statistical- Efficacy

- **Review Strategy**

Dr. Arthur Simone, MD PhD reviewed the efficacy and safety of this submission. I signed off on the primary review without comment and provided additional

commentary through this part of the CDTL memo. This review was substantially abstracted from Dr. Simone's review except where noted.

According to Dr. Simone, the approach taken by the Applicant was consistent with the advice provided by the Division during presubmission meetings. Randomized, prospective studies that met the following criteria were identified as the adequate and well-controlled studies to support the NDA:

1. Employed a control group (spontaneous recovery or placebo),
2. Statistically analyzed the effects of neostigmine versus the control group
3. Used an endpoint of time to a TOF ratio of 0.7 to 0.9 as determined by objective monitoring (i.e., acceleromyography, electromyography, or mechanomyography)

The Applicant identified five prospective, randomized, appropriately controlled trials in the literature that support a finding of efficacy for the ability of neostigmine to reverse the paralysis induced by nondepolarizing neuromuscular blockers (NMBs) in adult patients undergoing surgical procedures. These trials had a common primary endpoint, a return of the train-of-four twitch ratio to 90% (TOF0.9). They evaluated a range of neostigmine doses (10 mcg/kg - 70 mcg/kg), its ability to reverse several different NMBs (rocuronium, vecuronium, atracurium, cisatracurium, and mivacurium), and its efficacy when administered at varying points of spontaneous recovery. A number of supportive studies were also identified; these generally had primary efficacy endpoints of TOF<0.9.

• **Demographics**

The Applicant provided summaries of demographic information in their review of individual trials but did not integrate these data as the efficacy and demographic information for individual subjects or groups of subjects were not available with the exception of age. Based on neostigmine's mechanism of action and its widespread use on patients of both genders and various racial backgrounds, Dr. Simone asserted that there is no evidence to suggest that its efficacy would be affected by either of these demographics.

• **Disposition**

The Applicant did not perform an analysis of efficacy based on subject disposition. Dr. Simone felt that since the studies reported in the literature generally involved single-dose administration of neostigmine to the enrolled subjects; therefore, nearly all subjects completed the study and it is not likely that subject disposition had a clinically relevant impact on the evaluation of efficacy or safety.

• **Primary Efficacy Analysis**

Based on the findings in the principle published trials (See **Table 13** in **Appendices** as copied from Dr. Simone's review, and his summary in **Table 5**), the Applicant drew several conclusions regarding dosing:

Table 5 Dr Simone's Summary of the Principle Studies Supporting Efficacy of Neostigmine Methylsulfate in Adults

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

- The Applicant favors a lower dose recommendation of [REDACTED] ^{(b) (4)} and an upper limit of 70 µg/kg, which they note is consistent with those reported in standard anesthesia texts.
- They believe that reversal time may be longer when neostigmine is administered at the time of deep residual block, and suggest that additional neostigmine dosing can be considered; however, there are insufficient quantitative data to recommend any adjustment to standard, initial dosing with neostigmine based on depth of block.
- The Applicant's evaluation of data in pediatric, non-elderly adults, and elderly adult populations suggested that spontaneous and neostigmine-assisted recovery is more rapid in children than adults, and slightly slower in elderly adults, but the data do not support any change to standard dosing recommendations for either of these subpopulations.

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.

• **Secondary Efficacy Analyses**

The Applicant provided no analysis of secondary endpoints. The Applicant did identify a number of other trials reported in the literature that were supportive of the efficacy of neostigmine in that they demonstrated an accelerated recovery from neuromuscular blockade when neostigmine was administered compared to spontaneous recovery, a placebo control, or a dose control.

An analysis of secondary endpoints was not indicated in this application as these endpoints were either not included in the trial designs or were not as clinically relevant as the primary endpoint, e.g. TOF0.7 or TOF0.8 as secondary endpoints when the primary endpoint was TOF0.9.

• **Subpopulations**

Pediatric Patients

The Applicant identified five trials reported in the literature that they considered being adequate and well controlled.

Table 6³ Principle Studies Supporting Efficacy of Neostigmine Methylsulfate in Pediatric Patients

NMBA	Residual Block @ Neostigmine Administration				TOF Ratio	Reference [# neostigmine exposures]
	Profound T1 = 0	Deep 0<T1≤10%	Moderate 10<T1≤25%	Light T1>25%		
Rocuronium						
	70	70	70		0.9, 0.7	Bevan et al. (11)
			40		0.7	Motsch et al. (13)
		5 10 20 50			0.73 0.89 0.98 0.99	Abdulatif et al. (15)
Vecuronium						
	70	70	70	70	0.9	Bevan et al. (11)
	70	70		70	0.7	
Mivacurium						
		50			0.97	Bevan et al. (16)

In each study, neostigmine significantly hastened the recovery from the NMB compared to spontaneous recovery. From the data in these studies, the Applicant concluded that:

1. A neostigmine dose of 70 µg/kg effectively reduces recovery time to TOF0.9 from rocuronium- or vecuronium-induced NMB when administered at all levels of residual blockade; and
2. Neostigmine doses as low as 5 µg/kg may be effective in reducing recovery time to TOF0.7 or higher from deep and moderate residual blockade. Recovery of neuromuscular activity occurs more rapidly with smaller doses of anticholinesterases in infants and children than in adults. Residual weakness in the recovery room is found less frequently in children than in adults. However, infants and small children may be at greater risk of complications from incomplete reversal of neuromuscular blockade due to decreased respiratory reserve there is so much variability in the trial designs that is not possible to recommend a single weight-based neostigmine dose that will be effective in all or most clinical settings.

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:

³ Numbers in parentheses, e.g., (#), represent references from the review being described.

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

Dr Simone noted that several studies in the submission have shown that the duration of action of neostigmine is prolonged in the elderly. However, elderly subjects also experience slower spontaneous recovery from neuromuscular blocking agents. No adjustments to the dosing in the elderly appear to be warranted; however, elderly patients should be monitored closely.

11. Safety

• Adequacy of the database, major findings/signals, special studies

The literature provided by the Applicant that assessed the safety of neostigmine included:

- 5 prospective, controlled trials offering quantitative presentation of adverse events (200 patients treated with neostigmine),
- 10 additional studies offering qualitative safety information (624 patients treated with neostigmine; 5 studies (348 patients) also discussed in efficacy section),
- Safety information on neostigmine from controlled trials presented during FDA Advisory Committee meeting for sugammadex (167 patients treated with neostigmine; it is unclear if this population overlaps with published studies on sugammadex),
- 2 meta-analyses and a systematic review on gastrointestinal adverse events (a total of 2,570 patients treated with neostigmine or allowed to spontaneously recover),
- 1 randomized, controlled trial on the effects of neostigmine on heart rate (41 patients treated with neostigmine),
- 27 case reports (35 patients treated with neostigmine),
- 3 studies offering additional pediatric safety information (61 patients treated with neostigmine).

The Applicant submitted a 120-day safety update on November 30, 2012. In the update, they identified five articles, out of approximately 60 published since January 2011, that they considered relevant for the reporting of adverse events associated

with the use of neostigmine. These publications included three prospective clinical studies and two case reports.

In total, the studies identified by the Applicant for the evaluation of safety (see Tables 9 and 10 of Dr. Simone's review) reflect exposure to neostigmine in up to 3,637 adult and 61 pediatric patients. They were not able to determine whether any patients were included in more than one study, particularly, in the reports of meta-analyses and reports of the safety findings relative to sugammadex at the FDA advisory committee meeting.

The Applicant noted the following regarding 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 does not contain the amount of demographic information generally captured with clinical trials for which the full study reports are provided to the Agency, there is adequate information available to characterize the overall risks of neostigmine associated with the proposed indication and the populations in whom the product will be used.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

- i. 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.

ii. SAES

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.

iii. Discontinuations due to AEs

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.

iv. General (Common) AEs

Dr Simone described three sources of information for the labeling of common AEs that were provided by the Applicant. These were 1) publically available information regarding clinical trials for the Sugammadex clinical program that included neostigmine as a comparator, 2) published literature included in the NDA submission, and 3) an update to the published literature submitted in the 120 day Safety Update. All together, these sources contributed to the Applicants final proposal for labeling of common AEs.

The most common adverse events associated with neostigmine were cardiovascular effects, which appeared to be effectively prevented with the co-administration of atropine and glycopyrrolate. While not reported in the literature, it would be reasonable to anticipate that the cardiac effects of neostigmine are dose dependent unless the dose of the anticholinergic agent used in conjunction with it is similarly increased. The cardiac effects appeared within the time required for neostigmine to

circulate to the heart; nausea and vomiting tended to occur following extubation while the patients were in the post-anesthesia care units.

Post-operative nausea and vomiting were also commonly reported; however, as the Applicant notes, controlled clinical studies and meta-analyses have produced mixed conclusions about whether neostigmine is associated with an increased risk of these gastrointestinal side effects. Other adverse events that have been reported, for the controlled studies above, in $\geq 5\%$ of patients included: procedural pain, incision site complication, procedural hypertension, dizziness, headache, constipation, dry mouth, pain, insomnia, pharyngolaryngeal pain, postoperative shivering, and procedural complication.

In addition, it appears from the literature that doses of neostigmine substantially higher than required based on the extent of spontaneous recovery, may lead to muscle weakness.

The three sources for the Applicant's proposed labeling of Common Adverse Events and Dr. Simone's review is presented in the following passages.

Adverse Events Associated with Neostigmine from the Sugammadex Development Program

The Applicant relied upon information contained in studies involving the use of neostigmine with sugammadex, a reversal agent for nondepolarizing neuromuscular blocking agents. These studies were discussed publicly at an FDA Advisory Committee (AC) meeting in 2008, and the Applicant drew their information from the briefing package for that meeting. In that document, two Phase 3, active-comparator trials in neuromuscular blockade reversal were described including the adverse event information for neostigmine (dosed at 50-70 mcg/kg) administered to 167 treated patients (**Table 7**). Altogether, 149 subjects (89%) of those patients experienced adverse events associated with use of neostigmine.

Table 7 Common Adverse Events (frequency $\geq 2\%$) Associated with Neostigmine from the Sugammadex Development Program

SOC	Preferred Term	No. Adverse Events (%)
Injury, poisoning and procedural complications	Total	113 (67.7)
	Procedural pain	85 (50.9)
	Incision site pain	14 (8.4)
	Procedural nausea	13 (7.8)
	Procedural hypertension	9 (5.4)
	Procedural complication	14 (8.4)
	Procedural hypotension	11 (6.6)
	Procedural vomiting	5 (3.0)
	Airway complication of anesthesia	4 (2.4)
	Post procedural complication	4 (2.4)

SOC	Preferred Term	No. Adverse Events (%)
	Neuromuscular block prolonged	4 (2.4)
	Total	89 (53.3)
Gastrointestinal disorders	Nausea	61 (36.5)
	Vomiting	22 (13.2)
	Flatulence	4 (2.4)
	Constipation	11 (6.6)
	Retching	8 (4.8)
	Abdominal pain	6 (3.6)
	Dry mouth	14 (8.4)
	Oral pain	6 (3.6)
	Dyspepsia	5 (3.0)
		Total
General disorders and administration site conditions	Pain	14 (8.4)
	Chills	7 (4.2)
	Pyrexia	8 (4.8)
	Total	34 (20.4)
Nervous system disorders	Headache	13 (7.8)
	Dizziness	11 (6.6)
		Total
Investigations	Blood creatine phosphokinase increased	3 (1.8)
		Total
Psychiatric disorders	Insomnia	9 (5.4)
	Anxiety	8 (4.8)
	Sleep disorder	4 (2.4)
		Total
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	17 (10.2)
		Total
Musculoskeletal and connective tissue disorders	Back pain	7 (4.2)
	Muscular weakness	5 (3.0)
	Myalgia	6 (3.6)
	Total	13 (7.8)
Skin and subcutaneous tissue disorders	Pruritus	6 (3.6)
	Erythema	4 (2.4)
		Total
Renal and urinary disorders	Total	9 (5.4)
Blood and lymphatic system disorders	Total	7 (4.2)
Metabolism and nutrition disorders	Total	7 (4.2)
Infections and infestations	Total	7 (4.2)
Cardiac disorders	Total	5 (3.0)

Adverse Events Associated with Neostigmine from the Published Literature

A number of publications describing pharmacologic responses to neostigmine for reversal of non-polarizing neuromuscular blockade included discussions of safety findings. Five of these included quantitative presentations of the adverse events associated with neostigmine that were incorporated into a table in the original submission of the NDA, which is copied below (**Table 8**). Some of these literature publications involve studies comparing neostigmine to sugammadex; it is not clear if patients included in Tables 7 are duplicated in Table 8.

Table 8 Adverse Events Associated with Neostigmine from the Published Literature

Adverse Event	Schaller et al. 2010 (28)		Jones et al. 2008 ^A (35)	Lemmens et al. 2010 ^A (32)	Khuenl-Brady et al. 2010 ^B (33)	Flockton et al. 2008 ^C (34)	TOTAL
	Neostigmine n=42	Placebo n=9	Neostigmine n=38	Neostigmine n=36	Neostigmine n=45	Neostigmine n=39	Neostigmine n=200
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Procedural pain			29 (76.3)	24 (66.7)		16 (41.0)	53 (26.5)
Nausea			19 (50)	12 (33.3)	2 (4.4)	10 (25.6)	43 (21.5)
Incision site complication			8 (21.1)	8 (22.2)			16 (8.0)
Vomiting			7 (18.4)	4 (11.1)		4 (10.3)	15 (7.5)
Dizziness			5 (13.2)	4 (11.1)		4 (10.3)	13 (6.5)
Bradycardia	12 (27)	0 (0)					12 (6.0)
Headache			4 (10.5)	2 (5.6)		6 (15.4)	12 (6.0)
Pharyngolaryngeal pain			4 (10.5)	7 (19.4)			11 (5.5)
Postoperative shivering	11 (25)	0 (0)					11 (5.5)
Procedural complication			6 (15.8)		4 (8.9)		10 (5.0)
Insomnia			4 (10.5)			5 (12.8)	9 (4.5)
Postprocedural nausea			5 (13.2)	2 (5.6)			7 (3.5)
Pruritus			4 (10.5)	2 (5.6)			6 (3.0)
Dry mouth					4 (8.9)		4 (2.0)
Desaturation <90%	3 (7)	0 (0)					3 (1.5)
Hypotension	3 (7)	4 (44)					3 (1.5)
Tachycardia/Heart rate increase	2 (5)	0 (0)			1 (2.2)		3 (1.5)
Neuromuscular block prolonged					2 (4.4)		2 (1.0)
Acute lung failure	1 (2)	0 (0)					1 (0.5)

Adverse Event	Schaller et al. 2010 (28)		Jones et al. 2008 ^A (35)	Lemmens et al. 2010 ^A (32)	Khuenl-Brady et al. 2010 ^B (33)	Flockton et al. 2008 ^C (34)	TOTAL
	Neostigmine n=42	Placebo n=9	Neostigmine n=38	Neostigmine n=36	Neostigmine n=45	Neostigmine n=39	Neostigmine n=200
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anesthetic complications (cough/movement)	1 (2)	0 (0)					1 (0.5)
Beta-N-acetyl-D-glucosaminidase increase						1 (2.6)	1 (0.5)
Erythema					1 (2.2)		1 (0.5)
Gamma-glutamyl-transferase increase					1 (2.2)		1 (0.5)
Hypertension	1 (2)	0 (0)					1 (0.5)
Hypokalemia	1 (2)	1 (11)					1 (0.5)
Hypocalcemia	1 (2)	1 (11)					1 (0.5)
Procedural hypertension					1 (2.2)		1 (0.5)
Sleep disorder					1 (2.2)		1 (0.5)
Supraventricular extrasystoles					1 (2.2)		1 (0.5)
Tremor						1 (2.6)	1 (0.5)
Ventricular extrasystoles					1 (2.2)		1 (0.5)
Hypoglycemia	0 (0)	1 (11)					0 (0)
Paresthesia <i>nervus ulnaris</i>	0 (0)	1 (11)					0 (0)
Postoperative nausea & vomiting	0 (0)	2 (22)					0 (0)

^A Adverse events occurring in at least 10% of the patients in either the sugammadex or neostigmine treatment group

^B Adverse events considered by the investigator as possibly, probably or definitely related to study drug

^C Adverse events occurring in at least 10% of patients in either the sugammadex or neostigmine treatment group and/or considered drug-related

Based on the adverse event information contained in **Table 7** and **Table 8** above, **Table 9** below should be used in the label to reflect the quantitative data available from published trials. The Applicant has also included information from the work of Geldner et al. (See Reference 92 from Dr. Simone's review) that was included in the 120-day safety update, that “C-reactive protein increased.” The adverse events are listed in order of decreasing frequency. These reactions are largely expected based on the pharmacological action of neostigmine and those which may be due in part to other products administered during an anesthetic or to the surgical procedure itself, e.g., nausea, vomiting shivering, pharyngeal pain, and postoperative pain.

Table 9 Adverse reactions associated with neostigmine methylsulfate occurring with a frequency of \geq 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

One adverse event that deserves special attention is weakness or “prolonged neuromuscular blockade” following neostigmine administration. It is not possible to tell from the reports of the studies whether these events reflected an inadequate dose of neostigmine, which appears more likely based on the timing of administration, or muscle weakness due solely to the neostigmine, which has been reported when larger doses of neostigmine were administered following substantial spontaneous recovery.

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.

v. Significant AEs

As with serious adverse events, the Applicant did not analyze adverse events on the basis of their severity. Based on the review of the literature, specific adverse events were rarely graded on severity. When they were graded, most often the adverse events were considered as a whole and described as "mild or moderate."

vi. Laboratory Tests

Clinical laboratory testing to evaluate the effects, if any, of neostigmine on serum electrolytes and glucose, renal and hepatic function, hematology and coagulation parameters, acid-base parameters and urine composition were not reported in the literature, despite widespread use of neostigmine for the proposed indication for over half a century. The Applicant noted that three studies involving sugammadex reported safety information from analysis of blood or urine samples. There were no clinically significant findings in these.

Dr Simone noted that the limited amount of data available regarding the impact of neostigmine on parameters assessed by clinical laboratory methods is acceptable due to the acute use of the product and its long history of use for the proposed indication. Any effect neostigmine may have on these parameters, he felt is likely to be clinically irrelevant as those effects likely to have a substantial impact on patients' health would likely have been discerned and well characterized in the literature, similar to the way the hemodynamic effects of neostigmine have already been reported.

vii. Other Routine Clinical Tests

The Applicant neither summarized nor analyzed the limited ECG information provided in the literature. However, it is possible to generate a list of ECG-related adverse events based on safety findings reported in some of the published clinical studies.

The following list was constructed by Dr. Simone and includes the number of the references from his review for each adverse event:

1. Bradycardia [Ostheimer (62); Mirakhur (63); Goldhill (67); Nagiub (69); Suresh (71); Wetterslev (70); Caldwell (23); Lessard (36); Fuchs-Buder (38)]
2. A-V dissociation [Nagiub (69)]
3. Premature ventricular contraction [Ostheimer (62); Nagiub (69)]
4. First degree heart block [Nagiub (69); Wetterslev (70)]
5. Ventricular extrasystoles [Wetterslev (70)]
6. T-wave inversion [Mirakhur (63)]
7. Cardiac arrest [Clutton-Brock (79); Hill (80); Macintosh (83)]
8. Sinus arrhythmia [Mirakhur (63)]
9. Tachycardia [Mirakhur (63)]

Dr. Simone noted that as continuous electrocardiographic monitoring is the standard of care in both the operating room and post-anesthesia care unit, and neostigmine-induced rhythm changes are expected to occur within minutes of drug administration, it is likely that the adverse events reported accurately reflect the types of events that occur, if not the incidence for each.

- **Information derived from Post Marketing Experience**

Applicant Reported Findings

The Applicant conducted a search of the Agency's Adverse Event Reporting System (AERS) database for adverse events associated with the use of neostigmine methylsulfate. Other salt forms of neostigmine were excluded from the search. The query output was further limited to the intravenous route of administration with known or possible use of neostigmine for neuromuscular blockade reversal. Cases were included in the analysis if neostigmine was identified as a suspect medication, i.e., cases with neostigmine listed as a concomitant medication were excluded. The date range of the query was unrestricted through September 30, 2011, the most recent AERS quarterly update available at time of their query execution.

Their query identified 118 cases, 107 of which were categorized as serious, including 11 fatal outcomes. A total of 412 adverse events were recorded from all cases, with a majority, 397, derived from serious cases. Fatal cases had a total of 64 associated adverse events. The analysis was confounded in that many cases had medications other than neostigmine also identified as suspect; therefore, the Applicant focused their analysis on cases in which neostigmine was the sole suspect medication.

The administered doses, when provided, were often within the 1-5 mg range both for cases in which neostigmine was the sole suspect medication and in cases where other medications were suspect as well. The Applicant noted that this dose range is consistent with the neostigmine doses used in the majority of the supportive clinical literature (30-70 mcg/kg in adult patients), and suggests that the AERS data reflect

safety findings associated with standard and appropriate use of the drug. They further note that doses of neostigmine administered to the 6 pediatric patients ranged between 0.5-1.5 mg, suggesting that overdosage did not contribute to any adverse events in this population.

Other than drug ineffectiveness and post procedural complications, cardiac events were of the highest frequency. In particular, cardiac arrest (14 events), bradycardia (14 events), and tachycardia (10 events) were most frequently reported, although relatively few of these reports were from cases in which neostigmine was the sole suspect medication. Other events included coma (11 events) and hypotension (10 events). The majority of reports were from the adult population; 6 cases were from the pediatric population, specifically, ages 2-6 years old. Also of note, were a single case of Stevens-Johnson Syndrome (SJS) and 5 cases of toxic epidermal necrolysis (TEN). The cases of coma, SJS and TEN are discussed in further detail in Dr Simone's comments found on pp. 33-4 of this review.

The Sponsor evaluated the cases based on differences in incidence by gender, age, and dose (when available) of neostigmine. No causal relationship was suggested in any of these evaluations according to the Sponsor.

Based on their AERS analysis, the Applicant concluded there is no evidence to suggest any particular unsuspected events of interest not already reported in the neostigmine pharmacology literature. They further reason that given the 8 decades of neostigmine use combined with the long history of use of edrophonium and pyridostigmine, these anticholinergic agents have likely been administered to millions of surgical patients for reversal of neuromuscular blockade, and the adverse events identified in the AERS database suggest the drugs generally well-tolerated with only occasional adverse clinical outcomes.

Dr. Simone and I concur with the opinion of the Sponsor regarding their postmarketing AERS analysis.

Division of Pharmacovigilance II Findings – AERS Database

The Division of Pharmacovigilance II (DPV-2) conducted an AERS search on January 25, 2012, that covered the time period from January 1, 1969 to January 25, 2012. No limitations were imposed on the MedDRA search terms so that all events would be retrieved. The search identified 339 reports, 74 of which were determined to be duplicates. Of the remaining 265 cases, 48 were eliminated for various reasons, e.g., neostigmine had not been given, the event occurred prior to neostigmine administration, illegible report. Neostigmine was used for reversal of neuromuscular blockade in 150 (69%) of the remaining cases, which formed the case series for their analysis. These 150 cases were associated with 268 adverse events, which are listed by preferred terms in **Table 10** and **Table 11** below

Table 10 Adverse event counts for events described in the current unapproved label

Labeled Adverse Events by Preferred Term	Adverse Event Count
SOC (All)	268
Cardiac SOC (All)	129
Cardio and/or respiratory arrest	27
Bradycardia or decreased heart rate	23
Tachycardia or heart rate increased	19
Arrhythmias (ventricular, atrial, NOS)	18
Hypotension or blood pressure decreased	14
Atrioventricular block	13
EKG abnormal	10
Myocardial infarction	2
Resp SOC (All)	74
Oxygen saturation decreased/hypoxia	15
Respiratory arrest, depression, distress or failure	13
Dyspnoea or apnoea	12
Bronchospasm or laryngospasm	7
Respiratory acidosis	4
Cyanosis	3
Hypercapnia	3
Increased bronchial secretion/laryngedema	3
Stridor or wheezing	3
Cough	2
Hypoventilation	2
Respiration abnormal	2
Nervous SOC All	25
Sedation, somnolence or asthenia	10
Coma or LOC	7
Convulsion	3
GI SOC (All)	9
Nausea or vomiting	4
Abdominal pain/pain	2
Diarrhoea	2
Skin SOC (All)	9
Rash/erythema/urticaria	7
Vascular SOC (All)	7
Shock/circulatory collapse	5
Flushing	2
Immune SOC (All)	5
Anaphylaxis/hypersensitivity	5
Musc SOC (All)	5
Muscle spasms/twitching	4
Eye SOC (All)	4
Miosis/visual changes	4

Table 11 Adverse event counts for events not described in the current unapproved label

SOC	Adverse Events (n ≥ 2)
Blood (12)	Lymphocyte abnormalities (2); hemoglobin changes (2); decreased protein parameters (2); coagulation abnormalities (2)
Cardiac (15)	Blood pressure increased (11)
Gastrointestinal (7)	GI hemorrhage (2)
General (61)	Drug ineffective (36); drug interaction (7); pyrexia (3); malignant hyperthermia (3); injection site complication (3); edema (3); multi-organ failure (2)
Hepatobiliary (14)	Hepatic failure or injury (3); hepatitis (3); bilirubin increased (2); cholestasis or cholelithiasis (2); increased LFT (2)
Infection (3)	Sepsis (2)
Injury and poisoning (35)	Post procedural complication (11); delayed recovery from anesthesia or prolonged NM block (9); medication error-related (6); anesthetic complication (4)
Metabolic (7)	Metabolic acidosis (3)
Musculoskeletal (8)	Rhabdomyolysis-related (3)
Nervous (23)	Paralysis or hypotonia (7); unresponsive to stimuli or hypoaesthesia (5); serotonin syndrome (2); dyskinesia (2)
Psychiatric (10)	Anxiety related (6)
Renal (12)	Hematuria (3); oliguria (2); renal infarct or thrombosis (2)
Respiratory (18)	Pulmonary edema (5); breath sounds abnormal (2); bronchial or pulmonary hemorrhage (2)
Skin (7)	Blister or drug eruption (2)

The reviewers from DPV-2 noted numerous confounding factors in the AERS cases including concomitant medications, medical history (surgical or procedural complications occurring before neostigmine administration), and the lack of sufficient clinical information to assess neostigmine association. Therefore, they concluded that there was insufficient evidence to warrant inclusion of any of the adverse events in **Table 11** in the product's label.

Division of Pharmacovigilance II Findings – Literature Search

On March 28, 2012, DPV-2 conducted their literature search using PubMed to identify English-language literature using “neostigmine” in the title and the word “adverse” as an unrestricted search term. Those case reports that had not been submitted to the NDA or to AERS formed the basis for this portion of their review. The search resulted in 52 reports with dates of publication ranging from 1948 through 2011; Most of the reports (n=23) concerned patients who received neostigmine to reverse the effects of a nondepolarizing neuromuscular blocking agent after surgery.

Regardless of the indication for use, the adverse events associated with neostigmine administration were either labeled events or consistent with labeled events.

There were five deaths that were included in the review, two of which involved the proposed indicated use. The first was reported by Middleton et al. (95) and involved a patient who died from cardiovascular shock 23 hours after reversal of apnea with neostigmine during surgery for an abdominal gunshot wound. The authors attributed the apnea to neomycin rather than neuromuscular blockade and did not attribute the death to neostigmine. The second death was reported by Buzello et al. (96) and involved a 57 year-old woman with dystrophia myotonica who died of bronchopneumonia, hypoxemia, hypercapnia, and recurrent bradyarrhythmia approximately 3 weeks after neostigmine had been given for reversal of pancuronium following a cholecystectomy.

The DPV-2 reviewers concluded that the neostigmine associated adverse events reported in the literature, both related to the proposed indication and otherwise, primarily involved labeled events and deaths due to various causes that appeared to be unrelated to neostigmine. The review of these adverse events, including the deaths, did not reveal any safety concerns not already addressed in the proposed label.

Additional Analysis and Commentary from Dr Simone on Post-Marketing Reports

Reports of Coma, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Dr. Simone noted that although the DPV-2 review did not specifically report incidents of SJS or TEN, they noted 2 reports of “blister or drug eruption” that could represent cases of these life-threatening reactions. The DPV-2 review also identified multiple cases of coma. The individual reports for the incidents of coma, SJS and TEN were obtained by Dr. Simone through DPV-2 and are considered below.

The Applicant cited 11 reports of coma. The Applicant has listed “coma” in the adverse events section of their proposed label; however, they note that those adverse events are listed in the unapproved neostigmine labels [American Regent, Inc. Label (1/09), APP Pharmaceuticals, LLC Label (4/08), General Injectables and Vaccines Label (Baxter) (6/05)] and were included for completeness. They further note the

source information justifying the inclusion of these adverse events is not available, so it is difficult to assess the incidence of these adverse events as well as their possible relationship to intravenous neostigmine.

In each reported cases of coma, patients were unresponsive to external stimuli; however, the reasons appear attributable to

- the effects of other drugs, such as citalopram and atropine;
- residual weakness limiting the patient's ability to respond to stimuli;
- or the result of cardiac arrest (perhaps induced by neostigmine) that resulted in cerebral anoxia and a resultant comatose state.

It does not appear likely that neostigmine induced the comatose state by its direct effects on the brain given its being a quaternary amine. (b) (4)



For the reports of SJS and TEN, 84 listings were found in the adverse events reporting system's database. Of these, there were 18 unique individual study report numbers, and within these, there were seven unique cases. In each instance, there were multiple suspect drugs, from 5 to 76 products, administered in the days preceding the adverse event, some of which have been previously identified as causing either SJS or TEN. In addition, for two of the reports, there was too little information to determine the basis on which the diagnosis was made or the qualifications of the individual making the diagnosis.

Although the Applicant recorded the finding of one incident of SJS and five incidents of TEN in their review of the AERS database, they made no comments about these events in their discussion of the AERS data and have not incorporated them in the proposed product labeling. Although neostigmine cannot be ruled out, with certainty, as the direct cause of SJS or TEN for the three cases that reported signs consistent with the diagnoses, the reports are too confounded by the number of concomitant medications, including some that have been clearly demonstrated to be associated with SJS/TEN, to justify including these reactions in the product's label at this time.

Labeling

The following wording for the Postmarketing Adverse Reactions section of the labeling was recommended by Dr. Simone after his consideration of the published literature, the Sponsor's submission, and DPV's review:

Table 12 Post Marketing Adverse Reaction Reports from Literature and Other Sources

System Organ Class	Adverse Reaction
Allergic	allergic reactions
	anaphylaxis
Nervous System	fasciculation
	convulsions

	loss of consciousness
	drowsiness
	dysarthria
	miosis
	visual changes
	cardiac arrhythmias (A-V block, nodal rhythm)
Cardiovascular	nonspecific EKG changes
	cardiac arrest
	syncope
	hypotension
	increased oral, pharyngeal and bronchial secretions
Respiratory, Thoracic and Mediastinal	respiratory depression
	respiratory arrest
	bronchospasm
Skin and Subcutaneous Tissue	rash
	urticaria
Gastrointestinal	flatulence
	increased peristalsis
	bowel cramps
	diarrhea
	urinary frequency
Renal and Urinary	weakness
Musculoskeletal and Connective Tissue	muscle cramps
	spasms
	arthralgia
	diaphoresis
Miscellaneous	flushing

- **Immunogenicity**

The Applicant provided no information regarding the immunogenicity of neostigmine. According to Dr. Simone, none could be found in the literature search performed for this review. There appears to be no evidence suggesting neostigmine is immunogenic despite a history of extensive use of spanning more than five decades.

- **Special safety concerns**

Renal and Hepatic Impairment

Dr Simone noted that the literature did not provide sufficient information on the dosing of patients with renal impairment for such an assessment or analysis to be performed with the exception of renal failure, for which there are limited data.

One study compared patients with normal renal function to renal transplant patients and anephric patients. Neostigmine pharmacokinetics were not significantly different in patients with normal renal function from those having undergone renal transplantation; however, anephric patients had a significantly prolonged elimination half-life and decreased total serum clearance of neostigmine when compared to patients with normal renal function or those with recent renal transplantation

He further commented that if neostigmine, which is cleared by the kidneys, was used to reverse a renally cleared NMB, there should be no need, in theory, to adjust the neostigmine dose or observe the patient for a longer period than when the products are administered to a patient with normal renal function. The change in renal function would affect both drugs similarly, unless different mechanisms of clearance are involved, e.g., diffusion and active transport. As little is known about the mechanisms of renal clearance for the various NMBs and neostigmine, he recommended that labeling be included that patients be observed for signs of returning neuromuscular blockade for a period that would permit full spontaneous recovery from the NMB given the patient's level of renal function. Such a determination could be predicated on the NMB dosing intervals observed during the surgical procedure; if available, this information could be used to accurately predict duration of action for the NMB in any patient. He further stated that if a patient has hepatic impairment and receives an NMB cleared in part or completely by the liver, there is the possibility that the effects of the NMB may outlast those of the neostigmine and additional doses of neostigmine may be required. He also recommended that labeling be included that for these patients, extending the period of time for observation following neostigmine administration is warranted. The same would apply for NMBs that have active metabolites, which would further compound the issue.

Drug-Drug Interactions from the Clinical Literature

The following drugs or drug classes were identified by the Applicant as having deleterious effects:

1. Succinylcholine: Concurrent use of neostigmine and succinylcholine has been reported to produce a prolonged and intense neuromuscular block. (84)
2. Halogenated anesthetics: Halogenated anesthetics drugs can act as a neuromuscular junction stabilizing agent producing synergistic effects with neuromuscular blocking agents (NMBs). This effect can reduce the need for an NMB or require an increased dose of neostigmine. The effect of at least one of these anesthetics, sevoflurane, has been shown to be concentration dependent. (85)
3. Aminoglycoside and tetracycline antibiotics: These antibiotics may have inhibitory action at postsynaptic receptors or affect the neuromuscular junction by calcium chelation, causing accentuated block and potentially necessitating neostigmine dose adjustments. (84,86)
4. Other products with effects similar to antibiotics: Calcium channel blockers, antiarrhythmics, lithium, cyclosporin and other concomitant medications. (84,87) It appears that these drugs either enhance the potency of NMBs or act directly at the neuromuscular junction. (87) Furthermore, it appears that if neostigmine is administered after some spontaneous recovery has already occurred there may be no adverse effect on recovery of neuromuscular function. (88)

Dr. Simone noted that in addition to the Applicant's findings, the literature includes another key interaction that needs to be considered in clinical practice and that should be included in product labeling. Specifically, neostigmine-induced recovery is

attenuated in patients treated with magnesium sulfate (MgSO₄) due to the independent effects of MgSO₄ at the neuromuscular junction rather than a drug-induced decreased response to neostigmine.(38,89)

- **Discussion of notable safety issues (resolved or outstanding).**

The Applicant has proposed the following text for the safety related sections of the neostigmine label:

1. CONTRAINDICATIONS

NEOSTIGMINE METHYLSULFATE⁴ is contraindicated in patients with known hypersensitivity to (b) (4) with peritonitis or mechanical obstruction of the intestinal or urinary tract.

2. WARNINGS AND PRECAUTIONS

Atropine or glycopyrrolate should be administered prior to NEOSTIGMINE METHYLSULFATE to (b) (4) the risk of bradycardia. (b) (4)

(b) (4) NEOSTIGMINE METHYLSULFATE should be used with caution in patients with (b) (4), coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome, (b) (4), myasthenia gravis, (b) (4). Because of the possibility of hypersensitivity (b) (4), atropine and medications to treat anaphylaxis should always be readily available.

Large doses of NEOSTIGMINE METHYLSULFATE administered when neuromuscular blockade is minimal can produce neuromuscular dysfunction. The dose of NEOSTIGMINE METHYLSULFATE should be reduced if recovery from neuromuscular blockade is nearly complete.

It is important to differentiate between myasthenic crisis and cholinergic crisis caused by overdosage of NEOSTIGMINE METHYLSULFATE. Both conditions result in extreme muscle weakness but require radically different treatment. [see [Overdosage \(10\)](#)]

3. ADVERSE REACTIONS

Adverse reactions to NEOSTIGMINE METHYLSULFATE are (b) (4) attributable to exaggerated pharmacological effects. (b) (4)

⁴ The proposed proprietary name was replaced in the text of this section with the established name since the proprietary name had been found unacceptable by the Division of Medication Error and Analysis (See Section 15).

[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED]

4. DRUG INTERACTIONS

[REDACTED] (b) (4)



Dr Simone noted that based on the review of the safety data, the risks of neostigmine have been well characterized, are mostly consistent with the drug's mechanism of action, and can be readily monitored and treated in the perioperative setting. He felt that the Applicant's labeling accurately and adequately describes the product's safety profile although some minor changes are recommended and will be communicated to the Sponsor.

12. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. An advisory committee meeting was not deemed necessary to judge whether the data were adequate to establish the efficacy or safety of neostigmine methylsulfate injection for the indication of reversal of non-depolarizing neuromuscular blocking agents.

13. Pediatrics

The Division made a case to the PeRC that the NDA contained sufficient information for pediatric labeling and that further studies would not likely result in a further refinement of the dosing guidance or additional safety findings. This was based on the following rationale:

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 agreed with the Division's position without further comment and requested a copy of the final pediatric labeling be sent to them.

14. Other Relevant Regulatory Issues

Financial Disclosures – Not applicable. No new clinical trial data were reviewed for this application.

15. Labeling

On May 1, 2013, Carol Holquist from the Division of Medication Error and Analysis sent a letter to the Sponsor informing them that their propriety name request for

 (b) (4)

The communication acknowledged that this determination differed from a previous evaluation and conclusion communicated in the later dated October 25, 2012.

The reason DMEPA reached a different determination with respect to the safety of the proposed name is based upon our re-evaluation of the misinterpretation of (b) (4) in the inpatient prescription study as well as a comment from another participant indicating that the name looked similar to (b) (4)

16. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend Approval

- Risk Benefit Assessment

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

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.

As this product has been marketed for decades within the United States without identification of significant risks (see **Section 11** for a description of known risks) and given its acute use as a single dose per procedure in most all cases, I believe it has a favorable risk:benefit profile.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I do not feel a plan beyond routine post-marketing pharmacovigilance is required for this approval given its known safety profile, long history of use, and well established practices of monitoring for reversal of NMBs.

- Recommendation for other Postmarketing Requirements and Commitments

Based on the data submitted to date, the P/T team recommended the following studies 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.

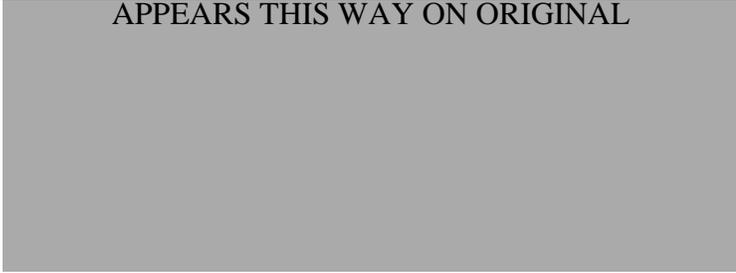
The CMC team had the following recommendations:

- a. We remind you that you must submit a PAS if the drug substance supplier (b) (4).
- b. We recommend making (b) (4) a Critical Process Parameter.
- c. We recommend amending the manufacturing directions in the master batch record to do the following:
 - i. Include (b) (4)
 - ii. Include (b) (4)

17. Comments to be conveyed to the applicant in the regulatory action letter

The Sponsor should be informed that until their proprietary name is approved, the established name should be on their labeling, including the carton and container label.

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18. Appendices

Tables related to the Primary Efficacy Variable

Table 13. Summary of pivotal efficacy trials that used TOF_{0.9}

Author/Year Country/ (Reference)	Total # Patients	Neuromuscular Blocking Agent and Dose	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)			
Fuchs-Buder et al. 2010 France (8)	120 adult ASA I-III undergoing elective surgery under general anesthesia	Atracurium 0.5 mg/kg + 0.1 mg/kg as needed	At TOF _{0.4} recovery	0 (saline)	15	Reversal to TOF_{0.9} <i>Median (range)</i> 13 (7 - 27)	Reversal to TOF_{1.0} <i>Median (range)</i> 19 (11 - 30)		
				10	15			6 (3 - 12)****	11 (7 - 15)****
				20	15			6 (4 - 9)****	9 (6 - 13)****
				30 µg/kg	15			4 (3 - 6)****	6 (4 - 11)****
Lederer et al. 2010 Austria (9)	60 adults M&F ASA I & II undergoing elective surgery under general anesthesia	Rocuronium 0.4 mg/kg	5 minutes after NMB	0 (saline)	15	Recovery to TOF_{0.9}	Recovery to TOF_{0.8}		
				10	15			10 (5 - 16)	15 (8 - 20)
				20	15			4 (2 - 9)****	6 (4 - 16)****
				30 µg/kg	15			3 (2 - 7)****	6 (4 - 14)****
Lederer et al. 2010 Austria (9)	60 adults M&F ASA I & II undergoing elective surgery under general anesthesia	Rocuronium 0.4 mg/kg	5 minutes after NMB	None (control)	20	39.0 ± 8.7	36.2 ± 8.5		
				30	20			22.6 ± 5.9***	20.2 ± 5.0***
				50 µg/kg + glycopyrrolate	20			19.4 ± 5.1***	17.8 ± 4.8***

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Author/Year Country	Total # Patients	NMB	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
Adamus et al. 2006 Czech Republic (10)	120 adults M&F ASA I & II undergoing elective surgery under general anesthesia	Cisatracurium 0.10 mg/kg 0.15 mg/kg	T1 @ 25% recovery	None (control)	15	Reversal to TOF_{0.9} <i>Mean (SD) [median]</i> 49.2 (8.0) [49]	Reversal to TOF_{0.7} <i>Mean (SD) [median]</i> 15.9 (1.8) [16.3]
				40 µg/kg + atropine	15		
			T1 @ 25% recovery	None (control)	15	52.5 (7.0) [54]	15.5 (1.7) [15.5]
				40 µg/kg + atropine	15	11.7* (2.7) [12]	4.5* (0.8) [4.7]
		Rocuronium 0.60 mg/kg 0.90 mg/kg	T1 @ 25% recovery	None (control)	15	43.1 (13.1) [41]	16.1 (3.7) [15.7]
				40 µg/kg + atropine	15	9.8* (2.0) [10]	4.3* (0.8) [4.3]
None (control)	15	56.7 (12.9) [56]	16.1 (4.0) [16.3]				
40 µg/kg + atropine	15	10.0* (2.7) [10]	4.7* (0.7) [4.6]				

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Author/Year Country/ Reference	Total # Patients	NMB	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
Bevan et al. 1999 Canada (11)	80 adults F ASA I & II undergoing gynecologic surgery	Rocuronium 0.45 mg/kg	5 minutes post-NMB T1 @ 1% recovery T1 @ 10% recovery T1 @ 25% recovery	None (control)	8	Recovery to TOF_{0.9} 54.3 ± 12.3	Recovery to TOF_{0.7} 45.7 ± 11.5
				70	8		
				70	8	35.3 ± 14.5	26.5 ± 9.2**
				70	8	27.0 ± 8.5**	23.9 ± 7.9**
				70 µg/kg + glycopyrrolate	8	28.2 ± 10.8**	26.3 ± 9.4**
				70 µg/kg + glycopyrrolate	8	28.2 ± 10.8**	26.3 ± 9.4**
	80 children 2-12 years undergoing dental treatment	Rocuronium 0.45 mg/kg	5 minutes post-NMB T1 @ 1% recovery T1 @ 10% recovery T1 @ 25% recovery	None (control)	8	34.7 ± 10.0	28.8 ± 7.8
				70	8		
				70	8	19.3 ± 6.6**	16.5 ± 5.7*
				70	8	20.0 ± 4.2**	18.4 ± 3.7*
				70 µg/kg + glycopyrrolate	8	24.4 ± 8.2	23.0 ± 8.3
				70 µg/kg + glycopyrrolate	8	24.4 ± 8.2	23.0 ± 8.3
80 children 2-12 years undergoing dental treatment	Vecuronium 0.075 mg/kg	5 minutes post-NMB T1 @ 1% recovery T1 @ 10% recovery T1 @ 25% recovery	None (control)	8	44.2 ± 12.3	36.4 ± 9.0	
			70	8			28.6 ± 10.4*
			70	8	25.1 ± 6.9**	20.7 ± 5.0**	
			70	8	29.2 ± 8.2*	25.9 ± 6.3	
			70 µg/kg + glycopyrrolate	8	23.4 ± 3.5*	21.3 ± 3.1**	
			70 µg/kg + glycopyrrolate	8	23.4 ± 3.5*	21.3 ± 3.1**	

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

Author/Year Country/ Reference	Total # Patients	NMB	Neostigmine Administration	Neostigmine Dose	# Patients /Group	Recovery or Reversal Time (minutes)	
Baurain et al. 1994 Belgium (12)	24 adults ASA I & II	Mivacurium 0.2 mg/kg + infusion	T1 @ 25% recovery	None(control) 40 µg/kg + atropine	12 12	Reversal to TOF0.9 <i>Mean (SEM)</i> 13 (0.5) 10*** (0.9)	Reversal to TOF0.7 <i>Mean (SEM)</i> 10 (0.6) 5*** (0.3)

*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 compared to spontaneous control

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/s/

CHRISTOPHER D BREDER
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