CLINICAL PHARMACOLOGY REVIEW

NDA: 204078	Submission Date: 07/31/2012
Submission Type; Code:	505(b)(2)
Brand/Code Name:	To-be-determined
Generic Name:	Neostigmine Methylsulfate Injection, USP
Primary Reviewer:	Suresh Babu Naraharisetti, Ph.D.
Team Leader:	Yun Xu, Ph.D.
OCP Division:	DCP 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	Eclat Pharmaceutcials
Relevant NDA(s)	-
Relevant IND(s):	111853
Formulation; Strength(s):	10 mL multiple dose vials: 0.5 mg/mL and 1 mg/mL
Proposed Indication:	For the reversal of the effects of non-depolarizing neuromuscular blocking agents.
Proposed Dosage Regimen:	• **Dosage in Adults (IV)** A peripheral nerve stimulator capable of delivering a train-of-four (TOF) stimuli is necessary to determine the appropriate timing and dose of neostigmine and to assess the extent of reversal • administer when a twitch response to the first stimulus in the TOF (b) (4) is at least 10% of its baseline level, i.e., the response prior to NMBA administration. • A 0.03 mg/kg to 0.07 mg/kg dose of neostigmine will generally achieve a TOF twitch (b) (4) ratio of 90% (TOF_{09}) within 10 to 20 minutes of administration. (b) (4) • Do not exceed a total dose of 0.07 mg/kg or 5 mg, whichever is less. • Continue TOF monitoring to evaluate the extent of recovery of neuromuscular function and the need for an additional dose of neostigmine. • Do not rely solely on TOF monitoring to determine the adequacy of reversal of neuromuscular blockade. • Continue to monitor patients for adequacy of reversal from NMBAs for an appropriate period of time (b) (4) • **Dosage in** (b) (4) (b) (4)

(b) (4) Pediatric dosing is similar to that of adults.

- **Dose of Anticholinergic (atropine or glycopyrrolate)** (b) (4) .

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the NDA 204078 for neostigmine methylsulfate intravenous injection. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CP Findings

Elcat Pharmaceuticals submitted on 07/31/2012, a New Drug Application (NDA) 204078, Neostigmine Methylsulfate Injection, USP, 0.5 and 1.0 mg/mL, accordance with 505(b)(2) provisions of the Food, Drug and Cosmetic Act for the use of "neostigmine" for reversal of non-depolarizing neuromuscular blocking agents. The Applicant's request for approval of this NDA is based on the literature studies for both pediatrics and adult population.

Neostigmine has been used since the late 1930s with extensive clinical experience most likely as an unapproved drug. It should be noted that, according to the published Federal Register Notice Vol. 61, No 151, Monday, August 5, 1996, Docket No. 96N-0257, Progstigmin (neostigmine bromide solution) Opthalmic Solution 5%, NDA 6-54, was withdrawn by Hoffmann-La Roche. Therefore, neostigmine is not a new molecular entity or new chemical entity. Since there are no approved neostigmine products on the market, there is no reference listed drug for this NDA. As well, the relative bioavailability comparison is not feasible. For this application, the Applicant did not conduct any clinical trials in this submission. Instead, the Applicant submitted supporting information, including the proposed dosing regimen, from the literature for approval.

For this NDA, during April 16, 2012 meeting with sponsor, the Agency stated that the Applicant may submit their NDA based the literature information. Agency also stated that the formal review of submitted information in the NDA application will determine the adequacy of literature to support approval and translation into labeling language for the product.

[redacted] (b) (4)

The proposed dosage for neostigmine in adults and pediatrics is 0.03 to 0.07 mg/kg. . The Package Insert recommends that anticholinergic agents, atropine sulfate (b) (4) or glycopyrrolate (b) (4), also be administered intravenously using separate syringes. It should be noted that atropine and glycopyrrolate have been used in clinical practice for at least a couple of decades as an adjunct to reversal of neuromuscular blockade. Atropine undergoes enzymatic hydrolysis. The majority of glycopyrrolate dose administered intravenously has been reported to be eliminated in urine as unchanged moiety. The pharmacokinetic interactions between neostigmine and atropine or glycopyrrolate are not expected. With respect to dosing, the Labeling stated that "the dose (b) (4) on an individual basis with the use of a peripheral nerve simulator device." As dictated by the indication, neostigmine usage in reversal of non-depolarizing neuromuscular blocking agents may be considered as a single administration with a titration scheme.

With respect to bioavailability/bioequivalence requirement as per the 21 CFR320, there are no concerns due to the fact that 1) the bioavailability is "self-evident" since the Applicant's formulation is for intravenous use; and, 2) that the Applicant and intravenous formulations described in the literature (based on the descriptions provided in the publications, e.g., neostigmine, preservatives (phenol and saline) appear to be simple solutions. Although the intravenous solutions submitted in the literature appear to use three different drug substances, neostigmine methylsulfate, neostigmine bromide and neostigmine, the main active ingredient in the formulations is neostigmine. Therefore, the formulations used in the literature seem to be appropriate for comparison from a clinical pharmacology perspective.

This NDA (204078) (b) (4) submitted similar clinical pharmacology literature articles. Overall 8 clinical pharmacology and 5 neostigmine bioanalytical publications are reviewed and presented in the table format. Most of the clinical pharmacology publications utilized the methods published by Chan et al. (1976) or De Ruyter et al. (1980). All submitted publications in this NDA submission were reviewed comprehensively based on the current review practice. In particular, study design, dosage administration, blood sampling scheme, and analytical methodology information were focused during the review.

Overall findings

The submitted literature information is presented following tables

- Table 1: Overview of the study design, treatments, dose and analytical methodology of clinical pharmacology publications including bioanalytical publications
- Table 2: Overview of bioanalytical assay methods used by the literature articles
- Table 3: Gist of the obtained PK parameters in different literature articles.

Table 1: Overview of the study design, treatments, and analytical methodology of clinical pharmacology publications

Author	Study objectives	# of patients	Treatment		Bioanalytcal 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 neuromus cular (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 provided	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 provided	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

Table 2: Overview of bioanalytical assay methods used in the literature articles.

	Matrix	**Assay Methodology**	**Analyte**	**Calibration / Assay Range**	**Analytical Sensitivity**
Chan (1976) J Chrom. 120: 349-358	Human plasma	Gas-liquid chrom with nitrogen detection, followed by MS	Neostigmine bromide	Neostigmine was dissolved in sterile water and a series of 3 mL solutions in plasma were prepared covering the range 50 – 1000 ng/mL	5 ng/mL
De Ruyter (1980) J of Chrom. 183: 193-201	Human plasma	Reverse phase, liquid chrom	Neostigmine	Calibration curves not described. Assay range 0 – 1000 ng/mL	5 ng/mL
Davison (1980) Methods and Findings Ex Clin Pharm, 2: 77-82 Cursory review only	Human plasma	Gas chrom with nitrogen detection	Neostigmine bromide	Neostigmine was dissolved in sterile water and a series of 3 mL solutions in plasma were prepared covering the range 5 – 100 ng/mL	4.7 ng/mL
Varin et al., (1999) *J of Chrom.(B), 723: 319-323* Cursory review only	Human plasma and CSF	High performance liquid chrom with UV detection	Neostigmine methylsulfate	Drug free plasma was spiked with neostigmine methylsulfate and serial dilutions between 2.6 – 167 ng/mL were prepared for calibration curves	2.6 ng/mL for plasma 6.9 ng/mL for CSF
Somani et al. (1980) *Clin Pharm Thera, 28: 66-68* Cursory review only	Human plasma and urine	Plasma: per Chan et al. Urine: Scintillation spect. of labeled drug	Neostigmine methylsulfate	Per method of Chan et al.	5-7 ng/mL for plasma

Table 3: Gist of the obtained PK parameters in different literature articles.

Study	No. of Subjects	Neostigmine Dose	Atropine Sulphate dose	Cmax, Tmax, AUC	$T_{1/2}$ β (min) Mean ± SD	Vdss (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		Cmax 83 ± 9 ng/ml Tmax 5 min AUC 127 ±16 (ng.h/mL)	113 ± 34	0.18 ± 0.05	1.14 ± 0.44 a
Young etal. 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
Heier 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/h/kg
b mean ± SE
c Based on median weight
d- Vd in liters
M- male; F-female

Adequacy of the neostigmine clinical pharmacology information from the publications:

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

Single dose half-life:

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

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

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

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

Renal
Cronnelly et al, determined the pharmacokinetics of neostigmine in patients with normal renal function (n = 8), undergoing renal transplantation (n = 6) or bilateral nephrectomy (n = 4). Neostigmine, 0.07 mg/kg, and atropine, 0.03 mg/kg, were given by infusion over a 2·min period. Blood samples were obtained at pre-, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min following neostigmine administration. Plasma conc vs time data was fitted to a two-compartment pharmacokinetic model. Elimination half life for normal, transplant and anephric patients were 79.8 ± 48.6, 104.7 ± 64 and 181 ± 54 min (mean ± SD), respectively. Clearances for normal, transplant and anephric patients were 16.7 ± 5.4, 18.8 ± 5.8 and 7.8 ± 2.6 mL/min/kg (mean ± SD), respectively. The clearance in patients with impaired renal function is lower compared to patients with normal renal function. Use with caution in patients with impaired renal function.

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

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

Gender, Race

No information was submitted.

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

2 QBR

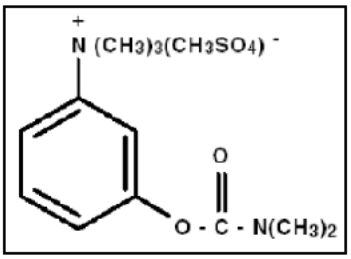
2.1 General Attributes of the Drug and Drug Product

2.1.1 What are known properties of neostigmine?

Neostigmine is an anticholinesterase agent. Neostigmine was first synthesized by Aeschlimann and Reinert in 1931 and was subsequently reported to be effective in the symptomatic treatment of myasthenia gravis.
Its molecular formula is $C_{13}H_{22}N_2O_6S$. It has a molecular weight of 334.39 g/mol. Neostigmine is soluble in water and sparely soluble in acetone.

Chemical name: 3-[(dimethylcarbamoyl)oxy]-N,N,N-trimethylanilinium methanesulfonate

Neostigmine methylsulfate structure:



2.1.2 What is neostigmine to-be-marketed formulation?

The proposed neostigmine formulation is presented below. It is a simple solution for intravenous use. Neostigmine methylsulfate injection, USP is available in two strengths, 0.5 mg/mL and 1.0 mg/mL, with a fill volume of 10 mL in a multi-dose glass vial. (b) (4)

The composition of the to-be-marketed drug product, which has not changed during development, is provided in Table 2.1.1

Table 2.1.1: Composition of Neostigmine Methylsulfate Injection, USP

Component	Function	Quality Standard	Quantity (mg/mL)	
			1:2000 Conc.	1:1000 Conc.
Neostigmine methylsulfate	API	USP, Ph. Eur., JP	0.5	1.0
Phenol	Preservative	USP-NF, Ph. Eur., JP	4.5	4.5
Sodium acetate trihydrate	(b) (4)	USP-NF, Ph. Eur., JP	0.2	0.2
Acetic acid/Sodium hydroxide	pH adjustment	USP-NF, Ph. Eur., JP	q.s. to pH 5.5	q.s. to pH 5.5
Water for Injection	(b) (4)	USP, Ph. Eur., JP	(b) (4)	

2.1.3 What is the proposed mechanism of action?

Neostigmine is a parasympathomimetic that acts as a reversible acetylcholinesterase inhibitor (anticholinesterase). Neostigmine inhibits the hydrolysis of acetylcholine by competing with acetylcholine for binding to acetylcholinesterase at sites of cholinergic transmission. By reducing the breakdown of acetylcholine, neuromuscular transmission is facilitated. Neostigmine also has direct postsynaptic cholinomimetic effects which can be managed clinically by the co-administration of atropine or glycopyrrolate. Neostigmine inhibition of acetylcholinesterase is fully reversible.

Neostigmine is commonly used at the end of general anesthesia to speed recovery from neuromuscular block, which shortens the wait time before it is safe to transfer patients from the operating room to post-operative care. Its role in the surgical arena is for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs).

2.1.4 What are the proposed dosage and route of administration?

- The proposed route of administration is via the intravenous route for the use of "neostigmine" for reversal of non-depolarizing neuromuscular blocking agents.

  Dosage in Adults (IV)

  A peripheral nerve stimulator capable of delivering a train-of-four (TOF) stimuli is necessary to determine the appropriate timing and dose of neostigmine and to assess the extent of reversal

  - administer when a twitch response to the first stimulus in the TOF (b) (4) is at least 10% of its baseline level, i.e., the response prior to NMBA administration.
  - A 0.03 mg/kg to 0.07 mg/kg dose of neostigmine will generally achieve a TOF twitch (b) (4) ratio of 90% (TOF_{09}) within 10 to 20 minutes of administration. (b) (4)
  - Do not exceed a total dose of 0.07 mg/kg or 5 mg, whichever is less.
  - Continue TOF monitoring to evaluate the extent of recovery of neuromuscular function and the need for an additional dose of neostigmine.
  - Do not rely solely on TOF monitoring to determine the adequacy of reversal of neuromuscular blockade.
  - Continue to monitor patients for adequacy of reversal from NMBAs for an appropriate period of time (b) (4).
- **Dosage in** (b) (4)

(b) (4)

Pediatric dosing is similar to that of adults.

- **Dose of Anticholinergic (atropine or glycopyrrolate)**

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials and efficacy measurements?

There were no clinical studies conducted under the application. However, the Applicant submitted literature information to support for the approval. The discussion regarding the efficacy and safety of neostigmine is beyond the scope of this review, as the Medical Reviewer is fully committed to review the submitted literature information. The reader is prompted to see Medical Officer's Review by Dr. Arthur Simone for additional information.

2.2.2 Does neostigmine prolong the QT interval?

No information was submitted to characterize neostigmine's effect on QT.

2.2.3 Protein binding, metabolism, enzyme induction/inhibition

The following information was obtained from the literature.

Protein Binding:
Protein binding to human serum albumin ranges from 15 to 25%.

Metabolism:
Nonclinical studies demonstrate that Neostigmine is eliminated in the urine and feces (unabsorbed material given by routes other than IV) unchanged, and also undergoes hepatic metabolism in the liver microsomes. Up to 5 metabolites of neostigmine have been reported as excreted in the urine.
Somani et al. (1980) studied the kinetics and metabolism of neostigmine administered intramuscularly to eight myasthenia gravis patients. Three patients received atropine 0.6 mg by subcutaneous injection and after 30 minutes received ^{14}C neostigmine (1000 or 2000 µg) by intramuscular injection. The urine was collected at 1, 2, 4, 8, and 24 hours. The principle metabolite of neostigmine, 3-hydroxy-phenyltrimethylammonium (PTMA), accounted for 15% of the radioactivity excreted in urine in 24 hours. Unchanged neostigmine accounted for 48.7% of the radioactivity excreted in urine in 24 hours. Small amounts of 3-hydroxyphenyltrimethylammonium glucuronide were also present in the urine. These clinical findings are supported by data reported in nonclinical studies

2.2.4 What are the single dose PK parameters?

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

2.3 Intrinsic Factors

No information was submitted to characterize neostigmine in race and gender.

2.3.1 What is the neostigmine exposure in pediatric subjects?

Fisher et al. determined the pharmacokinetics of neostigmine in infants, children and adults. Three groups of five patients (infants, 2-10 months; children, 1-6 years; and adults, 29-48 years) were administered neostigmine as a 2-min intravenous infusion. Infants' dose was 100 µg/kg; children and adults doses were 70 µg/kg. Atropine dose was 30 µg/kg. Blood samples were obtained intermittently for 4 h (pre-, 0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min. post drug administration), and concentrations of neostigmine were determined using a high-pressure liquid chromatographic technique (analytical method described by De Ruyter, et al, 1980; sensitivity: 3.0 ng/ml; coefficient of variation of 5%). The plasma conc vs. time data were fitted to a three-compartment pharmacokinetic model. Distribution half-lives and distribution volumes were similar for infants, children, and adults. Elimination half-life for infants, children and adults were 39 ± 5 min, 48 ± 16 min, and 67 ± 8 min (mean ± SD), respectively. Clearance for infants, children and adults were 13.6 ± 2.8, 11.1 ± 2.7 and 9.6 ± 2.3 mL/min/kg (mean ± SD), respectively. The following plasma profiles were presented in the publication.

Neostigmine conc. vs. time profiles for infants, children and adults

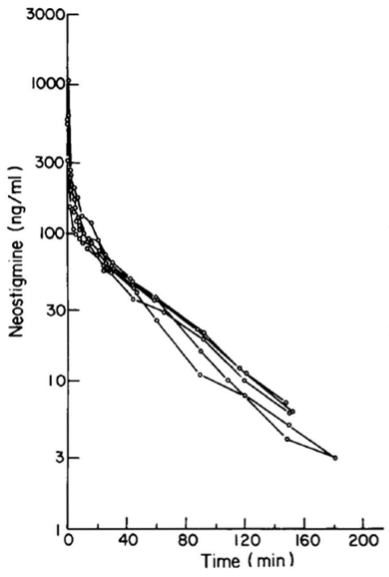


FIG. 4. Serum concentrations following a 2-min intravenou infusion of neostigmine (100 µg/kg) in five infants.

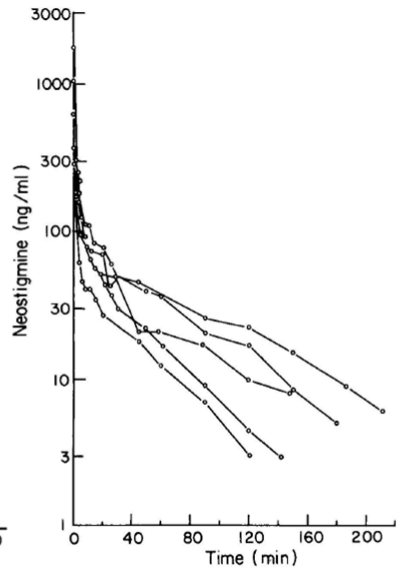


FIG. 5. Serum concentrations following a 2-min intravenous infusion of neostigmine (70 µg/kg) in five children.

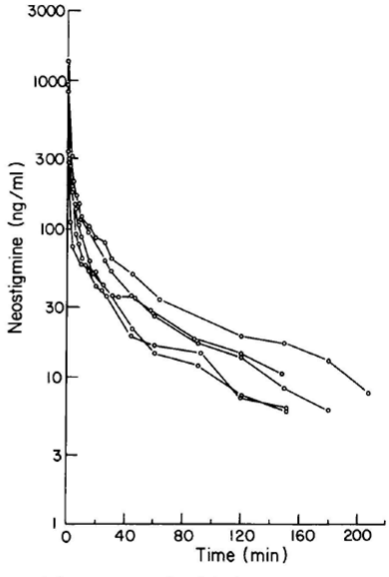


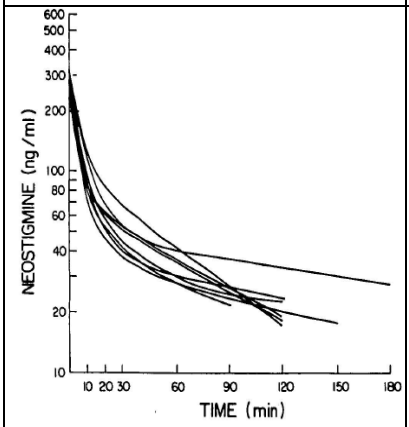
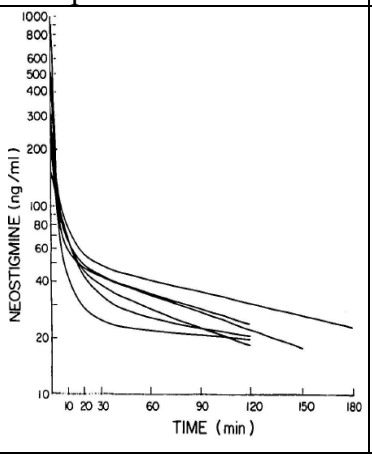
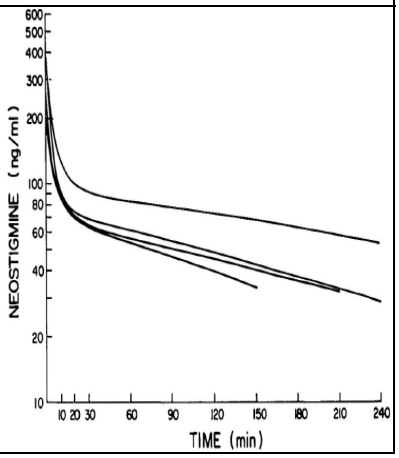
FIG. 6. Serum concentrations following a 2-min intravenous infusion of neostigmine (70 µg/kg) in five adults.

No individual parameters are presented. Additionally, no subject information was given (e.g., body weight, dose administered, etc.). It also should be noted that the publication did not contain adequate analytical information. However, by looking at the presented neostigmine profiles, there may be a reasonable assurance that the presented PK parameters are acceptable.

2.3.2 Renal impairment

Cronnelly et al., determined the pharmacokinetics of neostigmine in patients with normal renal function (n = 8), undergoing renal transplantation (n = 6) or bilateral nephrectomy (n = 4). Neostigmine, 0.07 mg/kg, and atropine, 0.03 mg/kg, were given by infusion over a 2·min period. Blood samples were obtained at pre-, 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min following neostigmine administration. Plasma conc vs time data was fitted to a two-compartment pharmacokinetic model. Elimination half life for normal, transplant and anephric patients were 79.8 ± 48.6, 104.7 ± 64 and 181 ± 54 min (mean ± SD), respectively. Clearances for normal, transplant and anephric patients were 16.7 ± 5.4, 18.8 ± 5.8 and 7.8 ± 2.6 mL/min/kg (mean ± SD), respectively.

Mean plasma conc. vs time profiles for normal, immediate renal transplantation and anephric patients, respectively, are presented below.

Normal:	Immediate renal transplantation:	Anephric patients:
		

No individual parameters were presented in the publication. Additionally, no subject information was given (e.g., body weight, dose administered, etc.). It also should be noted that the publication did not contain adequate analytical information. However, by looking at the presented neostigmine profiles, there may be a reasonable assurance that the presented PK parameters are acceptable. The clearance in patients with impaired renal function is lower compared to patients with normal renal function. Use with caution in patients with impaired renal function.

2.3.3 Hepatic impairment

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

2.3.4 Elderly

According to an abstract published (American Society of Anesthesiologists (ASA) meeting), Young et al. (1984) compared the neostigmine pharmacokinetics of five elderly

patients (ages 71-80) and seven younger patients (ages 34-56). A bolus of 70 µg/kg of neostigmine and 20 µg/kg of atropine were administered intravenously. The only significant difference between the young and elderly was initial volume of distribution (Vi), which was lower in the elderly. Numerically the clearance in elderly (23.4 ± 4 mL/kg/min) is also lower compared to younger patients (33.5 ± 4 mL/kg/min). Overall the duration of maximum response to neostigmine was significantly prolonged in the elderly (42 ± 10 minutes) compared to the younger group (13.14 ± 2.4 minutes). A caution should be exercised in interpreting the data since the fact that this abstract is not a fully peer reviewed article. However, considering the elderly patients will have decreased renal function which will lead to decreased neostigmine clearance, neostigmine should be used with caution in patients with impaired renal function.

Table 1. Pharmacokinetic Parameters (Mean ± SE)

	Young, n=7 (34-56 yrs)	Elderly, n=5 (71-80 yrs)	P
$t_{½}$ elim (min)	18.5 ± 7	16.7 ± 0.8	NS
Clp ($ml \cdot kg^{-1} \cdot min^{-1}$)	33.5 ± 4	23.4 ± 5	NS
V_i (l/kg)	.10 ± .04	.068 ± .018	<.05
Vd_{area} (l/kg)	.549 ± .12	.566 ± .13	NS

Table 2. Response Times (Min, Mean ± SE)

	Young, n=7 (34-56 yrs)	Elderly, n=5 (71-80 yrs)	P
Onset of Response	0.52 ± .008	0.77 ± 0.1	NS
Maximum Response	6.7 ± 1.3	6.7 ± 1.4	NS
Duration of Maximum Response	13.14 ± 2.4	42 ± 10	<.01

2.4 Extrinsic Factors

No information was submitted to characterize neostigmine. The pharmacokinetic interaction between neostigmine and other drugs has not been studied. Neostigmine is metabolized by microsomal enzymes in the liver. Use with caution when using neostigmine with other drugs which may alter the activity of metabolizing enzymes or transporters.

2.5 General Biopharmaceutics – Not applicable

2.6 Analytical Section

2.6.1 How are neostigmine and its metabolites measured in plasma?

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

Matrix **Assay** **Analyte** **Calibration / Assay** **Analytical**

		Methodology		Range	Sensitivity
Chan (1976) J Chrom. 120: 349-358	Human plasma	Gas-liquid chrom with nitrogen detection, followed by MS	Neostigmine bromide	Neostigmine was dissolved in sterile water and a series of 3 mL solutions in plasma were prepared covering the range 50 – 1000 ng/mL	5 ng/mL
De Ruyter (1980) J of Chrom. 183: 193-201	Human plasma	Reverse phase, liquid chrom	Neostigmine	Calibration curves not described. Assay range 0 – 1000 ng/mL	5 ng/mL
Davison (1980) Methods and Findings Ex Clin Pharm, 2: 77-82 Cursory review only	Human plasma	Gas chrom with nitrogen detection	Neostigmine bromide	Neostigmine was dissolved in sterile water and a series of 3 mL solutions in plasma were prepared covering the range 5 – 100 ng/mL	4.7 ng/mL
Varin et al., (1999) J of Chrom.(B), 723: 319-323 Cursory review only	Human plasma and CSF	High performance liquid chrom with UV detection	Neostigmine methylsulfate	Drug free plasma was spiked with neostigmine methylsulfate and serial dilutions between 2.6 – 167 ng/mL were prepared for calibration curves	2.6 ng/mL for plasma 6.9 ng/mL for CSF
Somani et al. (1980) Clin Pharm Thera, 28: 66-68 Cursory review only	Human plasma and urine	Plasma: per Chan et al. Urine: Scintillation spect. of labeled drug	Neostigmine methylsulfate	Per method of Chan et al.	5-7 ng/mL for plasma

3 Detailed Labeling Recommendations

(b) (4)

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

4.2 Individual study review

(b) (4)

4.3 Cover Sheet and OCPB Filing/Review Form

On **initial** review of the NDA/BLA application for filing:

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Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	***NDA*-204078**	**Brand Name**	
OCP Division (I, II, III, IV, V)	***II***	**Generic Name**	**Neostigmine Methylsulfate Injection, USP**
Medical Division	**DAAAP**	**Drug Class**	***Anti-cholinesterases***
OCP Reviewer	***Suresh B Naraharisetti***	**Indication(s)**	**For reversal of effects of non-depolarizing neuromuscular blocking agents**
OCP Team Leader	***Yun Xu***	**Dosage Form**	**Injection 0.5 and 1 mg**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	07/31/2012	**Route of Administration**	**Injection**
Estimated Due Date of OCP Review		**Sponsor**	**Eclat Pharmaceuticals**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date			
Clin. Pharm. and Biopharm. Information			

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				The NDA is literature based; the Applicant submitted literature clinical pharmacology studies.
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				

Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	No clinical pharmacology studies were conducted with the proposed product
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			The NDA is literature based; the Applicant submitted literature clinical pharmacology studies.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response			X	

	guidance?				
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	The applicant submitted literature information
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

BACKGROUND

Eclat Pharmaceutcials submitted a New Drug Application (NDA) for Neostigmine Methylsulfate Injection, USP, in accordance with Section 505(b)(2) of the Federal Food, Drugs, and Cosmetic Act. Neostigmine Methylsulfate Injection has a long history of clinical use in patients as a reversal agent to the neuromuscular blocking agents and has been marketed as an unapproved drug. The Applicant seeks an indication of a reversal agent to the neuromuscular blocking effects of non-depolarizing muscle relaxants. The Applicant's request for approval of this NDA submission is based on the literature for both pediatrics and adult population. (b) (4)

The pre-IND and EOP2 meeting with the applicant was held in June 2011 and May 2012, respectively to discuss the appropriateness of literature information to support approval. The Agency conveyed to the applicant to summarize all available Clinical Pharmacology information in the NDA submission. The referenced literature in the submission included studies with neostigmine intravenous injections. It is noted that the proposed Neostigmine Methylsulfate Injection formulation contains two inactive ingredients namely (b) (4) phenol, USP, and sodium acetate, USP. (b) (4) acetic acid, USP, and sodium hydroxide, NF, are used to adjust pH of the injection solution. (b) (4)

(b) (4)

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From a clinical pharmacology perspective, the adequacy of the literature information in the application for the product labeling purpose will be a review issue. The application is recommended for filing, and, there are no comments/information requests to be conveyed to the Applicant at this time.

Suresh Babu Naraharisetti	September 9, 2012
Reviewing Clinical Pharmacologist	Date
Xu Yun	September 9, 2012
Team Leader/Supervisor	Date

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

/s/

SURESH B NARAHARISETTI
03/14/2013

YUN XU
03/14/2013