CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216903Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	216903
Link to EDR	\\CDSESUB1\evsprod\NDA216903\0002
Submission Date	4/23/2022
Submission Type	*[Standard review]*
Brand Name	Neostigmine and Glycopyrrolate Injection
Generic Name	Neostigmine Methylsulfate and Glycopyrrolate Injection
Dosage Form and Strength	Parenteral Solution
Route of Administration	Intravenous
Proposed Indication	(b) (4)
Applicant	Slayback Pharma
Associated IND	*[IND 139866]*
OCP Division:	*Division of Neuropsychiatric Pharmacology*
OND Division:	*Division of Anesthesia, Addiction and Pain Medicine*
Clinical Pharmacology Reviewer	*[Srikanth C. Nallani, Ph.D.]*
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1. EXECUTIVE SUMMARY

1.1 Recommendations

The submission is acceptable from a clinical pharmacology perspective. The submission comprises of information on chemistry manufacturing and controls, a biowaiver/bio-bridge request to waive the PK bridging study between the new product and the listed drugs for this 505(b)(2) application, labeling and clinical safety discussion. No new clinical pharmacology study was submitted in this NDA. Please refer to the biopharmaceutics review regarding the biowaiver/bio-bridge request. The labeling is acceptable, as it describes clinical pharmacology information already described in the reference drug labels.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	In clinical practice, neostigmine and glycopyrrolate are administered separately. The product plans to administer simultaneously. No clinical and clinical pharmacology studies were conducted.
General dosing instructions	Neostigmine methylsulfate and Glycopyrrolate Injection is for intravenous use only and should be injected slowly over a period of at least 1 minute. The Neostigmine methylsulfate and Glycopyrrolate Injection dosage is weight-based
Dosing in patient subgroups (intrinsic and extrinsic factors)	For pediatric population age >2 years, adult guidelines should be followed when Neostigmine methylsulfate and Glycopyrrolate Injection is administered.
Labeling	The fixed-dose combination product label consists of labeling from Bloxiverz (neostigmine methylsulfate) and Robinul (glycopyrrolate Inj)
Bridge between the to-be-marketed and clinical trial formulations	No clinical or clinical pharmacology studies were conducted. Slayback Pharma submitted a biowaiver/bio-bridge request to waive the PK bridging study between the new product and the listed drugs for this 505(b)(2) application, as the proposed combination is an IV injection as is the case with Robinul and Bloxiverz.
Other (specify)	None.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Slayback Pharma's proposed 505(b)(2) NDA product relies on the Agency's findings of safety, efficacy, and PK for the reference drugs Bloxiverz and Robinul. The clinical pharmacology aspects of product labels for BLOXIVERZ (Neostigmine Methylsulfate Injection, NDA 204078) and ROBINUL (Glycopyrrolate Injection, USP, NDA 017558) serve as a basic description of the PK of neostigmine and glycopyrrolate.

Slayback Pharma's neostigmine methylsulfate, a cholinesterase inhibitor, and glycopyrrolate bromide, an antimuscarinic agent, have been developed as a fixed-dose combination for intravenous (IV) injection. The proposed indication of this combination product is for the reversal of the effects of non-depolarizing neuromuscular blocking (NMB) agents after surgery, (b) (4) in patients 2 years and older.

There are no clinical studies of absolute or relative bioavailability of the Slayback Pharma's combination neostigmine/glycopyrrolate product because these products are administered IV and bioequivalence is self-evident. Slayback Pharma has submitted a biowaiver/bio-bridge request to waive the PK bridging study between the new product and the listed drugs in accordance with 21 Code of Federal Regulations (CFR) 320.22(b)(1) and 21 CFR 320.24(b)(6) because Slayback Pharma's proposed combination product's in vivo bioavailability or bioequivalence is considered self-evident (given it is a parenteral solution product and intended solely for administration by IV injection), and the differences in the excipients are not expected to affect in vivo performance.

The use of anticholinesterases (neostigmine in this case), along with the use of anticholinergics (glycopyrrolate in this case), to reverse neuromuscular blockade at the end of surgery is an important part of an anesthesiologists' practice for the prevention of residual neuromuscular block after administration of neostigmine.

2.1 Pharmacology and Clinical Pharmacokinetics

Neostigmine methylsulfate is a competitive cholinesterase inhibitor. By reducing the breakdown of acetylcholine, neostigmine methylsulfate induces an increase in acetylcholine in the synaptic cleft which competes for the same binding site as nondepolarizing neuromuscular blocking agents, and reverses the neuromuscular blockade. Neostigmine methylsulfate-induced increases in acetylcholine levels results in the potentiation of both muscarinic and nicotinic cholinergic activity. The resulting elevation of acetylcholine competes with nondepolarizing neuromuscular blocking agents to reverse neuromuscular blockade.

Because of the known pharmacology (muscarinic effects) of neostigmine methylsulfate as an acetylcholinesterase inhibitor, cardiovascular effects such as bradycardia, hypotension or dysrhythmia would be anticipated. Adverse reactions to neostigmine methylsulfate are most often attributable to exaggerated pharmacological effects, in particular, at muscarinic receptor sites. The use of an anticholinergic agent, e.g., atropine sulfate or glycopyrrolate, may prevent or mitigate these reactions. An anticholinergic (glycopyrrolate in this case) is always administered in conjunction with an acetylcholinesterase inhibitor in the clinical settings since it can offset the increased activation of

muscarinic receptors. With the proposed product, these agents are administered simultaneously with the administration of a mixture of neostigmine with glycopyrrolate in the same syringe.

2.2 Dosing and Therapeutic Individualization

Table: Comparison of Proposed Drug Product and Reference Listed Drugs.

	Slayback Pharma's Proposed Drug Product	**RLD – BLOXIVERZ®**	**RLD - ROBINUL®**
Condition(s) of Use and/or Indication(s)	Neostigmine Methylsulfate and Glycopyrrolate Injection, a fixed-dose combination of a cholinesterase inhibitor and antimuscarinic agent, is indicated for the reversal of the effects of NMB agents after surgery, [redacted] (b) (4)	BLOXIVERZ®, a cholinesterase inhibitor, is indicated for the reversal of the effects of NMB agents after surgery.	In Anaesthesia: ROBINUL® indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anaesthesia and intubation. When indicated, it may be used intraoperatively to counteract surgically- or drug-induced or vagal reflexes associated arrhythmias. Glycopyrrolate protects against peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents, such as neostigmine and pyridostigmine, given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants.
Dosage and Administration	Should be administered by trained healthcare providers. Peripheral nerve stimulator and monitoring for twitch responses should be used to determine when Neostigmine Methylsulfate and Glycopyrrolate Injection should be initiated and if additional doses are needed. For reversal of NMB agents with shorter half-lives in patients aged 2 years and up, when first twitch response is substantially >10% of baseline, or when a second twitch is present: 0.03 (b) (4) /kg by IV route. For reversal of NMB agents with longer half-lives or when first twitch response is close to 10% of baseline in patients aged 2 years and up: 0.07 (b) (4) /kg by IV route. Maximum total dosage is 0.07 (b) (4) /kg or up to a total of 5 (b) (4) (whichever is less).	Should be administered by trained healthcare providers. Peripheral nerve stimulator and monitoring for twitch responses should be used to determine when BLOXIVERZ should be initiated and if additional doses are needed. For reversal of NMB agents with shorter half-lives, when first twitch response is substantially >10% of baseline, or when a second twitch is present: 0.03 mg/kg by IV route. For reversal of NMB agents with longer half-lives or when first twitch response is close to 10% of baseline: 0.07 mg/kg by IV route. Maximum total dosage is 0.07mg/kg or up to a total of 5 mg (whichever is less). An anticholinergic agent (e.g., atropine sulfate or glycopyrrolate) should be administered prior to or concomitantly with BLOXIVERZ.	***Reversal of Neuromuscular Blockade***. The recommended dose of ROBINUL Injection is 0.2 mg for each 1.0 mg of neostigmine or 5.0 mg of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by IV injection and may be mixed in the same syringe.

2.2.1 General dosing

Neostigmine and glycopyrrolate are administered IV for the indication of reversal of effects of nondepolarizing neuromuscular blocking agents after surgery, while minimizing the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) associated with cholinesterase inhibition.

2.2.2 Therapeutic individualization

The Division and Pediatric Review Committee (PeRC) agreed to a waiver in pediatric patients from birth to 2 years because the drug or biologic product would be ineffective or unsafe for this pediatric age group, per 17 December 2019 and 22 September 2020, 13 December 2022 PeRC meetings.

Glycopyrrolate is approved for pediatric patients older than one month of age up to 16 years.

Neostigmine is approved for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery in pediatric patients of all ages.

2.3 Summary of Labeling Recommendations

The sponsor proposed labeling is based on clinical pharmacology aspects described in reference drugs Robinul and Bloxiverz. Additions and deletions are marked by bold text and strikethrough text, respectively.

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

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