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

Cross-Discipline Team Leader and Division Director Summary Review

Date	February 23, 2023
From	Lee Anne Connell-Templin, MD; Renee Petit-Scott, MD; Alla Bazini, MD; Rigoberto Roca, MD
NDA#	216903
Applicant	Slayback Pharma LLC
Date of Original Submission	April 25, 2022
PDUFA Goal Date	February 25, 2023
Proprietary Names	Prevduo
Established or Proper Name	Neostigmine methylsulfate and glycopyrrolate injection
Dosage Form	Intravenous injection; neostigmine methylsulfate 3 mg/3 mL (1 mg/mL), glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) in a prefilled syringe (PFS)
Applicant Proposed Indication	For the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery, while (b) (4)
Approved Indication	For the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery, while decreasing the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) associated with cholinesterase inhibition following NMBA reversal administration.
Applicant Proposed Dosing Regimen	For reversal of neuromuscular blocking agents (NMBAs) with shorter half-lives in patients age 2 years and up, when first twitch response is substantially greater than 10% of baseline, or when a second twitch is present: • (b) (4) For reversal of NMBAs with longer half-lives or when first twitch response is close to 10% of baseline in patients age 2 years and up: (b) (4)
Approved Dosing Regimen	For reversal of NMBAs with shorter half-lives in patients age 2 years and up, when first twitch response is substantially greater than 10% of baseline, or when a second twitch is present: • 0.03 mg/kg of neostigmine methylsulfate (0.006 mg/kg glycopyrrolate) by intravenous route For reversal of NMBAs with longer half-lives or when first twitch response is close to 10% of baseline in patients age 2 years and up: • 0.07 mg/kg of neostigmine methylsulfate (0.014 mg/kg of glycopyrrolate) by intravenous route Maximum total dosage is 0.07 mg/kg neostigmine methylsulfate or up to a total of 5 mg neostigmine methylsulfate (whichever is less)
Regulatory Action	Approval

OND Action Package included reviews by the following:		
Clinical Reviewer	Lee Anne Connell-Templin, MD	CDER/OND/DAAP
Clinical Team Leader	Renee Petit-Scott, MD	CDER/OND/DAAP
Clinical Pharmacology Reviewer	Srikanth C. Nallani, PhD	CDER/OTS/OCP/DNP

OND Action Package included reviews by the following:		
Clinical Pharmacology Team Leader	Yun Xu, PhD	CDER/OTS/OCP/DNP
Nonclinical Reviewer	Alexander Son, PhD	CDER/OND/ON/DPTN
Nonclinical Team Leader	Newton Woo, PhD	CDER/OND/ON/DPTN
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)		
Safety Evaluator	Damon Birkemeier, PharmD	CDER/OSE/OMEPRM/DMEPAI
Safety Team Leader	Valerie S. Vaughan, PharmD	CDER/OSE/OMEPRM/DMEPA1
Human Factors Evaluator	Murewa Oguntimein, PhD, MHS, CPH, MCHES	CDER/OSE/OMEPRM/DMEPA1
Associate Director for Human Factors	Jason Flint, MBA, PMP	CDER/OSE/OMEPRM/DMEPA1
Office of Product Quality		
Drug Substance	Zhixing Shan, PhD	CDER/OPQ/ONDP/DNDAPI/NDB2
	Gaetan Ladouceur, PhD	CDER/OPQ/ONDP/DNDAPI/NDB2
Drug Product	Grace Chiou, PhD	CDER/OPQ/ONDP/DNDPII/NDPB3
	Julia Pinto, PhD	CDER/OPQ/ONDP/DNDPII/NDPB3
Process/Facilities	Paul Dexter, MS	CDER/OPQ/OPMA/DMAI/MAB1
	David Anderson, PhD	CDER/OPQ/OPMA/DMAI/MAB1
Biopharmaceutics	Hansong Chen, PhD	CDER/OPQ/ONDP/DB/BB2
	Ta-Chen Wu, PhD	CDER/OPQ/ONDP/DB/BB2
Microbiology	George Arhin, PhD	CDER/OPQ/OPMA/DMAII/MAB1
	Paul Dexter, MS	CDER/OPQ/OPMA/DMAII/MAB1
Applications Technical Lead	Valerie Amspacher, PhD	CDER/OPQ/ONDP/DNDPII/NDPB3
RBPM	Anika Lalmansingh, PhD	CDER/OPQ/OPRO/DRBPMI/RBPMB2
Regulatory Project Manager	Rita Joshi, PharmD	CDER/OND/ORO/DRON

1. Benefit-Risk Assessment

Slayback Pharma LLC (Slayback) submitted NDA 216903 for a fixed dose combination of neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) in a prefilled syringe (PFS) for intravenous (IV) injection, on April 25, 2022. This 505(b)(2) application relies upon the Agency's previous findings of safety and effectiveness for two listed drugs (LDs). The first, Bloxiverz®, NDA 204078, by Exela Pharma Sciences LLC, was approved on May 31, 2013, and is available as 5 mg/10 mL (0.5 mg/mL), and 10 mg/10 mL (1 mg/mL) multi-dose vials. The second, Robinul®, NDA 017558, by Hikma Pharmaceuticals USA INC, was approved on February 6, 1975, and was marketed in 0.2 mg/mL concentrations in 1 mL and 2 mL single-dose vials, and 5 mL and 20 mL multi-dose vials. Robinul was discontinued from sale, not for safety or effectiveness reasons per the Federal Register, on September 6, 2016. The Orange Book: Approved Drug Products with Therapeutic Equivalents (Orange Book) lists several glycopyrrolate products (i.e., two NDAs, 21 ANDAs) currently available.

The Applicant's proposed indication for this fixed dose, drug-device combination drug product was for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery, (b) (4) The agreed upon indication after labeling discussion is for the reversal of the effects of non-depolarizing NMBAs after surgery, *while decreasing* the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) associated with cholinesterase inhibition *following non-depolarizing NMBA reversal administration* (b) (4) The proposed indication represents a combination of the labeled indications for both active ingredients. Specifically, information regarding reversal of NMBAs is from the Bloxiverz label, and information regarding decreased muscarinic effects associated with neostigmine administration is from the

Robinul label. The Applicant's rationale for developing this new fixed dose, drug-device combination product is that it will provide clinicians a convenient combined neostigmine and glycopyrrolate option for reversal of non-depolarizing NMBAs.

The Applicant's proposed benefits of the fixed dose combination of neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) PFS presentation include the following:

- Reduces the number of administration steps compared to the use of individual neostigmine and glycopyrrolate products
- Provides convenient combined administration of neostigmine and glycopyrrolate in a single syringe
- Active ingredients, route of administration (IV), therapeutic indication, and dosing regimens are the same as those of the individual products (LDs) when administered simultaneously
- The PFS presentation contains graduation marks to facilitate administration of selected doses based on weight and clinical response, within the dose ranges established in the approved labeling for the respective LDs
- Increases efficiency in hospital workflows by reducing medication preparation time and decreasing medical waste
- Decreased risks of:
  - medication error due to no need for pharmacy or individual practitioner syringe labeling
  - microbial contamination due to no need for withdrawing medication from a vial, and single patient use PFS

The Applicant has acknowledged the following possible risk associated with the use of the proposed product:

- Increased risk of significant bradycardia in pediatric patients under two years of age – Since the blood pressure in pediatric patients, particularly infants and neonates, is sensitive to changes in heart rate, the effects of an anticholinergic agent (e.g., atropine) should be observed prior to administration of neostigmine to lessen the probability of bradycardia and hypotension. The proposed presentation is not appropriate for pediatric patients below the age of two.

The Division notes the additional possible risks associated with the use of the proposed product include:

- Possible worsening of bradycardia in a bradycardic patient
- Hemodynamic instability in a patient who may not tolerate bradycardia
- The proposed presentation contains less than the maximum total neostigmine dosage for reversal of non-depolarizing NMBAs (i.e., 3mg versus 5 mg), which may lead to underdosing or necessitate use of a second PFS.

Based on review of the information included in the NDA submission, specifically the clinical overview containing the benefit:risk analysis, and clinical expertise, the Division concludes that the benefits of the fixed dose combination of neostigmine methylsulfate 3 mg/3 mL (1

mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) PFS, outweigh the risks for six main reasons.

1. The Division agrees that the proposed fixed dose combination product reduces the number of administration steps compared to those required for preparation of the individual neostigmine and glycopyrrolate products.

2. Provides clinicians a convenient option for combined administration of neostigmine and glycopyrrolate for NMBA reversal.

3. The fixed dose combination may result in less waste of neostigmine than that associated with use of the currently marketed 10 mL vials, and decrease the use of multiple vials or prefilled syringes of lower strength glycopyrrolate.

4. The proposed PFS strength of each drug product (i.e., 3 mg neostigmine, 0.6 mg glycopyrrolate) is commonly used to reverse non-depolarizing NMBAs. The determination of optimal reversal of neuromuscular blockade, and dose of neostigmine and corresponding dose of glycopyrrolate, is based on a number of factors, including the type of non-depolarizing NMBA administered, twitch (train-of-four) response, patient history, type of procedure, spontaneous ventilatory effort, and practitioner experience. While neostigmine up to 5 mg can be safely administered for NMBA reversal, most anesthesia providers will administer only the dose required to minimize the occurrence of muscarinic effects. Therefore, despite the 3 mg (below maximum) dose of neostigmine in the proposed presentation, the PFS strength is reasonable.

5. In the case that greater than 3 mg of neostigmine, and thereby, greater than 0.6 mg of glycopyrrolate, is deemed necessary for adequate neuromuscular blockade reversal, additional doses can be administered by use of additional prefilled syringes. While there may be a risk of overdose if two or more syringes are used and the entire volume from each syringe administered, the Division concludes the risk is low based on the familiarity of anesthesia providers with NMBA reversal. Additionally, given the highly monitored clinical setting in which these drugs are administered, adverse reactions associated with overdose would be quickly recognized and treated.

6. The Applicant has proposed adequate risk mitigation for bradycardia in patients less than two years of age (i.e., not indicated for use in this population), and for worsening bradycardia (i.e., adequate information regarding this risk is included in the label).

In sum, the Division concludes that the benefits of the proposed fixed dose combination of neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) PFS outweigh the risks and offers a convenient dosing alternative for reversal of non-depolarizing NMBAs. Therefore, the Division recommends approval of this NDA.

2. Background

This document will serve as the Cross-Discipline Team Leader and the Division Director Summary Review of NDA 216903 for the proposed fixed dose combination of neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) PFS by Slayback.

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 non-depolarizing NMBAs and reverses the neuromuscular blockade. Because neostigmine increases the concentration of acetylcholine in the synaptic cleft, stimulation of both nicotinic and muscarinic postsynaptic receptors occurs. The most common adverse reactions during treatment with neostigmine are bradycardia, nausea, and vomiting.

Glycopyrrolate is an anticholinergic (antimuscarinic) agent that inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. It is indicated to protect against the peripheral muscarinic effects of cholinergic agents, such as neostigmine, given to reverse neuromuscular blockade due to non-depolarizing NMBAs. The most common adverse reactions of glycopyrrolate include xerostomia (dry mouth); urinary hesitancy and retention; blurred vision and photophobia due to mydriasis (dilation of the pupil); cycloplegia; increased ocular tension; tachycardia; bradycardia; palpitation; and decreased sweating.

The following discussion will include a brief overview of the regulatory history of this application, beginning with PIND 139866 submission.

During a meeting held on November 19, 2018, under PIND 139866, the Division provided advice regarding the proposed indication, the request for a biowaiver, bioequivalence or other clinical studies, the acceptability of the proposed PFS strength and dose of each drug product, the integrated summaries, and human factors requirements. Additional nonclinical, and chemistry manufacturing and controls information was also discussed. The Applicant requested a meeting, held on April 24, 2020, to discuss the Division's comments, dated January 2, 2020, regarding the initial pediatric study plan (iPSP). During this meeting, the Division provided advice on submission of a partial pediatric study waiver, the extrapolation of efficacy data, the need for additional support for use of the proposed combination product, and nonclinical evaluations. On February 1, 2021, the Division agreed with the Applicant's Agreed iPSP.

On April 25, 2022, the Applicant submitted NDA 216903 for a fixed dose combination of neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) in a PFS under the provisions of Section 505(b)(2) of the United States Food, Drug, and Cosmetic Act (FD & C Act), relying on the Agency's previous findings of safety and effectiveness for the LDs, Bloxiverz, NDA 204078, and Robinul, NDA 017558.

On July 7, 2022, the Division provided the 74-day correspondence to the Applicant, which included one potential clinical review issue, in addition to two potential nonclinical and two potential clinical pharmacology review issues. The clinical review issue involved the risk of the proposed presentation worsening bradycardia (in a bradycardic patient), or the occurrence of clinically significant bradycardia when neostigmine and glycopyrrolate are administered in the same syringe. The nonclinical review issues included the submission of a local tolerance study conducted under non-GLP conditions, and an inadequate nonclinical literature search to support Pregnancy Lactation Labeling Rule (PLLR) format. The clinical pharmacology issues included the lack of primary sources to support the pharmacokinetic (PK) information in the draft label, and the reliance on PK data from the published literature.

In the July 29, 2022, Response to Filing Communication, the Applicant acknowledged the Divisions' clinical, nonclinical, and clinical pharmacology comments. Regarding use of the proposed presentation in the setting of bradycardia, the Applicant agreed that clinicians should be informed of the risk of worsening bradycardia with use of the combination product in patients with bradycardia. Updated draft labeling included a warning regarding bradycardia in Section 5.1.

On November 8, 2022, the Division of Medication Error Prevention and Analysis (DMEPA 1) determined that the proposed proprietary name, Prevduo®, is acceptable.

On December 13, 2022, the Division and the Pediatric Review Committee (PeRC) agreed to the Applicant's partial waiver in the pediatric age group birth to less than two years, and that the submitted scientific literature is an adequate assessment of safety and efficacy for the pediatric age group two to less than 17 years. No additional pediatric studies are required.

On January 27, 2023, in response to an IR, the 120-day Safety Update was received.

3. Product Quality

The Office of Product Quality (OPQ) recommends approval of this NDA based on the reviews completed by the drug substance, drug product, process and facilities, biopharmaceutics, and microbiology teams.

The following assessment was reproduced from the Integrated Quality Assessment, dated January 11, 2023 (verbatim):

> *Drug Substance: Adequate*
> The Applicant has provided adequate general information on the drug substance, Neostigmine Methylsulfate, USP. The Applicant has provided adequate general information on the drug substance, Glycopyrrolate, USP.
>
> *Drug Product: Adequate*
> The proposed drug product is a fixed dose combination of a cholinesterase inhibitor and antimuscarinic agent, indicated for the reversal of NMBAs. It is a 3.0 mL prefilled syringe containing 3 mg of neostigmine methylsulfate and 0.6 mg glycopyrrolate (or

1.0 mg/0.2 mg per mL, respectively). The maximum total dosage is 0.07 mL/kg or up to a total of 5 mL (whichever is less). The excipients used in the to be marketed formulation are EDTA, sodium chloride, hydrochloric acid and sodium hydroxide (for pH adjustment), and water. The final drug product is a prefilled syringe packaged in a plastic tray within a carton. It is to be stored at 20-25°C and has a proposed shelf life of (b) (4) months. Based on the data provided, the proposed shelf life of 18 months is granted.

The solution is clear, colorless, and free from any visible particulate matter. The proposed drug product is provided as a single strength for each drug substance, so there is no concern regarding the ability to distinguish strengths. The excipients are common and compendial. It is noted that disodium edetate dihydrate is not listed in the FDA Inactive Ingredients Database (IID) but is listed as edetate disodium. This is acceptable and based on listings of edetate disodium, the excipient is used within the limits of the IID. With regards to the RLDs (*sic)* noted by the Applicant, they do differ from the proposed drug product. The proposed drug product is a fixed-dose combination of the two drug substances, however, the RLDs contain only one of the drug substances. Additionally, the RLDs contain (b) (4) preservatives and/or pH adjusters. None of the RLDs contain EDTA which is utilized in the Applicant's formulation as a (b) (4). The Applicant notes there are no overages in the proposed drug product.

There are no scientific or regulatory concerns regarding the proposed composition of the product.

Environmental: Adequate
Pursuant to 21 CFR 25.31 (a), Gland Pharma Limited and Slayback Pharma claim a categorical exclusion regarding an environmental assessment for the drug product because action on the NDA is not expected to increase use of the active moiety. A statement of no extraordinary circumstances has been submitted per 21 CFR 25.21(d). The Applicant's claim for categorical exclusion is acceptable and adequate for approval of the application.

Quality Labeling: Adequate
The carton and container labeling is adequate, pending the Applicant's acceptance of OPQ's recommended revisions.

Manufacturing: Adequate
The Facility Assessment and Process Assessment have been deemed adequate. The sterile drug product is (b) (4) All relevant facilities deemed adequate based on good manufacturing practice (GMP) compliance. No preapproval inspections (PAIs) requested.

Biopharmaceutics: Adequate

By citing 21 CFR 320.22(b)(1) and 21 CFR 320.24(b)(6), the Applicant requests a waiver of the requirement to conduct in-vivo bioavailability/bioequivalence studies for the proposed drug product. However, 21CFR § 320.22(b)(1) is not applicable because the proposed drug product is a fixed dose combination of two LDs and has different excipients from those presented in two LDs. The Applicant has provided an adequate scientific justification to establish a scientific bridge between the proposed drug product and LDs. permitting reliance on the Agency's findings of efficacy and safety of both LDs, in accordance with 21 CFR 320.24(b)(6) given the following consideration:

1. The LDs were approved for IV and/or IM administration but this proposed drug product is proposed for the IV route only for the same respective indication.
2. The proposed drug product contains different excipients from those presented in individual LDs. The differences in formulation are not expected to affect the drug disposition of Neostigmine Methylsulfate and Glycopyrrolate in humans.
3. The proposed drug product and LD/Reference Standard (RS) have different osmolarities and pHs; however, the differences are not expected to bring any additional safety issues.
4. There is no drug-drug interaction potential between neostigmine and glycopyrrolate that could potentially alter the drug absorption and pharmacokinetics profile of each drug substance.

From a Biopharmaceutics perspective, NDA 216903-Orig-1 for Neostigmine Methylsulfate and Glycopyrrolate Injection, 1.0 mg and 0.2 mg per mL (3 mL Prefilled Syringe) is adequate.

Microbiology: Adequate
The submission is recommended for approval on the basis of sterility assurance.

For additional information refer to the Integrated Quality Review completed by the Chemistry, Manufacturing and Controls (CMC) team, dated January 11, 2023. OPQ recommends approval with no postmarketing commitments or requirements. The Division agrees with the recommendations by the OPQ review team.

4. Nonclinical Pharmacology/Toxicology

The following assessment was reproduced from the pharmacology/toxicology review, dated February 8, 2023 (verbatim).

In support of their drug product, the Applicant submitted a literature search from the time of approval of the LDs to the date of submission regarding pharmacology, pharmacokinetic, ADME, toxicokinetic, and toxicology data for each API. There were no data from published studies that warrant changes to the proposed labeling. The Applicant also submitted a comparison of physiochemical properties between their proposed product, Bloxiverz (neostigmine methylsulfate), Glycopyrrolate Injection, USP (0.2 mg/mL), and a combined mixture between these products in a 1:1 ratio. The proposed drug product is isotonic and within the pH range of the respective LDs.

The Applicant's proposed specifications for drug substance and drug product impurities are within the levels outlined in International Conference on Harmonization (ICH) Q3A(R2) and Q3B(R2). Residual solvent specifications are within the levels as stated in ICH Q3C(R8). Elemental impurities are below the control threshold of 30 percent, as per ICH Q3D. To support the safety of the container closure system, the Applicant provided extractables and leachables studies. One leachable above the safety concern threshold (SCT) of (b) (4) mcg/day were identified and was properly qualified, and therefore there are no concerns with the safety of the prefilled syringe container closure system.

To support the local safety of the combination product, the Applicant conducted an in vitro hemolysis study and a local tolerance (IV/PV) study. It is noted that while the hemolysis study was conducted under good laboratory practice (GLP), the local tolerance was non-GLP and utilized only male rabbits. In response to an IR, the Applicant informed the Division that the local tolerance study was conducted in the spirit of GLP. The Applicant also provided literature indicating that sex-dependent differences regarding local toxicity from parenteral drugs are unlikely, which the Division agrees with. In discussions with the Clinical Review Team, it is noted that neostigmine methylsulfate and glycopyrrolate are commonly used in combination. Taking into consideration the clinical experience with the individual active pharmaceutical ingredients (APIs) and with the combination, there are no outstanding safety concerns with the nonclinical data submitted in support of the fixed-dose prefilled syringe combination product.

The Division agrees with the recommendations of the pharmacology/toxicology review team.

5. Clinical Pharmacology

As per the clinical pharmacology review completed by Dr. Srikanth Nallani, dated January 12, 2023, there were no concerns identified during the review cycle that would preclude approval. The following information is from the clinical pharmacology review (verbatim):

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.

The labeling is acceptable, as it describes clinical pharmacology information already described in the reference drug labels.

Refer to the biopharmaceutics assessment described in Section 3 of this review for additional information regarding the biowaiver request. The Division agrees with the recommendations of the clinical pharmacology review team.

6. Clinical Microbiology

Neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) PFS is not a therapeutic antimicrobial. Therefore, clinical microbial data were neither required nor submitted.

7. Clinical/Statistical- Efficacy

This application relies upon the Agency's previous findings of effectiveness (and safety) for the LDs, Bloxiverz, NDA 204078, and Robinul, NDA 017558. The Applicant did not conduct any clinical efficacy studies; therefore, Section 7 is not relevant to this 505(b)(2) Application.

8. Safety

The Applicant did not conduct any clinical studies in support of this marketing application and is relying upon the Agency's previous findings of safety (and effectiveness) for the LDs, Bloxiverz, NDA 204078, and Robinul, NDA 017558.

In response to the potential clinical review issue described in the 74-day letter, the Applicant agreed that the proposed presentation may not be appropriate in bradycardic patients and updated the draft label accordingly. Specifically, the Applicant included recommendations to consider using an anticholinergic agent prior to neostigmine in the setting of bradycardia, and added a new bradycardia warning to Section 5.1. Refer to Section 12 of this summary review for additional labeling information.

Regarding safety updates during the review cycle, the Applicant provided a safety report in the NDA submission and a 120-Day Safety Update Report on January 27, 2023 (in response to an IR request). Both documents were reviewed by Dr. Lee Anne Connell-Templin, who determined that there were no new safety findings that needed to be included in labeling. The following is a high-level summary of the information included in the safety updates.

- The Safety Literature Report, included in the initial NDA submission, included a search of the published literature using PubMed, FDA Adverse Events Reporting System (FAERS) Database, and Google Scholar. The Applicant also provided a summary of adverse events. Postmarketing adverse events identified for Bloxiverz were from the approval date (2013) through 2021. Post marketing adverse events identified for glycopyrrolate were from the approval date of Glyrx-PF (a benzyl alcohol-free formulation of glycopyrrolate; 2018) through 2021.

- The 120-Day Safety Update Report included a search of the published literature using PubMed, FAERS Database, and Google Scholar. The Applicant also provided a summary of adverse events for neostigmine and glycopyrrolate.

While there were several adverse events identified in the searches for each drug product that are not included in the most recently approved LD labeling, the Division acknowledges that interpretation of postmarket safety data has limitations, and that it is often not possible to

definitively determine adverse event causality due to concomitant diagnoses and medication administration, and variations in use (e.g., surgical procedure variability). Therefore, the results from these safety database searches do not adversely impact the benefit:risk assessment for the proposed drug product, and the Division concludes that there are no new safety findings that needed to be included in labeling.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

Safety and effectiveness of Bloxiverz have been established in pediatric age groups, from neonate to adolescent. Safety and effectiveness of Robinul have been established in pediatric age groups one month to adolescent. Robinul is not indicated in neonates due to the benzyl alcohol component. The proposed combination formulation of neostigmine and glycopyrrolate was considered a new active ingredient and, therefore, the Pediatric Research Equity Act (PREA) was triggered, and pediatric use information was required.

As per the Agreed Initial Pediatric Study Plan (iPSP), reviewed under PIND 139866, dated February 1, 2021, the Applicant provided information from the published literature to support the safety and efficacy of neostigmine and glycopyrrolate administered simultaneously in the same syringe in the pediatric population age two years and above.

The Agreed iPSP included a partial pediatric study waiver for pediatric patients less than two years of age based on the risk of bradycardia. The Division and the Pediatric Review Committee (PeRC) agree with the Applicant's waiver request in pediatric patients from birth to less than two years because the drug would be unsafe for this pediatric age group. The rationale for this waiver is that the administration of the individual components has a more favorable benefit:risk profile than administration of the proposed combination product in infants and neonates. Specifically, as stated in Section 8.4 Pediatric Use of the approved product label for Bloxiverz, "Since the blood pressure in pediatric patients, particularly infants and neonates, is sensitive to changes in heart rate, the effects of an anticholinergic agent (e.g., atropine) should be observed prior to administration of neostigmine to lessen the probability of bradycardia and hypotension." Due to this risk, the Division (and PeRC) agrees with the partial waiver of pediatric patients from birth to less than two years of age, and this product is not indicated in this population.

The Division (and PeRC) also concludes that the Applicant's review of the information from the published literature is an adequate assessment of the use of the proposed combination product in the pediatric age group two to less than 17 years, and additional clinical studies are not required.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

The indication for patients two years of age and above, noted below in italicized font, is an amalgamation of the Bloxiverz indication (i.e., indicated for the reversal of the effects of non-depolarizing NMBAs after surgery) and a "carve out" of the Robinul indications [i.e., protects against peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents, such as neostigmine given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants].

> *Reversal of effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery, while decreasing the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) associated with cholinesterase inhibition following NMBA reversal administration.*

Although the approved Robinul label includes additional indications (i.e., for preoperative and intraoperative use, and for treatment of peptic ulcer in adults), the proposed combined presentation would not be appropriate for these indications. Therefore, the Applicant has appropriately removed all language relating to these indications. Additionally, information regarding dosing for patients less than two years of age has been removed. Refer to the discussion regarding pediatrics in Section 10 of this summary review. The Division agrees with the rationale for the differences in labeling between the proposed product and the LDs.

The draft label complies with the Physicians Labeling Rule (PLR) and PLLR.

On July 11, 2022, DMEPA 1 reviewed the proposed Use Related Risk Analysis and Threshold Analysis and concluded that results of a human factors (HF) validation study were not required to support the NDA submission. As noted above, DMEPA I concluded that the proposed proprietary name, Prevduo, is acceptable.

The Division agrees with the recommendations from the DMEPA team and has no outstanding concerns regarding the drug labeling.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit: Risk Assessment
The Benefit:Risk Assessment for the proposed presentation, a fixed dose drug-device combination product of neostigmine methylsulfate 3 mg/3 mL (1 mg/mL) and glycopyrrolate 0.6 mg/3 mL (0.2 mg/mL) in a PFS, outweigh the risks, in the setting of reversal of neuromuscular blockade in patients two years of age and older. The potential primary benefit

of the combined presentation is to provide convenient, single syringe dosing for the two drugs, which will decrease the preparation steps required for administration.

Post Marketing Requirements

There are no post marketing requirements or commitments for this application. As noted in Section 10, PREA was triggered; however, the partial waiver for birth to less than two years of age is granted, and an assessment of pediatric patients from two to less than 17 years of age is complete. No pediatric studies are required.

14. Comments to the Applicant

There are no comments to the Applicant.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LEE ANNE A CONNELL-TEMPLIN
02/23/2023 08:59:07 AM

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RIGOBERTO A ROCA
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