CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215868Orig1s000

SUMMARY REVIEW

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	July 19, 2022
From	Lisa Banta, MD; Renee Petit-Scott, MD; Alla Bazini, MD; Rigoberto Roca, MD
NDA#	215868
Applicant	Exela Pharma Sciences
Date of Submission	September 20, 2021
PDUFA Goal Date	July 20, 2022
Proprietary Name	N/A
Established or Proper Name	Midazolam in 0.8% Sodium Chloride injection (1 mg/mL), 50 mg/50mL and 100 mg/100 mL
Dosage Form	Intravenous injection
Applicant Proposed and Approved Indication	For continuous intravenous infusion for sedation of intubated and mechanically ventilated adult, pediatric, and neonatal patients as a component of anesthesia or during treatment in a critical care setting
Applicant Proposed and Approved Dosing Regimen	• Adults: – Loading dose: 0.01 to 0.05 mg/kg – Maintenance Dose: 0.02 to 0.10 mg/kg/h (1 to 7 mg/h) • Pediatrics: Dosed mg/kg, and titrated to effect • Preterm and neonatal patients: – Loading dose not recommended – Neonates <32 weeks: initiate infusion at 0.03 mg/kg/h – Neonates >32 weeks: initiate infusion at 0.06 mg/kg/h
Regulatory Action	Approval

OND Action Package included reviews by the following:	
Clinical Pharmacology Review Team	David Lee, PhD.; Yun Xu, PhD
Pharmacology-Toxicology Review Team	Alexander Son, Ph.D.; Newton Woo, PhD.; R. Daniel Mellon, PhD
Office of Product Quality Review Team	Acting Team Leader - Valerie Amspacher, PhD
Drug Substance	Zhixing Shan, Ph.D.; Gaetan Ladouceur, Ph.D.
Drug Product	Mariappan Chelliah, Ph.D.; Julia Pinto, Ph.D.
Process/Facilities	Yan Xu, Ph.D.; Tianhong Tim Zhou, Ph.D.
Microbiology	George Arhin, Ph.D.; Elizabeth Bearr, Ph.D.
Biopharmaceutics	Jia Yin, Ph.D.; Okponanabofa Eradiri, Ph.D.
Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis	Damon Birkemeier, PharmD; Valerie S. Vaughan, PharmD

1. Benefit-Risk Assessment

Exela Pharma Sciences (Exela) submitted this new drug application (NDA) through the 505(b)(2) marketing pathway with reliance on the Agency's previous findings of safety and effectiveness for the listed drugs, Versed® (Midazolam Hydrochloride) injection (NDA 018654), approved on May 26, 1985, and Midazolam in Sodium Chloride injection (NDA 211844), approved on March 22, 2021. Because Versed is no longer marketed, not due to safety or effectiveness reasons, Preservative Free Midazolam Hydrochloride injection 1 mg/mL (ANDA 075857) is the reference standard identified in the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). The Applicant is also relying on information in the published literature to support the safety profile of the proposed product.

Exela has developed a preservative-free formulation of midazolam hydrochloride (1 mg/mL) in strengths of 50 mg/50 mL and 100 mg/100 mL glass vials. The rationale for developing this presentation is to provide an additional ready-to-use midazolam product to the market to help alleviate a nationwide drug shortage due to increased demand during the coronavirus disease pandemic of 2019 (COVID-19). Prior to submission of the current NDA, Exela supplied the market with Midazolam injection 1 mg/mL in 50 mL and 100 mL vials, as 503B compounded drug products. Specifically, from April 2020 through October 2021, Exela distributed nearly (b) (4) vials of midazolam drug product to the U.S. market. The Sponsor notes in the benefit-risk assessment submitted under the NDA that there were no adverse event reports associated with the marketed compounded products.

There were no major clinical safety concerns for this drug-device combination product. However, the Division did seek clarification from the Applicant regarding two issues related to the volume of drug solution in the vials. First, the Division requested clarification regarding mitigation strategies for potential microbial contamination during use of this product, particularly when used for extended intravenous (i.v.) infusion. The Applicant provided additional data demonstrating the risk of microbial contamination can be mitigated by limiting infusions to 48 hours, and edited the prescribing information accordingly. And second, the Division requested clarification regarding mitigation strategies for multi-patient use with this product. The Applicant stated that clear, single-dose labeling and instructions to penetrate the vial once would mitigate this risk. Additionally, the Applicant performed a search of the FDA Adverse Event Reporting System (FAERS), the Joint Commission Website, Council of State and Territorial Epidemiologists, Institute for Safe Medication Practices, and the published literature to assess this risk associated with use of other, large-volume presentations of midazolam, including Midazolam in Sodium Chloride, which is marketed in 50 mL and 100 mL infusion bags. The Applicant concluded that the proposed products do not present "significant additional risk of multi-patient dosing."

The benefits of this presentation of midazolam include the following:

- Ready-to-use, dilution not required
  - Commonly administered concentration, 1 mg/mL
- Larger volume presentation suitable for continuous infusion by directly connecting an i.v. administration line to the vial

  - Avoids the need to compound an infusion bag (i.e., multiple smaller volume vials not needed), thereby decreasing the risks of medication errors and microbial contamination associated with compounding pharmacies
- Preservative-free
  - Intended as a single-dose vial
- Additional midazolam hydrochloride product available

The risks and drawbacks of this presentation of midazolam include the following:

- Larger volume with potential for increased waste of a controlled substance, particularly relevant for smaller patients and children
- Technical issues with the vial presentation, including withdrawing the medication from the vial or connecting an i.v. administration line to the vial
- Potential for microbial contamination and proliferation if infusion is longer than 48 hours
- Those associated with administration of midazolam, including but not limited to:
  - Cardiorespiratory (arrhythmias, bradycardia, tachycardia, laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction,) adverse reactions
  - Paradoxical behavior
  - Dependence and withdrawal
  - Impaired cognitive function
  - Hypotension and seizures in preterm infants and neonates
  - Neonatal sedation
  - Pediatric neurotoxicity

The Division concludes that the benefits of midazolam, preservative-free in glass vials of 50 mg/50 mL and 100 mg/100mL, outweigh the risks. The most notable benefits include an additional midazolam product on the market, the preferred clinical concentration (i.e., 1 mg/mL), and the large volume suitable for continuous infusion.

There do not appear to be any new risks associated with this midazolam hydrochloride presentation that would preclude approval.

2. Background

This document will serve as the Cross-Discipline Team Leader and Division Director Summary Review of NDA 215868 for the decision on regulatory action for the proposed product, Midazolam in 0.8% Sodium Chloride injection, in 50 mg/50 mL and 100 mg/100 mL glass vials. Exela submitted NDA 215868 on September 20, 2021, through the 505(b)(2) marketing pathway with reliance on the Agency's previous findings of safety and effectiveness for Versed (NDA 018654) and Midazolam in Sodium Chloride injection (NDA 211844). Because Versed is no longer marketed, not due to safety or effectiveness reasons, Preservative Free Midazolam Hydrochloride injection 1 mg/mL (ANDA 075857) is the reference standard identified in the Orange Book. The Applicant is also relying on information in the published literature to support the safety profile of the proposed product. There were no interactions with

the Applicant regarding the proposed drug product prior to submission of the NDA. The proposed product is indicated for continuous i.v. infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.

Midazolam is a short-acting benzodiazepine, and similar to other benzodiazepines, acts at the gamma aminobutyric acid ($GABA_A$)-benzodiazepine receptor complex. Midazolam enhances the affinity for GABA at the $GABA_A$ receptor, resulting in sedation, anxiolysis, and amnesia. Midazolam is commonly administered in the pre-operative period, and as an adjunct to general anesthesia to produce sedation, anxiolysis, and amnesia. Midazolam is also utilized in the intensive care unit as a sedative and anxiolytic for intubated patients.

The following table is a high-level summary of the key interactions with the Applicant during the NDA review cycle.

Table 1. Summary of Key Interactions During NDA Review Cycle

Date	Correspondence / Summary
September 20, 2021	NDA received
October 18, 2021	Information Request (IR) regarding lack of benefit:risk assessment
October 26, 2021	IR for clarification on which listed drugs (LD) the Applicant relied upon
October 29, 2021	IR for: – Additional justification requested to support the increased concentration of midazolam (1 mg/mL) proposed for i.v. infusion compared to Versed (0.5 mg/mL) – Additional justification requested to support the proposed maximum daily dose (MDD)
November 5 and 30, 2021	IRs for clarification on whether information from NDA 211844 is being relied upon for approval of this NDA, and if so, whether the NDA holder had been notified
December 2, 2021	NDA filed; 74-day letter issued with the following potential review issue identified: – Extractable and leachable assessment to support the higher maximum daily dose (MDD) not adequate
February 22, 2022	IR for 120-day safety update
February 25, 2022	IR regarding justification that longer infusion durations would not result in microbial contamination, given the product is preservative-free
May 23, 2022	IR for clarification on mitigation of potential multi-patient vial use, drug diversion, and misuse and abuse
May 31, and June 1, 2022	IRs for further clarification on mitigation of potential multi-patient vial use

All IRs were adequately addressed and there were no outstanding safety (or efficacy concerns) with the proposed product.

The Applicant did not conduct any clinical studies, including safety, efficacy, or QT studies, and submitted a Request for Waiver of In Vivo Bioavailability Studies (biowaiver), which was determined by the biopharmaceutics and clinical pharmacology review teams to be acceptable.

3. Product Quality

The following assessment is adapted from the reviews completed by the teams in the Office of Product Quality (OPQ).

Product Overview

Exela's proposed product is a clear, colorless solution in 50 mL or 100 mL clear glass (b) (4) vials stoppered with gray rubber stoppers, and an aluminum overseal. Based upon stability data in DMF (b) (4), the (b) (4) (b) (4) The Applicant has committed to test the drug substance on a (b) (4) basis up to the (b) (4)

Quality Assessment Overview

Drug Substance

Midazolam is manufactured by the holder of the referenced DMF, (b) (4) (b) (4)., which was originally submitted on October 8, 1997. Since that time, the DMF has been reviewed 11times, with the last three times being found adequate by the Agency. Review of the most recent quality amendment was completed on February 22, 2022, and determined to be adequate.

The Applicant provided a brief description of the general properties, specifications, impurities, analytical methods and validations, batch analyses, stability, etc. for the drug substance. The review team in OPQ has determined that the Applicant provided satisfactory justifications for all the testing parameters and their acceptance criteria. The Applicant's specification for the midazolam drug substance is adequate, and all drug substance information is adequate. There were no potentially genotoxic impurities detected in the drug substance; therefore, the drug substance is not likely to pose any potential genotoxicity concerns.

Drug Product

Midazolam in 0.8% Sodium Chloride injection (1 mg/mL) in 50 mL and 100 mL vials contains sodium chloride as a (b) (4). In addition, hydrochloric acid and sodium hydroxide are used as pH adjusting agents. All excipients are compendial grade. Compared with the listed drug (Versed), the proposed product is a preservative- and (b) (4)-free formulation with a different labeled volume. Compared with the reference standard (ANDA 075857), the proposed product only differs in the labeled volume.

The proposed primary container closure system, glass vials closed with a rubber stopper and aluminum overseal, is commonly used for packaging parenteral drug products. The available stability data demonstrated adequate protection to the drug product. In addition, the primary container closure components have an adequate extractable and leachable profile.

The proposed specification included tests appropriate to control the quality of an injection product. The impurities are controlled per ICH Q3B Guideline, and the Applicant's risk assessment for elemental impurities is acceptable. All the noncompendial analytical methods have been adequately validated. The Applicant has manufactured three primary batches per strength and they met specification. No impurities were present at detectable levels. The batch data demonstrated consistency in the manufacturing quality of the drug product. Twelve months of long-term and six months of accelerated stability data for the six primary batches were reviewed, and no trending was noted under both long-term and accelerated storage conditions. Impurities were either not detected or remained below their respective quantitation limits. The results from a photostability study demonstrated the drug product is light sensitive. The review team in OPQ has determined that the proposed shelf-life of 24 months, when stored at 20°C to 25°C (68°F to 77° F), may be granted.

The proposed product is formulated at a slightly higher target pH than the reference standard. Because midazolam solubility is pH-dependent, there was concern regarding midazolam precipitation out of solution. The Applicant adequately addressed this concern by demonstrating the absence of precipitation during the manufacture of formulations at pH 3.0 and 4.0 to cover the proposed acceptance range for this attribute. In addition, the solubility data show that although midazolam hydrochloride has a low solubility of 2.3 mg/mL at the proposed upper pH limit of 4.0, it is still above the formulation concentration of 1 mg/mL.

Manufacturing

The manufacturing process (b) (4) (b) (4) The drug product is packaged in two fill volumes, with glass vial sizes 50 mL and 100 mL. The final pH of the solution is adjusted to 3.5 (range (b) (4) The Applicant manufactured three registration batches ((b) (4) with acceptable quality. While there will be a (b) (4) scale-up to (b) (4) for the commercial batches, this was determined to be acceptable.

The drug substance manufacturing facility has experience manufacturing the active pharmaceutical ingredients and is currently cGMP compliant. The drug product facility has experience with sterile injectables and is currently cGMP compliant. OPQ did not recommend a pre-approval inspection (PAI) for the manufacturing facility; however, a Fiscal Year 2022 PAI was recommended for an NDA and ANDA product manufactured by the Applicant. The outcome of an inspection during the week of December 6, 2021, was classified as no action indicated.

Biopharmaceutics

The Applicant requested a biowaiver for the proposed product in accordance with 21 CFR 320.22(b)(1). The differences between the listed drug NDA 211844 and the proposed drug product are as follows:

- Sodium chloride concentration is 0.8% in this product, versus 0.9% in the listed drug
- The presentation for this product is glass vials, versus infusion bags for the listed drug

The Applicant provided a side-by-side comparison of the physicochemical properties of the listed drugs and the proposed drug product. The physicochemical property data are comparable, no bridging study is needed, and the biowaiver can be granted. The biopharmaceutics review team had no additional concerns.

Microbiology

Based on the possible 48-hour infusion duration, microbial contamination and subsequent adverse patient safety issues were a concern. The Division requested additional information from the Applicant to support the sterility of the product over the maximum proposed treatment duration. The Applicant submitted data from a microbial hold-time study simulating the infusion conditions. The study evaluated the potential for adventitious microbial contamination to proliferate in the drug product over 48 hours at room temperature. A minimally countable amount (i.e., less than (b) (4) Colony Forming Units (CFU)) of representative bacteria, yeasts, and molds were inoculated into drug product vials. The inoculated vials were incubated at room temperature, samples were taken at specified intervals up to 48 hours and cultured on appropriate media, and resulting colonies were counted.

No microbial proliferation was observed for any of the challenge microorganisms at any time point, and at most time points, no colonies were recovered in the samples. Positive controls demonstrated the viability of the challenge organisms over the 48-hour testing period. Based on these results, the Applicant concludes that the maximum allowable infusion duration from one drug product vial is 48 hours. The Applicant has included a statement in the draft labeling stating infusions from a single vial should not exceed 48 hours. The Division concludes that the results from the study in combination with the proposed labeling information have adequately addressed the concern regarding potential microbial contamination, and there are no outstanding microbiology concerns.

In summary, the review teams in OPQ had no outstanding issues with the proposed product, and the Division concurs with this conclusion.

4. Nonclinical Pharmacology/Toxicology

The following assessment is adapted from the review completed by the pharmacology/toxicology review team.

Local Toxicity

No nonclinical pharmacology or toxicology studies were submitted in support of this NDA application. The Applicant submitted information from the published literature to support the pharmacology; pharmacokinetic; absorption, distribution, metabolism, and excretion (ADME); and toxicology profiles of the drug product. The Applicant is relying on the Agency's previous findings of safety and efficacy of the listed drugs, described in Sections 1 and 2 of this review.

The Applicant provided a side-by-side comparison of the proposed drug product to the listed drugs. As noted previously, compared to Versed, a solution that requires dilution to 0.5 mg/mL prior to continuous infusion, the proposed drug product is a ready-to-use product, no dilution required. Midazolam in Sodium Chloride injection (NDA 211844), the other listed drug for this application, has a lower concentration of sodium chloride, has a pH range similar, and is the same concentration (i.e., 1 mg/mL) as the proposed product. The proposed drug product is isotonic, has a lower concentration of sodium chloride. The pharmacology/toxicology review team concluded that an i.v. toxicology and blood compatibility studies were not necessary to support the safety profile of this proposed drug product.

Container Closure System

Midazolam in 0.8% Sodium Chloride injection solution is packaged in 50 mL and 100 mL molded clear glass vials with gray stoppers. To support the safety of the container closure system, data from extractables and leachables studies were submitted. There were 15 leachables above the qualification threshold of 5 mcg/day identified. Toxicological risk assessments, however, were reviewed and deemed adequate. The pharmacology/toxicology review team had no additional concerns regarding the container closure system for this drug product.

Maximum Daily Dose (MDD)

The MDD for the proposed drug product is the same that described in the labels for the listed drugs. Specifically, a loading dose of 0.01 to 0.05 mg/kg may be given, followed by a maintenance dose ranging from 0.02 to 0.1 mg/kg/h. The infusion rate can be adjusted up to 50% of the initial infusion rate, resulting in a maximum dose per hour of 0.15 mg/kg/h. The MDD for a 60 kg person is 219 mg/day, based on the following calculations:

Loading Dose = (0.05 mg/kg x 60 kg) = 3 mg
Maintenance Dose per Day = 0.15 mg/kg/h x 60 kg x 24 h = 216 mg
MDD = Loading Dose + Maintenance Dose = 3 mg + 216 mg = 219 mg/day

The Division concurs with the pharmacology/toxicology review team that there are no outstanding nonclinical issues that would prevent approval.

5. Clinical Pharmacology

The Applicant did not conduct any clinical pharmacology or biopharmaceutics studies, and no clinical pharmacology published literature was submitted in support of this application. As previously discussed, a biowaiver was submitted and reviewed by the biopharmaceutics team.

Refer to Section 3 of this review for additional information regarding the biopharmaceutics review.

The clinical pharmacology review team did not identify any issues that would prevent approval, and the Division concurs.

6. Clinical Microbiology

Midazolam in 8% Sodium Chloride injection is not a therapeutic antimicrobial agent, therefore, clinical microbiology data were neither required nor submitted.

7. Clinical/Statistical- Efficacy

The Applicant did not conduct any clinical studies in support of the efficacy of their drug product, and is relying on the Agency's previous findings of effectiveness for the listed drugs, Versed (NDA 018654), and Midazolam in Sodium Chloride injection (NDA 211844). Therefore, Section 7 is not relevant to this 505(b)(2) Application.

The Division has no efficacy concerns regarding this drug product that would preclude approval.

8. Safety

The Applicant did not conduct any clinical studies in support of the safety of midazolam, and is relying on the Agency's previous findings of safety for Versed and Midazolam in Sodium Chloride injection. This section will summarize the safety information included in the NDA submission and in the 120-Day Safety Update with emphasis on adverse events associated with continuous i.v. infusion of midazolam, the proposed indication.

The Applicant initially conducted a review of the published literature and FAERS database from January 1, 2018, the date of the most recently approved labeling for the reference standard (ANDA 075857), through August 31, 2021, to identify new safety information about midazolam. In response to an IR, the Applicant clarified that because NDA 211844 was approved in March 2021, and ANDA 075857 labeling was updated in July 2021, the Summary of Clinical Safety included information from searches using those dates. Based on safety information reviewed during this time, the Applicant concluded that no new safety signals have been identified that would adversely impact the benefit:risk assessment of this product. The most commonly reported adverse reactions associated with administration of midazolam for continuous i.v. infusion include cardiorespiratory adverse reactions, paradoxical behavior, dependence and withdrawal, impaired cognitive function, hypotension and seizures in preterm infants and neonates, neonatal sedation, and pediatric neurotoxicity.

Regarding the 120-day Safety Update, the Applicant conducted a search of the published literature from the time of the NDA submission (August 2021) through March 2022. Four clinical studies were identified that provided safety information for midazolam. The studies

were not entirely relevant to the proposed product, however, because they were either evaluations in healthy volunteers, or they did not evaluate continuous i.v. infusion (i.e., an evaluation of bolus dosing during bronchoscopy, evaluations of buccal and intranasal administration).

Included in the 120-day Safety Update were the results of a FAERS search of 2021 (through June 30, 2021) and 2022 (through March 3, 2022). The results from the 2021 search indicated a large number of total adverse events, serious adverse events, and deaths, compared to the results from the 2022 search. Of the 1,540 SAEs (including deaths) in 2021, over 50% were categorized as drug ineffective, off-label use, hypotension, seizure, drug interaction with eosinophilia and systemic symptoms, and drug interactions. While the Applicant did not provide an explanation for the apparent increase in SAEs and deaths in 2021, our review of the available information suggests that the COVID-19 pandemic and the need for high-dose sedative agents in intubated and mechanically ventilated patients were likely contributing factors.

In summary, results from the published literature and FAERS searches conducted by the Applicant did not identify any new safety signals or adverse reactions that are not described in labeling for either listed drug or the reference standard.

An additional issue related to the large-volume presentation of midazolam (i.e., 50 mL and 100 mL), is the risk of drug diversion, and misuse and abuse. In response to an IR seeking clarification on proposed mitigation strategies for these risks, the Applicant stated the following:

- Review of safety information has not identified this as a risk with use of other large-volume midazolam presentations, including Midazolam in Sodium Chloride injection (NDA 211844).
- Information in Section 9, Drug Abuse and Dependence, of the proposed labeling is identical to the approved labeling of Midazolam Sodium Chloride injection, and clearly describes the risks of midazolam abuse and dependence.

The Applicant concluded that the potential for misuse and abuse of the proposed product is no greater than that of the midazolam product presentations currently marketed, and the Division agrees. Regarding (b) (4) the Applicant updated the package insert to specifically state (b) (4)
This labeling change is adequate to address the Division's concern. While the Applicant did not specifically comment on these safety concerns related to their products marketed under the 503B compounding pathway, it does not appear that the proposed drug products would confer increased risk of multi-patient use, drug diversion, and misuse and abuse compared to other, large-volume marketed midazolam products.

In summary, there do not appear to be any specific safety concerns related to the clinical use of this presentation of midazolam indicated for continuous i.v. infusion that would preclude approval.

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 midazolam have been established in pediatric patient age groups, neonate to adolescent. Because this formulation does not represent a new route of administration, new indication, new dosage form, or new dosing regimen, and does not contain new active ingredients, pediatric studies under the Pediatric Research Equity Act (PREA) are not required.

11. Other Relevant Regulatory Issues

The Applicant did not conduct any clinical studies, therefore it was not required and a financial disclosure statement was not submitted.

The Controlled Substance Staff (CSS) was consulted during review of NDA 211844, and made the following conclusions regarding that midazolam product:

- Midazolam is a schedule IV substance under the Controlled Substances Act (CSA).
- Midazolam is a short-acting benzodiazepine that is associated with misuse and abuse, as well as dependence and a well-characterized withdrawal syndrome. The proposed indication for midazolam injection encompasses a condition of use in which dependence may develop (i.e., continuous sedation in a critical care setting).
- The Applicant of NDA 211844 conducted a published literature and FAERS database review, and concluded that there was no new information identified that would alter the known abuse and dependence profile of midazolam.
- CSS noted that there are two versions of Safety Labeling Change (SLC) language for benzodiazepines; one for benzodiazepines in general, and one for benzodiazepines with very short-term conditions of use. CSS and the Division agreed that neither version of the benzodiazepine SLC labeling language is fully applicable to the proposed midazolam product, which is indicated for procedural and continuous sedation in inpatient, monitored clinical settings. Refer to Section 12, Labeling, for CSS recommendations regarding the potential for misuse and abuse, and dependence.

The Division concludes that the recommendations from CSS for NDA 211844 also apply to this NDA, and there are no outstanding issues.

12. Labeling

The proposed prescribing information for Midazolam in 0.8% Sodium Chloride injection is based on the approved labeling for the listed drugs, and is compliant with the Physician's Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

The proposed indication, for continuous intravenous infusion for sedation of intubated and mechanically ventilated adult, pediatric, and neonatal patients as a component of anesthesia or during treatment in a critical care setting, is identical to the approved indication for Midazolam in Sodium Chloride injection (NDA 211844), and includes only one of the four approved indications for Versed (NDA 018654). The Applicant removed all language relating to intramuscular administration of the drug product from the prescribing information.

All box warnings and other safety information are the same for the listed drug, Midazolam in Sodium Chloride injection, and the proposed drug. As discussed in Section 11 of this review, CSS was consulted during review of NDA 211844, the recommendations for which also apply to this drug product. CSS recommended that the prescribing information reflect the potential for misuse and abuse, as well as the potential for dependence when midazolam is used for extended periods of time.

To mitigate the risks of microbial contamination during long infusions, and multi-patient use, the Applicant has proposed to include the following statements in the prescribing information:

Once the vial has been penetrated, limit the infusion duration to 48 hours maximum.
(b) (4)

A label and labeling review was completed by DMEPA on January 10, 2022. The Applicant has incorporated the team's recommendations, including clarification of the expiration date format on the carton/container, and there are no outstanding issues. Refer to the review completed by Dr. Damon Birkemeier for additional information.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit:Risk Assessment
The benefits of Midazolam in 0.8% Sodium Chloride injection outweigh the potential risks and the application is approved.

Postmarketing Requirements
There are no postmarketing requirements or commitments for this application. As noted in Section 10, PREA is not triggered and pediatric studies are not required.

14. Recommended Comments to the Applicant

None.

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/

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