CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215868Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 215868
Supporting document/s:	SDN 1, 4, 5, 6, 8, 27
Applicant's letter and CDER stamp date:	September 20, 2021; November 1, 2021; November 5, 2021; November 12, 2021; December 6, 2021; June 30, 2022
Product:	Midazolam
Indication:	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:	Exela Pharma Sciences, LLC
Clinical Review Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Pharm/Tox Division:	Division of Pharm/Tox for Neuroscience (DPT-N)
DPT-N Reviewer:	Alexander I. Son, PhD
DPT-N Supervisor:	Newton Woo, PhD
Clinical Division Director:	Rigoberto Roca, MD
Project Manager:	Allison Meyer, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 215868 are owned by Exela Pharma Sciences, LLC or are data for which Exela Pharma Sciences, LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 215868 that Exela Pharma Sciences, LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 215868.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

This application for NDA 215868 is regarding a midazolam drug product, which is a ready-to0use product with a concentration of 1 mg/mL, via the 505(b)(2) regulatory pathway. The Sponsor has cited NDA 018654 (Versed) and Midazolam by InfoRLife (NDA 211844) as the Reference Drugs (RDs) and are relying upon data in the referenced product labeling. The Maximum Daily Dosage (MDD) for this product 219 mg/day.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical pharmacology or toxicology studies were submitted in support of this NDA application. The Sponsor had submitted literature from the time of approval of the RD to the date of submission regarding pharmacology, pharmacokinetic, ADME, toxicokinetic, and toxicology studies.

The Sponsor provided a side-by-side comparison to the proposed drug product and reference drugs. In comparison to Versed, which is a concentrated solution that requires to be diluted to 0.5 mg/mL for continuous infusion, the proposed drug product is a ready to use product for infusion. The proposed drug product has different excipients and a higher concentration than the reference drug. The Sponsor also references NDA 211844, which is a midazolam product that has similar excipients with the exception of a lower concentration of sodium chloride and is the same concentration as the current product. The proposed drug product is isotonic, has a lower concentration of sodium chloride, and has a pH range within the range of the referenced product of NDA 211844. As such the Division concluded that an IV toxicology study and blood compatibility studies were not necessary for this drug product.

The Sponsor's proposed specifications for drug substance and drug product impurities are within qualification thresholds outlined in ICH Q3A(R2) and Q3B(R2), respectively. (b) (4) specifications were within the levels as stated in (b) (4) Elemental impurities are below the control threshold of 30% as per ICH Q3D.

To support safety of the container closure system that is a glass vial and stopper, extractables and leachables studies were provided. In total, 15 leachables above the qualification threshold of 5 mcg/day were identified and toxicological risk assessments were submitted by the Applicant. Risk assessments were reviewed and deemed adequate. Therefore, the leachables were adequately qualified.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology/toxicology perspective, this 505(b)(2) NDA for midazolam is recommended for approval at this time.

1.3.2 Additional Nonclinical Recommendations

N/A

1.3.3 Labeling

The Sponsor has submitted draft labeling found in 1.14.1.3 Draft Labeling Text Word Seq 0001. The proposed labeling was reviewed to be identical to the reference product (NDA 211844). No changes to the label are recommended at this time. Refer to the action letter for final drug product labeling.

2 Drug Information

2.1 Drug

CAS Registry Number: 59467-70-8

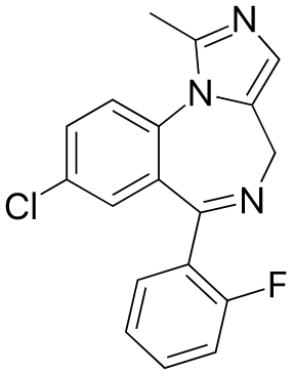
Generic Name: Midazolam

Code Name: Midazolam

Chemical Name: 8-Chloro-6-(2-fuorophenyl)-1-methyl-4H-Imidazo [1,5-a] [1,4]-benzodiazepine

Molecular Formula/Molecular Weight: $C_{18}H_{13}ClFN_3$/325.77 g/mol

Structure or Biochemical Description:



Established Pharmacologic Class (EPC): Benzodiazepine

2.2 Relevant INDs, NDAs, BLAs and DMFs

Table 1: INDs and NDAs

Application ID	Drug	Route	Sponsor	Status
NDA 018654 (RD)	Versed (Midazolam)	Intravenous, Intramuscular	HLR Technology	Withdrawn, FR Effective

ANDA 075857 (RS)	Midazolam Hydrochloride	Intravenous, Intramuscular	Hospira Inc	Approved
ANDA 075293 (RS)	Midazolam Hydrochloride	Intravenous, Intramuscular	Hospira Inc	Approved
NDA 211844 (RD)	Midazolam in 0.9% Sodium Chloride	Intravenous	InfoRLife SA	Approved

RD = Reference Drug, RS = Reference Standard

Table 2: DMFs

Application ID	Product Name	Supplier/DMF Holder	Comment
(b) (4)			API
			CCS
			CCS
			CCS
			CCS, Incorrectly listed on 365h form as DMF (b) (4)

2.3 Drug Formulation

The Sponsor provided a side-by-side comparison to the proposed drug product and reference drugs. Of note, the Sponsor's drug product does not contain Benzyl alcohol and Edetate disodium, which is present in the listed drug, Versed, NDA 018654. The composition of the proposed drug product is similar to that of ANDA 075857 and NDA 211844.

Composition per mL	LD product[1] Versed (midazolam hydrochloride) Injection NDA 018654	RS Product[2] Midazolam Hydrochloride Injection ANDA075857	Midazolam in 0.9% Sodium Chloride Injection[3] NDA 211844	Exela's Proposed Midazolam in 0.8% Sodium Chloride Injection[4] NDA215868
Midazolam	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL
Sodium chloride	8 mg/mL	8 mg/mL	9 mg/mL	8 mg/mL
Edetate disodium	0.1 mg/mL	Nil	Nil	Nil
Benzyl alcohol	10 mg/mL	Nil	Nil	Nil
Hydrochloric acid	Approx. 3	Approx. 3	q.s. to pH 2.5 - 3.5	q.s. to pH 3.5
Sodium hydroxide	Approx. 3	Approx. 3	q.s. to pH 2.5 - 3.5	q.s. to pH 3.5
Water for Injection	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL
How supplied	2/5/10 mL vials	2/5 mL vials	50/100 mL IV Bags	50/100 mL vials
Midazolam/unit	2 mg/5 mg/10 mg	2 mg/5 mg	50 mg/100 mg	50 mg/100 mg

Composition per mL	LD product[1] Versed (midazolam hydrochloride) Injection NDA 018654	RS Product[2] Midazolam Hydrochloride Injection ANDA075857	Midazolam in 0.9% Sodium Chloride Injection[3] NDA 211844	Exela's Proposed Midazolam in 0.8% Sodium Chloride Injection[4] NDA215868
Indications and use	As per the LD product label	As per the RS product label	As per the approved product label – intravenous infusion only	Similar to LD - Carved out for intravenous infusion only

[1] Information regarding RLD product, Versed (midazolam hydrochloride) Injection 1mg/mL of HLR Technology, was obtained from PDR, 2000.

[2]Information regarding RS product, Midazolam Hydrochloride Injection 1mg/mL, Hospira Inc., was obtained from the package insert (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1abda8b8-48a8-4995-af86-39220d1aa240).

[3]Information regarding, Midazolam in Sodium Chloride Injection 1mg/mL, Inforlife SA, was obtained from the package insert (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211844s000lbl.pdf).

[4]Information regarding, Midazolam in 0.8% Sodium Chloride Injection 1mg/mL, is provided in Module 1.14 labeling of seq 0001.

From 1.12 Comparison of Generic Drug and References Listed Drug Seq 0003, pg. 3/4.

In comparison to the reference drug, which needs to be diluted to 0.5 mg/mL for continuous infusion, the proposed drug product is ready to use for infusion. Although the proposed drug product has different excipients and a higher concentration of use than the reference drug, the Sponsor also lists NDA 211844 as a reference product, which is a midazolam product that has the same excipients and concentration as the current product. The proposed drug product is isotonic, has a lower concentration of sodium chloride, and has a pH range within the range of the referenced product of NDA 211844. As such the Division concluded that an IV toxicology study and blood compatibility studies were not necessary for this drug product.

The proposed product is within the osmolarity (between (b) (4) mOsm/kg) and pH (between pH 3.0 to 4.0) ranges of both RDs.

Table 3: Midazolam and RS Physiochemical Data Comparison

Parameter	[redacted]	Appearance of Solution	Container Closure	Visual Particulate Matter	Osmolality	pH
Exela Specification	[redacted]	Clear, Colorless Solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	(b) (4)	3.0 – 4.0
Sample ID	Data Reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Midazolam Injection, USP, Hospira, Lot 16-036-DK, Exp: 01APR2022	2021-026/ 29 - 34	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.0
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.0
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.0
Midazolam Injection, USP, Hospira, Lot 13-434-DK, Exp: 01JAN2022	2020-258/ 85	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	259 mOsm/kg	3.1
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	259 mOsm/kg	3.1
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.1
Midazolam Injection, USP, Hospira, Lot 14-111-DK, Exp: 01FEB2022	2020-258/ 85	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.1
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	265 mOsm/kg	3.1
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.1

Parameter	[redacted]	Appearance of Solution	Container Closure	Visual Particulate Matter	Osmolality	pH
Exela Specification	[redacted]	Clear, Colorless Solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	(b) (4)	3.0 – 4.0
Sample ID	Data Reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exela, Midazolam in 0.8% Sodium Chloride, 50 mL Vial, Lot B0000006 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	260 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 50 mL Vial, Lot B0000007 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 50 mL Vial, Lot B0000008 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 100 mL Vial, Lot B0000009 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5

Parameter	[redacted]	Appearance of Solution	Container Closure	Visual Particulate Matter	Osmolality	pH
Exela Specification	[redacted]	Clear, Colorless Solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	240 – 290 mOsm/kg	3.0 – 4.0
Sample ID	Data Reference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exela, Midazolam in 0.8% Sodium Chloride, 100 mL Vial, Lot B0000010 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 100 mL Vial, Lot B0000011, Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.5

From 3.2.P.2 Pharmaceutical Development Drug Product, pgs. 60-62/115.

Table 4: Midazolam and InfoRLife Midazolam Physiochemical Data Comparison

Parameter		Appearance of Solution	Container Closure	Visual Particulate Matter	Osmolality	pH
Sample ID	Data Reference					
Midazolam in Sodium Chloride Injection, 100 mg/100 mL InfoRLife Lot 10238, Exp: NOV2023	2022-418 Page 21 2022-404 Page 50	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	292 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	292 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	292 mOsm/kg	2.9
Midazolam in Sodium Chloride Injection, 100 mg/100 mL InfoRLife Lot 10239, Exp: NOV2023	2022-418 Page 21 2022-404 Page 50	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	292 mOsm/kg	3.1
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	293 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	293 mOsm/kg	2.9
Midazolam in Sodium Chloride Injection, 100 mg/100 mL InfoRLife Lot 10224, Exp: OCT2023	2022-418 Page 21 2022-404 Page 50	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	293 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	292 mOsm/kg	3.0
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	292 mOsm/kg	3.0
Midazolam in Sodium Chloride Injection, 50 mg/50 mL InfoRLife Lot 10230, Exp: OCT2023	2022-418 Page 21 2022-404 Page 50	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	294 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	294 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	293 mOsm/kg	2.9

Parameter		Appearance of Solution	Container Closure	Visual Particulate Matter	Osmolality	pH
Midazolam in Sodium Chloride Injection50 mg/50 mL InfoRLife Lot 10229, Exp: OCT2023	2022-418 Page 21 2022-404 Page 50	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	293 mOsm/kg	3.0
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	294 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	292 mOsm/kg	2.9
Midazolam in Sodium Chloride Injection, , 50 mg/50 mL InfoRLife Lot 10210, Exp: SEP2023	2022-418 Page 21 2022-404 Pages 50 - 51	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	295 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	295 mOsm/kg	2.9
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	295 mOsm/kg	2.9

Exela Specification		Clear, Colorless Solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	(b) (4)	3.0 – 4.0
Sample ID	Data Reference					
Exela, Midazolam in 0.8% Sodium Chloride, 50 mL Vial, Lot B0000006 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	260 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 50 mL Vial, Lot B0000007 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 50 mL Vial, Lot B0000008 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	261 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 100 mL Vial, Lot B0000009 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	262 mOsm/kg	3.5

Parameter		Appearance of Solution	Container Closure	Visual Particulate Matter	Osmolality	pH
Exela Specification		Clear, Colorless Solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	(b) (4)	3.0 – 4.0
Sample ID	Data Reference					
Exela, Midazolam in 0.8% Sodium Chloride, 100 mL Vial, Lot B0000010 Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
Exela, Midazolam in 0.8% Sodium Chloride, 100 mL Vial, Lot B0000011, Upright, 12 M	2020-208/176	Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	263 mOsm/kg	3.5
		Clear, colorless solution	No Visible leak, precipitate, or other abnormalities	Essentially free of visible particulate matter	264 mOsm/kg	3.5

From 3.2.P.2 Pharmaceutical Development Drug Product, pgs. 69-72/115.

The maximum daily dose (MDD) of the proposed drug product is the same as the labeled use for the reference drug products. As per the approved label, a loading dose of 0.01 to 0.05 mg/kg may be given. This may be followed by a maintenance dose which can range from 0.02 to 0.1 mg/kg/h, and the infusion rate can be adjusted up to

50% of the initial infusion rate. At a maximum dose of 0.1 mg/kg/h and a 50% increase in the infusion rate, the maximum dose per hour is 0.15 mg/kg/h. Therefore, the **MDD for a 60 kg person is 219 mg/day**. This is based on the following calculation:

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

2.4 Comments on Novel Excipients

The excipients for the proposed drug product are as follows:

Component	Quantity per Unit (50 mg Vial, 100 mg Vial)	Maximum Daily Intake (MDI)	MDI in Inactive Ingredients Database (IID)	Comment
Sodium Chloride, USP	8 mg/mL (400 mg, 800 mg)	0.8% w/v, 1.752 g	0.9% w/v, 28.773 g	Within limits listed in IID.
Hydrochloric Acid	q.s. to pH to 3.5	q.s. to pH to 3.5	-	-
Sodium Hydroxide	q.s. to pH to 3.5	q.s. to pH to 3.5	-	-
Water for Injection	q.s. to 1 mL (q.s. to 50 mL, q.s. to 100 mL)	-	-	-

Data from 3.2.P.1 Description and Composition of the Drug Product Seq 0001, pg. 2/3.

The excipients have been utilized within levels contained in approved drug products as listed in the FDA Inactive Ingredients Database (IID). Therefore, there are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

Based on the MDD = 219 mg/day, the qualification thresholds (QT) are as follows:

- Drug Substance Impurities as per ICH Q3A(R2)
  = 0.15% or 1.0 mg/day, whichever is lower

- Drug Product Degradants as per ICH Q3B(R2)
  = 0.2% or 3 mg TDI, whichever is lower

Drug Substance Impurities and Qualifications

Table 5: Specified Drug Substance Impurities

Impurity/Degradants	Structure	Proposed Specification	Acceptability

(b) (4)	
	Acceptable
	Acceptable
	Acceptable
	Acceptable
	Acceptable

(b) (4)	
	Acceptable
	Acceptable
	Acceptable
	Acceptable
	Acceptable
	Acceptable

Data from 3.2.S.4.5 Justification of Specification DS Seq 0006, pgs. 6-7/16.

The specification limits for the drug substance impurities are set at (b) (4)%, with the exception of (b) (4)%. All the proposed levels are within the qualification threshold outlined in ICH Q3A(R2).

Drug Product Degradants and Qualifications

Table 6: Specified Drug Product Degradants

Impurity/Degradants	Structure	Proposed Specification	Acceptability
[redacted]	[redacted]	(b) (4)	Acceptable.
[redacted]	[redacted]		Acceptable
[redacted]	[redacted]		Acceptable
[redacted]	[redacted]		Acceptable
[redacted]	[redacted]		Acceptable

[redacted]	Acceptable
	Acceptable
	Acceptable

Data from 3.2.S.4.5 Justification of Specification DS Seq 0006, pgs. 6-7/16.

The specification limits for the drug substance impurities are set at [redacted]%, and specification limits for unspecified impurities are set at [redacted]%. All the proposed levels are within the thresholds outlined in ICH Q3B(R2).

[redacted] Qualifications

Table 7: [redacted] Qualifications

[redacted]	Specification	Acceptability and Justification
[redacted]	NMT [redacted] ppm	Acceptable, below ICH [redacted] threshold
	NMT [redacted] ppm	Acceptable, below ICH [redacted] threshold
	NMT [redacted] PPM	Acceptable, below ICH [redacted] threshold

From 3.2.S.4.5 Justification of Specification DP Seq 0006, pgs. 3-4/23.

[redacted] qualifications are below that of ICH [redacted] acceptable daily intake levels and are acceptable.

Elemental Impurities

The Sponsor provided an Elemental Impurities Risk Assessment, study summary report SMRY-001616 (see 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 387/528). The risk assessment considers the drug product formulation, manufacturing process, and leachables from the containment closure system. The following list of elemental impurities and their associated PDE and Allowable Elemental Concentration (AEC) values are as follows.

Table 8: Elemental Impurity PDE's and AEC's for Midazolam in 0.8% Sodium Chloride Injection

Element	Parenteral PDE (µg/day)	30% PDE (µg/day)	AEC (ppb)/(w/v)	30% AEC (ppb)/(w/v)
(b) (4)				

APPEARS THIS WAY ON ORIGINAL

An example calculation for the determination of the AEC for (b) (4) s sh

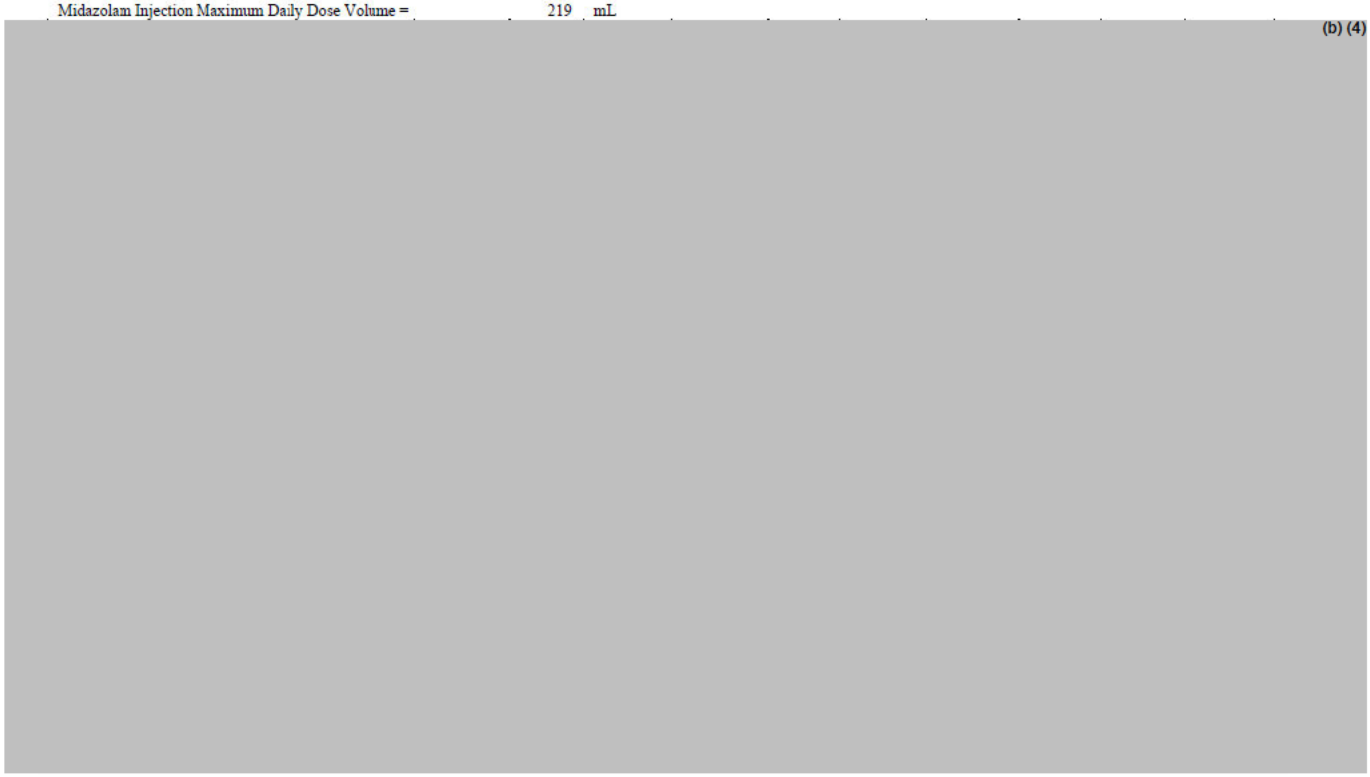
$$[\text{AEC}]\ ((\text{ppb})/\text{day}) = \frac{\text{PDE}\ (\mu\text{g/day})}{V_{MDD}} * 1000\ \frac{\text{ng}}{\mu\text{g}} = \frac{\frac{(b)\ \mu\text{g}}{(4)\ \text{day}}}{219\ \text{mL/day}} = \frac{(b)}{(4)}\text{ppb}$$

From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 416/535.

The Sponsor calculated maximum potential elemental impurity levels based on specification limits for each element listed on the COA for the drug substance and each excipient. The risk assessment included the drug substance, manufacturing equipment, containment closure system, excipients, and water for injection. Values were then compared to 30% of the PDE for each element to determine whether additional testing was necessary for the drug product.

Table 9: Potential Exposure Limits for Elemental Impurities for Midazolam in 0.8% Sodium Chloride Injection

Midazolam Injection Maximum Daily Dose Volume = 219 mL



From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 417/535.

As the calculated potential maximum exposure did not exceed the 30% PDE threshold, the Sponsor has stated that the control strategy will be to test the raw materials and drug substance per the vendor's Certificate of Authenticity (CoA). See CMC review for the adequacy of the above strategy. There are no issues identified for elemental impurities in the proposed drug product.

Nitrosamine Impurity Risk Assessment

The Sponsor has provided a risk assessment regarding the levels of nitrosamines within their drug product found in 4.2.P.5.5 Characterisation of Impurities DP Seq 0006, pgs. 6-18. In the risk assessment, the Sponsor noted that there is low risk for nitrosamine impurities originating from the formula, manufacturing components or process, container closure system, and stability testing. No nitrites were observed in any of these sources (for additional details see CMC review).

2.6 Container Closure System

Midazolam in 0.8% Sodium Chloride Injection solution is to be packaged in 50 mL and 100 mL molded clear glass vials with (b) (4) (b) (4).

Table 10: Midazolam in 0.8% Sodium Chloride Injection Container Closure Components

Product Description	Container	Closure
Midazolam in 0.8% Sodium Chloride Injection (1 mg/mL) 50 mg/50 mL	50 mL molded clear glass vial (b) (4)	(b) (4), 20 mm, (b) (4); 20 mm, Overseal w/ Flip-off Top- (b) (4)
Midazolam in 0.8% Sodium Chloride Injection (1 mg/mL) 100 mg/100 mL	50 mL molded clear glass vial (b) (4)	(b) (4) 20 mm, (b) (4) 20 mm, Overseal w/ Flip-off Top (b) (4)

From 3.2.P.7 Container Closure System Summary DP Seq 0001, pg. 3/15

The Sponsor has submitted extractable and leachable information under 3.2.P.2 Pharmaceutical Development Container Closure System Seq 0008. Extractables and leachables risk assessment is found in study report section 2.9 SMRY-001775 Leachables Impurities in Midazolam in 0.8% Sodium Chloride Injection (1 mg/mL) 50 mg/50mL, 50 mL vial, (b) (4) L batch, and (1 mg/mL) 100 mg/100 mL, 100 mL vial, (b) (4) L batch.

Extraction Study of Container Closure System

The Sponsor conducted extraction studies on the primary container-closure components and manufacturing components. These components include the (b) (4) (b) (4) 50 and 100 mL Molded Clear Vial, and (b) (4) Stopper.

Samples with the exception of the 50 and 100 mL molded clear vials were pulverized and reduced prior to exposure and refluxed or heated (in the case of the (b) (4) (b) (4) in an oven in 25 mM NaH_2PO_4, pH 1.8 or 2, 6, and 12 for a minimum of 8 hours. For the 50 and 100 mL molded clear vials, containers were filled with 22.9 mL of purified water and kept in an autoclave at 121 °C for 60 min. Metal concentrations of the final extract were measured via ICP-MS.

Table 11: Materials Evaluated for Extractables Analysis

Exela Part #	Component Name	Supplier
(b) (4)		
(b) (4)	50 mL Molded Clear Vial	(b) (4)
	100 mL Molded Clear Vial	
	(b) (4) 20 mm, (b) (4)	
		(b) (4)

From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 356/535.

Table 12: Extracted Surface Areas for Reflux Componentry

Componentry	Approximate Extracted Surface Area/Volume (cm^2/mL)
	(b) (4)

From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 356/535.

Table 13: Extraction Test Sample Preparation Summary

EXTRACTABLE TEST SAMPLE PREPARATION		
Extraction Method / Parameters		(b) (4)
Extraction Solvent		
Analytical Method	Volatile OC by HS-GC/MS	
	Semi-volatile OC by DI-GC/MS	
	Non-volatile OC by	

OC = organic compound; HS = headspace; DI = Direct injection; GC/MS = gas chromatography mass spectrometry; PTV = programmed temperature vaporizing injections; PA = polymer additives; LC/MS = liquid chromatography mass spectrometry; ICP/MS = inductively coupled plasma mass spectroscopy; LC/MC = liquid chromatography mass spectrometry; QL = quantitation limit (ppb) and DL = detection limit (ppb). Information obtained from 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 355/535.

The Sponsor has utilized the analytical evaluation threshold (AET) = (b) (4) ppb based on the maximum daily dose of midazolam at 219 mg/day, a safety control threshold (SCT) at (b) (4) mcg/day, and a qualification threshold (QT) at (b) (4) mcg/day. The calculations are presented in the following table:

Table 14: Formulas and Calculations for the SCT and AET Values for Midazolam in 0.8% Sodium Chloride Injection

Max Daily Dose Midazolam=	219000	µg/day					
[Midazolam]-DP =	1000	µg/mL					
Max Daily Dose Volume =	219	mL/day					
Duration of Treatment =	≤ 1	month					
Safety Concern Threshold (SCT) =	(b) (4)	µg/day	Qualification Threshold (QT)	(b) (4)	µg/day	(b) (4)	µg/day
Analytical Evaluation Threshold (AET) =		ppb	Analytical Evaluation Threshold (AET)		ppb		ppb

Note: The concentration units of ppb for the AET are expressed in units of w/v with respect to maximum daily dose volume of the drug product.
† - ICH M7[13] limit for dosage durations of less than 30 days for a single mutagenic compound

From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 353/535.

Reviewer Comment: *The analytical methods to detect volatile, semi-volatile, and non-volatile organic and inorganic compounds appear appropriate. The QL for these studies has the appropriate sensitivity to detect compounds at the SCT. The methods used to analyze the primary container closure system are within the appropriate range for detection. The extraction solvents used were relevant to the drug product given that they were aqueous and bracketed the pH range of the drug product. However, see CMC review for the assessment and final determination of the adequacy of these methods.*

The following is this Reviewer's calculation of the AET:

Safety Concern Threshold (SCT) = (b) (4) mcg/day

Maximum daily dose (MDD) of Midazolam = 219 mg/day

Concentration of drug product = 1 mg/mL

Maximum daily volume (MDV) of Midazolam = MDD/Concentration of drug product = 219 mL/day

Unit = Vial

Analytical Evaluation Threshold (AET) = SCT/MDV = (b) (4) mcg/day / 219 mL/day = (b) (4) mcg/mL = (b) (4) ppm = (b) (4) ppb

	Reviewer's AET	Sponsor's AET	Adequate
Safety Concern Threshold (SCT)	(b) (4) mcg/day	(b) (4) mcg/day (maximum AET)	Yes, Sponsor's AET is more conservative than Reviewer's AET
MDD	219 mg/day	219 mg/day	
AET	(b) (4) ppb	(b) (4) ppb	

The methods of the extraction study appear adequate from a pharmacology/toxicology perspective; however, refer to the CMC review for the final determination on the adequacy of the extraction methods.

(b) (4)

9 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer Comment: *The AET is adequate in detecting leachables that have the potential to exceed (b) (4) mcg/day in the final product.*

Selection of Targeted Leachables from Extraction

The Sponsor states that compounds at or above the SCT of (b) (4) mcg/day or AET of (b) (4) ppb were used for known and unknown extractables, which were to then be tracked in the leachables testing. The QT of (b) (4) mcg/day or AET of (b) (4) ppb was used as the qualification threshold for observed unknown leachables that were to be identified, and for which systemic toxicity of compounds were to be analyzed. For compounds with known mutagenic properties and those with insufficient toxicological data to determine mutagenicity, ICH M7 limit of (b) (4) mcg/day, or (b) (4) ppb, was to be used.

Reviewer Comment: *The following compounds within the extraction study exceeded the Reviewer's AET and should be targeted in the leachable studies.*

	Compound	Max. extracted conc. (mcg/day)	Max. Source of Extractable	Comment
Reflux				
(b) (4)				

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

All listed compounds above the AET should be targeted in the leachables evaluation. The Reader is referred to the CMC review to determine if the leachable studies adequately evaluate the compounds listed in the table above.

Leachables Study of Container Closure System

As per the report SMRY-001775, leachables testing was done on 6 exhibit batches (3 50 mL vials, 3 100 mL vials) at 0, 6-month, and 12-month time-points. Both the 50 mL and 100 mL vial configurations were tested at initial release, at long-term term conditions (25°C/40%RH) at 3 and 12 months, and at accelerated conditions (40°C/25%RH) at 3 months.

Table 20: Drug Product and Container-Closure Information

Drug Product Lot #	Vial	Fill V (mL)	Time points and conditions analyzed			
			0	6 Months		12 Months
				25/60	40/75	25/60
B0000006	(b) (4)	50	X	X	X	X
B0000007		50	X	X	X	X
B0000008		50	X	X	X	X
B0000009		100	X	X	X	X
B0000010		100	X	X	X	X
B0000011		100	X	X	X	X

NT = Not Tested, TBA= To be analyzed, stability time point has not been pulled yet.

From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 368-369/535.

Table 21: Leachables Testing Method

LEACHABLE TEST METHOD						
Containment Closure System	50 mL			100 mL		
Drug Product Lot #	B0000006	B0000007	B0000008	B0000009	B0000010	B0000011
Manufacture Date	Not Specified in Report	Not Specified in Report	Not Specified in Report	Not Specified in Report	Not Specified in Report	Not Specified in Report
Months on Stability (25°C/40%RH)	0, 6, 12	0, 6, 12	0, 6, 12	0, 6, 12	0, 6, 12	0, 6, 12
Months at Accelerated Conditions (40°C/25%RH)	6	6	6	6	6	6
Initial Release	3 Lots			3 Lots		
Analytical Method Used	Headspace Gas Chromatography (HS-GC) with flame ionization detection for volatiles (QL = (b) (4) ppb; DL = (b) (4) ppb)					
	Direct Inject Gas Chromatography (DI-GC) with flame ionization detection for semi-volatiles (QL = (b) (4) ppb; DL = (b) (4) ppb)					
	Ultra High-Performance Liquid Chromatography (UPLC) with UV detection for non-volatiles (QL = (b) (4) ppb; DL = (b) (4) ppb)					
	Inductively Coupled Plasma Mass Spectrometry Method for elementals					

The Sponsor states that an AET value of (b) (4) ppb (equivalent to (b) (4) mcg/day) will be used as the qualification threshold for observed unknown leachables that are to be identified. They state that compounds with known mutagenic properties and those for which insufficient toxicological data exists to determine mutagenicity, the ICH M7 limit of (b) (4) ppb (equivalent to (b) (4) mcg/day) will be used.

Reviewer Comment: *The Sponsor evaluated leachables at release (0), 3, and 12 months of stability for the drug product in 50 mL and 100 mL glass vials. The leachables were evaluated in three different lots at each time point. It is noted that the time points evaluated for both the 50 mL and 100 mL glass vials do not span the entire 2 year shelf-life of the proposed drug product. However, review of the protocols by CMC were found to be acceptable for determining leachable compounds from the CCS. The reviewer is referred to the CMC review for the adequacy of the leachables methodology.*

Based on the information provided, the following calculation is made regarding the AET for the leachables study:

$$MDV = MDD \div \text{drug concentration}$$
$$219\ mg/day^{a} \div 1\ mg/mL^{b} = 219\ mL/day$$

$$AET = QT / MDV$$
$$AET = (b)\ (4)\ mcg/day^{c} \div 219\ mL/day = (b)\ (4)\ mcg/mL = (b)\ (4)\ ppb$$

a. *The maximum daily dose of midazolam is 219 mg/day.*
b. *Concentration of the drug product in this presentation is 1 mg/mL.*
c. *The AET is calculated using the qualification threshold (QT) of (b) (4) mcg/day.*

The limit of quantitation (LOQ) for organic and inorganic compounds appears adequate when compared to the AET calculated by this reviewer.

LEACHABLE STUDY					
				Applicant's AET (ppb) (b) (4)	Reviewer's AET (ppb) (b) (4)
Analytical Method	Compound type	LOQ (ppb)	LOD (ppb)	Acceptable Y/N	
(HS)-GC/MS	(b) (4)		(b) (4)	Y	Y
Direct Inject-GC				Y	Y
UPLC				Y	Y
ICP/MS				Y	Y

LOQ = limit of quantitation; LOD = limit of detection; AET = acceptable evaluation threshold. LOQ and LOD were taken from the reported Quantitation Limit (QL) and Detection Limit (DL) for each analytical method in PD of CCS.

Results of Leachable Study

The results of the leachable study are presented below.

Table 22: Volatile Leachable Results for Midazolam in 0.8% Sodium Chloride Injection, (ppb), at T0

Compound	T0 (b) (4) vial	
	50 mL Fill Volume	100 mL Fill Volume
(b) (4)		

From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 371/535.

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Table 33: Elemental Leachables Results for Midazolam in 0.8% Sodium Chloride Injection (ppb), 100 mL Fill Volume

Compound	PDE (µg/day)	AEC (ppb) (w/v)	QL (ppb)	B0000009			B0000010			B0000011		
				6M		12M	6M		12M	6M		12M
				25/60	40/75	25/60	25/60	40/75	25/60	25/60	40/75	25/60
(b) (4)												

From 3.2.P.2 Pharmaceutical Development Containment Closure System Seq 0008, pg. 377/535.

All elementals were observed below each element's respective AEC, with levels being in low ppb levels. There did not appear to be a trend with respect to time or temperature.

Reviewer Comment: *The leachable study analyzed three batches of drug product for both the 50 mL and 100 mL vials. Both vials were analyzed at release, 6 months (25°C/40%RH and 40°C/25%RH), and 12 months. The targeted compounds in the leachable study for these vials were based on all compounds from the extractables study about the AET of (b) (4) mcg/day, or (b) (4) ppb.*

A total of 15 compounds were identified in the leachables study that were above the AET of (b) (4) mcg/day, or (b) (4) ppb. 4 compounds were identified in the leachables study that were above the AET of (b) (4) mcg/day but not identified in the extraction.

A risk assessment for the following compounds was submitted by the Sponsor and reviewed by this Reviewer:

Table 34: Compounds for Risk Assessment

	Compound	Highest Detected Level		Reviewer's PDE (mcg/day)	Trend Analysis	Adequacy
		ppb	mcg/day			

(b) (4)

[redacted]

20 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

The PDEs calculated by this Reviewer ([(b) (4)] mg/day for [(b) (4)] and [(b) (4)] mg/day for [(b) (4)] is more conservative than that reported by the Sponsor ([(b) (4)] mg/day). However, the MDE [(b) (4)] as a leachable ([(b) (4)] mcg/day) does not exceed either calculated PDEs. The resulting safety margin 229x and 18.3x. Based on these data, there are no safety concerns for MDE [(b) (4)] as a leachable compound associated with the maximum daily dose of midazolam.

2.7 Regulatory Background

This is a 505(b)(2) application referencing the Agency's previous findings of safety and efficacy of Versed (NDA 018654) and InfoRLife's midazolam drug product (NDA 211844).

The Sponsor did not submit a Pre-IND prior to the submission of this NDA.

3 Studies Submitted

No nonclinical studies were submitted in this NDA.

4 Pharmacology

The Sponsor has not submitted new primary pharmacology studies with midazolam for review and are relying upon the data in the referenced product label.

The referenced product labeling contains the following statement:

> Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant.

5 Pharmacokinetics/ADME/Toxicokinetics

The Sponsor has not submitted pharmacokinetic, ADME, or toxicokinetic studies for review and are relying on the labeling based on the RDs, (NDA 018654 and NDA 211844).

6 General Toxicology

The Sponsor submitted no studies and found no relevant studies during their search for either single- or repeat-dose toxicity. The Sponsor is relying upon the Agency previous findings of safety and efficacy of the referenced products.

7 Genetic Toxicology

The Sponsor submitted no studies and found no relevant studies during their search. The Sponsor is relying upon the Agency previous findings of safety and efficacy of the referenced products.

8 Carcinogenicity

The Sponsor submitted no studies and found no relevant studies during their search. The Sponsor is relying upon the Agency previous findings of safety and efficacy of the referenced products. As the proposed drug product is for acute use, a carcinogenicity evaluation for midazolam is not required.

9 Reproductive and Developmental Toxicology

The Sponsor has not submitted new studies regarding reproductive and developmental toxicology. The Sponsor is relying upon the Agency previous findings of safety and efficacy of the referenced products.

10 Special Toxicology Studies

Local Tolerance Studies

The Sponsor submitted no studies and found no relevant animal studies during their search. The Sponsor is relying upon the Agency previous findings of safety and efficacy of the referenced product.

11 Integrated Summary and Safety Evaluation

This application for NDA 215868 is regarding a midazolam drug product via the 505(b)(2) regulatory pathway. The Sponsor has cited NDA 018654 (Versed) and NDA 211844 as the Reference Drugs (RD) and are relying upon data in the referenced product labeling. The Maximum Daily Dosage (MDD) for this product 219 mg/day. The proposed drug product is a ready-to-infuse product at a concentration of 1 mg/mL.

No nonclinical pharmacology or toxicology studies were submitted in support of this NDA application. The Sponsor had submitted literature from the time of approval of the RD to the date of submission regarding pharmacology, pharmacokinetic, ADME, toxicokinetic, and toxicology studies.

The Sponsor provided a side-by-side comparison to the proposed drug product and reference drugs. In comparison to the reference drug, Versed, which should be diluted to 0.5 mg/mL for continuous infusion, the proposed drug product is ready to be infuse without dilution. The Sponsor also references NDA 211844, which is a midazolam product that has similar excipients with the exception of a lower concentration of sodium

chloride and is the same concentration as the current product. The proposed drug product is isotonic, has a lower concentration of sodium chloride, and has a pH range within the range of the referenced product of NDA 211844. As such the Division concluded that an IV toxicology study and blood compatibility studies were not necessary for this drug product.

The Sponsor's proposed specifications for drug substance and drug product impurities are within the levels outlined in ICH Q3A(R2) and Q3B(R2). Solvent specifications were within the levels as stated in ICH Q3C(R8). Elemental impurities are below the control threshold of (b) (4)% as per ICH Q3D.

To support the safety of the container closure system, glass vial and rubber stopper, extractables and leachables studies were provided. In total, 15 leachables above the SCT were identified and toxicological risk assessments were submitted. The leachables were adequately qualified and therefore there are no concerns with the safety of the container closure system.

Taken together, this NDA for midazolam is recommended for approval from a pharmacology/toxicology perspective.

12 Appendix/Attachments

12.1 References

1. (b) (4)
2. Halder, C.A., et al., *Hydrocarbon nephropathy in male rats: identification of the nephrotoxic components of unleaded gasoline.* Toxicol Ind Health, 1985. **1**(3): p. 67-87.
3. (b) (4)
4.
5.
6.
7.
8.

9. (b) (4)

10. Derelanko, M., *The Toxicologist's Pocket Handbook.* New York: Informa Healthcare, 2008.
11. Chung, Y.H., et al., *Subacute Inhalation Toxicity of 3-Methylpentane.* Toxicol Res, 2016. **32**(3): p. 245-50.
12. (b) (4)

13.

14.

15.

16.
17.

18.

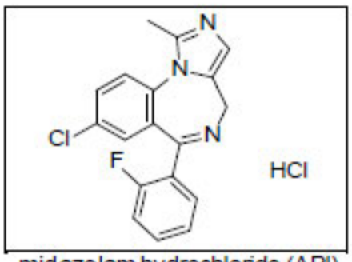
19.

20.

12.2 NDA 215868 QSAR Report

To: Alexander Son (CDER/OND/ON/DPTN)
cc: Newton Woo (CDER/OND/ON/DPTN)
From: CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service
Re: NDA 215868
Date: March 17, 2022

Summary



midazolam hydrochloride (API)

An extractables/leachables study was conducted by the applicant for the drug product midazolam hydrochloride (API), where two organic compounds were detected. General toxicity study data for the extractables/leachables are limited or not available. The applicant identified surrogate chemicals and applied a read-across approach to assess the general toxicity of the extractables/leachables.

The CDER/OTS/OCP/DARS Computational Toxicology Consultation Service (CTCS) was consulted to:

- Evaluate the surrogates proposed by the applicant to determine their acceptability.
- Propose alternative surrogates to assess general toxicity where the applicant's surrogates are unsuitable.

The agency concludes:

- For [redacted] (No CAS)
  - [redacted] (CAS [redacted]) is structurally acceptable as a surrogate.
  - CTCS also proposes [redacted] (CAS [redacted]) as a second surrogate since, taken together, the two surrogates cover the [redacted] functionalities of the extractable/leachable, in addition to the [redacted]
- For [redacted] CAS [redacted]
  - The applicant's proposal of [redacted] (aka [redacted] (CAS [redacted]) as a surrogate is not acceptable as better surrogates are available. Although the [redacted] of [redacted] is the same as the extractable/leachable structure, CTCS proposes [redacted] (CAS [redacted]) which has a [redacted] than the [redacted]
  - CTCS also proposes [redacted] (CAS [redacted]) as it shares the same substituted [redacted] core structure.

Surrogate Analysis for General Toxicity

CTCS evaluated the chemical structure of the extractables/leachables and the applicant's proposed surrogates. SciFinder (https://scifinder-n.cas.org) was used to confirm the chemical structures of all substances included in this report. Where available, additional surrogates were proposed by CTCS. CTCS performed a literature search and identified relevant published references and technical reports, which are provided below. References for each surrogate are provided at the end of the report, while references for extractables/leachables are provided in the following table.

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

ALEXANDER I SON
07/07/2022 12:30:44 PM

NEWTON H WOO
07/07/2022 12:33:34 PM