CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209566Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 10, 2018

To: Teresa Buracchio, M.D.
Division of Neurology Products (DNP)

Harold Sano, Regulatory Project Manager, (DNP)

Tracey Peters, PharmD, Associate Director for Labeling, (DNP)

From: Sapna Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for SEIZALAM™ (midazolam injection) for intramuscular use, CIV

NDA: 209566

In response to the DNP consult request dated December 4, 2017, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for SEIZALAM™ (midazolam injection) for intramuscular use, CIV (Seizalam).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Harold Sano) on August 29, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 29, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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

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/s/

SAPNA P SHAH
09/10/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 31, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209566
Product Name and Strength:	Seizalam (midazolam) injection, 5 mg/mL
Applicant/Sponsor Name:	Meridian Medical Technologies Inc.
FDA Received Date:	August 29, 2018
OSE RCM #:	2017-2445-2
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

Division of Neurology Products (DNP) requested that we review the revised carton labeling, container label and (b) (4) for Seizalam (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note that in the submission document, the sponsor clarified the expiration date format for the carton labeling and container label will be "DDMMMYYYY" and we find the format acceptable. We also note that sponsor revised the net quantity statement on the carton labeling. The revised carton labeling and container label are acceptable from a medication error perspective. We have no further recommendations at this time.

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

[a] Whaley, E. Label and Labeling Memorandum for Seizalam NDA 209566. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 15. RCM No.: 2017-2445-1.

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/

EBONY A WHALEY
08/31/2018

LOLITA G WHITE
09/04/2018

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 17, 2018

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

Subject: **NDA 209566**: Midazolam Multi-Use Vials for Intramuscular Injection
Trade Name: Seizalam
Dosages: Adult patients ≥18 years of age should receive 10 mg midazolam administered intramuscularly (2 mL of undiluted Seizalam Multi-Use Vial), which contains 5 mg/mL midazolam.
IND Numbers: 123121, 102540
Indication: Treatment of status epilepticus in patients ≥ 18 years of age
Sponsor: Meridian Medical Technologies, Inc./Pfizer Co.
PDUFA Goal Date: September 14, 2018

Materials Reviewed:

- 2.5 Clinical Overview
- 2..4 Nonclinical Overview
- 2.7.6 Synopses of Individual Studies
- 3.2 Drug Substance
- 4.2.1 Pharmacology
- 5.3.5 Reports of Efficacy and Safety Studies
- 1.14. Labeling

Table of Contents

I. Summary

1. Background

Midazolam, a short-acting benzodiazepine, was initially approved in the United States (US) in 1985 under the trade name Versed (NDA 018654). Midazolam is currently marketed in the US as a generic drug in intravenous (IV) and intramuscular (IM) dosage forms for adults and children for sedation/anxiolysis/amnesia, induction of anesthesia prior to administration of other anesthetic agents, and for sedation of intubated and mechanically ventilated patients. Buccal midazolam is marketed in over 50 other countries worldwide for the treatment of prolonged seizures in children, however, not in the US where it is not approved for the treatment of seizures.

Status epilepticus (SE) is defined as seizure activity >5 minutes duration, resulting from abnormal electrical activity in the brain due to a variety of different etiologies. It can have significant morbidity and mortality unless terminated rapidly. With increasing duration, status epilepticus can become

refractory to first-line treatments, including the benzodiazepines, which are the most common first-line pharmacotherapies for status epilepticus.

While standard treatments, such as lorazepam, are effective for rapid termination of seizure activity when administered IV to a hospitalized patient, achieving rapid IV access in the field while a patient exhibits motor seizures is difficult and time consuming, and is not always possible for emergency service teams. Furthermore, personnel skilled at starting an IV line may not always routinely be present or available.

This is a 505(b)(2) submission that cites as the listed drug (LD) Versed injection (NDA 018654), and relies on the previous FDA findings related to drug safety and/or efficacy for the LD, and other data from the published literature. Since Versed Injection has been discontinued, the Sponsor has used Midazolam Injection, USP (ANDA 075293, Hospira). The Sponsor's midazolam injections are formulated as 50 mg/10 ml multi-use vial. The Department of Defense selected midazolam for development as an adjunctive treatment for nerve agent-induced seizures following exposure of personnel to nerve agents, (b) (4) One clinical study (# 11903) was performed under Army IND 68432. The Sponsor's request for priority review was denied.

IM administration is a more practical approach in the pre-hospital setting. This option is not feasible with drugs such as diazepam and lorazepam, since systemic absorption after IM administration of these drugs is significantly slower than by the IV route. Additionally, benzodiazepines such as lorazepam require either refrigeration to maintain their shelf-life or frequent re-stocking, which can be impractical in the pre-hospital setting. The average time to maximum plasma concentration (C_{max}) of diazepam following IM administration is up to 90 minutes, while for lorazepam this can be 3 hours after IM administration. Consequently, the onset of anticonvulsant activity of diazepam may be delayed during the time in which it is important to terminate seizure activity. Furthermore, the injectable formulations of lorazepam require storage in a refrigerator, which can be impractical for an emergency response team.

Although midazolam for IM injection for the treatment of any seizure type, particularly SE, are not approved in any country, midazolam has properties that may make it an effective IM therapy for SE. The diazepine ring of midazolam opens reversibly at pH <4, forming a highly stable, water-soluble, primary amine derivative that allows midazolam to be formulated and stored in a non-refrigerated environment. Additionally, the aqueous state improves absorption when midazolam is administered by IM injection, with peak serum levels of midazolam reached within 20 to 30 minutes. Once it is absorbed into the muscle and blood stream, and physiological pH is attained, the diazepine ring closes and midazolam becomes lipophilic, allowing rapid central nervous system (CNS) penetration.

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) data (December 2012) were submitted to the FDA (b) (4) On April 19, 2013, the FDA advised the Sponsor to gather hospital records and all available results for all subjects who were admitted into the hospital or intensive care unit (ICU) as part of RAMPART, in order to adequately evaluate the safety of midazolam. (b) (4)

(b) (4)

The Sponsor proposed a dose of 10 mg/2 mL of Midazolam Multi-Use Vials for patients ≥18 years of age, delivered by healthcare professionals, including first responders and emergency service personnel.

2. Conclusions

1. This 505(b)(2) application for IM midazolam for the treatment of SE is supported by data from:
   - Two animal efficacy studies, sponsored by the US Office of the Surgeon General, Department of the Army (OTSG-DA) under IND 068432.
   - Five Phase 1 studies conducted under IND 068432 and sponsored by the OTSG-DA; and other studies under IND 102540, sponsored by Meridian.
   - A Phase 1 safety study conducted under IND 102540 and sponsored by Meridian, with extended follow-up to 30 days.
   - A Phase 3 multicenter clinical study, RAMPART, sponsored by the University of Michigan (under IND 102254) that has evaluated the efficacy and safety of midazolam administered IM by auto-injector compared to lorazepam administered IV in the pre-hospital treatment of adult subjects experiencing SE.

2. Because all patients enrolled in the RAMPART study are suffering from SE, it is not possible to collect abuse-related adverse events (AEs). Similarly, since only single doses of IM midazolam will be administered it is not possible to assess dependence and withdrawal in this study. Midazolam abuse and dependence are well-characterized for its currently approved uses and detailed in the NDA submission (ISS, Sections 4.7.5 and 4.7.6; Module 5, Section 5.3.5.3). The manifestations of midazolam overdose reports are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, and untoward effects on vital signs.

3. Midazolam is a Schedule IV in the Controlled Substance Act (CSA). It produced physical dependence of a mild to moderate intensity in Cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam. There were no reported cases of misuse, abuse, addiction, diversion, or overdose within any of the midazolam clinical studies supporting this application.

4. Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, hallucinations, tremor, abdominal and muscle cramps, vomiting and sweating) have occurred following abrupt discontinuation of benzodiazepines, including midazolam. More

severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time.

5. Although no specific studies on mental function or on the ability to drive or use machines have been performed, midazolam, similar to other benzodiazepines, induces sedation, somnolence, confusion, impaired coordination, and diminished reflexes, thus prohibiting the ability to drive or operate machinery.

3. Recommendations

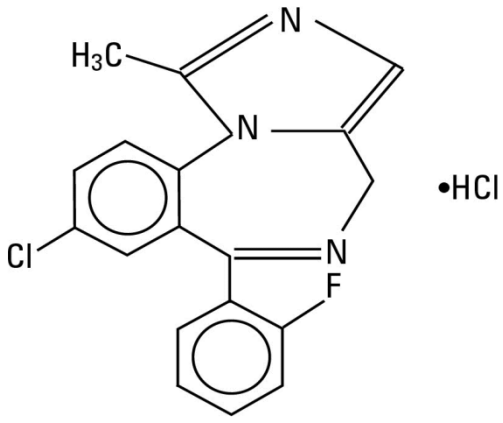
Status epilepticus is a potentially life-threatening condition associated with a high risk of permanent neurological impairment and death. The Investigational Product, a single 10 mg dose of the Midazolam IM Auto-Injector, appears to be an important addition to the armamentarium available to abort these recurrent seizures. Since the morbidity and mortality associated with these seizures is proportional to their length, Seizalam, because of its ability to be used easily and quickly in the field, should provide significant improvement in the treatment of this disease. Seizelam's abuse potential is well understood, and we recommend it be approved. It should remain a Schedule IV controlled substance under the Controlled Substance Act.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Chemical Name: 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*imadazo[1,5-a] [1,4] benzodiazepine hydrochloride
Midazolam Hydrochloride (Midazolam HCl)
Molecular Structure



Physical Description: White or yellowish crystalline powder
Pharmacologic Class: Benzodiazepine

Solubility characteristics: Practically insoluble in water, freely soluble in acetone and in alcohol, soluble in methanol.
Chemical formula: C18H13ClFN3•HCl
Molecular Weight: 362.24

1.2 Product Information

The Midazolam Multi-Use Vials for IM manual injection are parenteral solutions intended solely for administration by injection. Both the Midazolam IM Auto-Injectors (Investigational Product) and the Midazolam Multi-Use Vials for IM manual injection are parenteral solutions intended solely for administration by injection. Both the Midazolam IM Auto-Injectors and the Midazolam Multi-Use Vials for IM manual injection contain the same active and inactive ingredients in the same concentrations (50 mg/10 ml vial) as the approved drug products (Versed Injection [NDA 018654] and Midazolam Injection, USP [ANDA 075293]).

2. Nonclinical Pharmacology

Midazolam has a high affinity for the benzodiazepine receptor in the central nervous system (CNS). Benzodiazepine receptors have been identified in different body tissues including the heart and skeletal muscle, although their predominance appears to be in the CNS. Midazolam is a short-acting benzodiazepine which works by enhancing gamma aminobutyric acid (GABA) mediated inhibition, which is the basis for their antiepileptic and sedating effects. Midazolam is unique among the benzodiazepines in that when its diazepine ring opens reversibly at pH <4, it forms a highly stable, water-soluble compound. This property allows it to be formulated and injected as an aqueous solution that can be stored in a non-refrigerated environment. Above pH 4, and therefore at physiological pH (i.e., in the muscle and bloodstream), the ring closes with a half-life of less than 2 minutes, becoming a lipophilic compound. The time in an aqueous state improves absorption when midazolam is administered through IM injection while the lipophilic state preserves rapid CNS penetration.

Midazolam has been tested as an anticonvulsant in numerous animal seizure models utilizing a variety of seizure-inducing treatments including electrical stimulation, treatment with kainic acid, pilocarpine, organophosphates, and nerve agents. It demonstrated seizure cessation activity in these models, and seems to be more potent (on a mg/kg dose basis) and worked faster than comparator benzodiazepines such as diazepam.

3. Clinical Pharmacology

Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the cerebral cortex, which maintains the inhibitory tone that counterbalances neuronal excitation. When this balance is altered, seizures may ensue. Benzodiazepines work by enhancing GABA-mediated inhibition. Midazolam is a short-acting benzodiazepine.

The objective of the Sponsor's clinical pharmacology program was to characterize the pharmacokinetic (PK) properties of midazolam following IM administration. The rate and extent of systemic exposure,

assessed by Cmax and area under the curve (AUC), tended to increase proportionally with increasing dose from 5 mg to 30 mg (or 0.10 mg/kg to 0.49 mg/kg). Additionally, the PK analyses indicate that the mean C_{max} and AUC values for midazolam from the treatment with 2 × 10 mg Midazolam IM Auto-Injectors with injections separated by <1 minute were similar to the treatment with 2 × 10 mg Midazolam IM Auto-Injectors with injections separated by 10 minutes. The comparison studies suggest that midazolam exposures (C_{max} and AUC) were comparable between the Midazolam IM Auto-Injector and the midazolam IM manual injection. The T_{max} data suggested that there is a similarly rapid absorption of midazolam following IM administration with auto-injector or manual injection. Additionally, there was similar bioavailability of midazolam when administered via the Midazolam IM Auto-Injector or the midazolam IM manual injection.

3.1 Drug/Product Interactions

The comparison of midazolam PK following administration of either midazolam alone, midazolam combined with atropine, midazolam combined with atropine + 2-PAM, or midazolam combined with atropine + 2-PAM + pyridostigmine, indicated that the midazolam PK was not altered by combination treatment with these agents. There were no meaningful differences between male and female subjects in the PK characterization of IM midazolam administered with the Midazolam IM Auto-Injector.

4. Clinical Studies

4.1 RAMPART

Study Design

The clinical efficacy and safety of midazolam for the treatment of status SE was evaluated in the Phase 3 clinical trial Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), a double-blind, multicenter, double-dummy, randomized, non-inferiority study conducted by the University of Michigan (IND 102254). RAMPART evaluated the efficacy and safety of midazolam administered IM (5 mg and 10 mg doses [10 mg/2 mL]) by auto-injector compared to lorazepam (2 mg and 4 mg) administered IV in the pre-hospital setting treatment of adults experiencing status epilepticus.

On April 19, 2013, the FDA advised the Sponsor to gather hospital records and all available results for all subjects who were admitted into the hospital or intensive care unit (ICU) as part of RAMPART, in order to adequately evaluate the safety of midazolam. (b) (4) In accordance with the FDA's requests, The Midazolam IM Auto-Injector RAMPART Medical Records Project (Medical Records Project) was a more thorough retrospective investigation of the safety events, serious safety events (SSEs), and safety events of interest (SEOIs) (specifically, respiratory depression and renal failure) that occurred in RAMPART participants. Additionally, analyses were conducted in other subgroups, as well as analyses of the safety and efficacy of the study drugs in relation to medications taken prior to enrollment and during RAMPART, as well as the subject's history of co-morbid disease.

Participants in the RAMPART study were subjects with convulsive seizures, as reported by reliable witnesses, that continued for longer than 5 minutes or were having intermittent seizures for longer than 5 minutes without regaining consciousness. It was, therefore, not possible to collect abuse-related adverse events (AEs) after the IM injection of midazolam by Auto-Injector.

The primary outcome measure was the termination of convulsive seizure activity prior to arrival at the emergency department after 1 dose of study drug without the need for rescue medication. Termination of seizure was considered to have occurred at emergency department arrival if major motor convulsions had stopped, unless:

- the subject continued to be unresponsive and had a subsequent EEG documenting ongoing electrical seizure activity; or
- the subject had subsequent clinical seizure activity for which specific anticonvulsant drug treatment was given.

The determination of convulsive seizure activity cessation upon arrival at the emergency department was made by the attending emergency physician. If the subject was seizing upon arrival and/or had received a rescue dose of benzodiazepine, then the subject was considered a failure for the primary study outcome.

Efficacy Results

RAMPART demonstrated efficacy of a single 10 mg dose of the Midazolam IM Auto-Injector compared to 4 mg IV lorazepam for the primary outcome of cessation of seizures without use of rescue medication in adults before arrival in the emergency department in the pre-hospital treatment of SE. In the primary outcome analysis IM midazolam was non-inferior to IV lorazepam, and in a post-hoc analysis of the primary outcome IM midazolam was superior to IV lorazepam. These support the efficacy of 10 mg/2 mL midazolam administered via Midazolam Multi-Use Vials and manual syringe for the proposed indication of SE.

The primary outcome results demonstrated that seizures were absent without rescue therapy at emergency department arrival for 329 (73.4%) subjects who were assigned to receive IM midazolam and 282 (63.4%) subjects who were assigned to receive IV lorazepam. The absolute difference in the percentage of subjects who met the primary outcome was 10.1% (95% CI = 4.0%, 16.1%; non-inferiority $p < 0.0001$). Therefore, IM midazolam was non-inferior to IV lorazepam for the primary outcome based on the pre-specified criteria. Since non-inferiority was demonstrated, an additional post-hoc superiority analysis was performed; IM midazolam was significantly superior to IV lorazepam with 10.1% more subjects achieving the primary outcome ($p = 0.0015$, 95% CI = 4.0%, 16.1%).

The secondary outcome confirmed that fewer subjects were admitted to the hospital in the IM midazolam group than in the IV lorazepam group (258 [57.6%] subjects versus 292 [65.6%] subjects, respectively; $p = 0.016$). The number of subjects admitted to the ICU was also significantly lower in the IM midazolam group compared with the IV lorazepam group (128 [28.6%] subjects versus 161 [36.2%] subjects, respectively; $p = 0.018$). Overall, the efficacy results in subgroups, including age, gender and race, showed a similar trend as in the ITT population.

Of the 1023 enrollments for 893 subjects in the RAMPART clinical study, medical records from 1020 enrollments for 890 unique subjects were available and were included in the Medical Records Project database: 446 subjects in the IM midazolam group and 444 subjects in the IV lorazepam group. No association between termination of seizure and medical history was observed for any of the medical history disease subgroups (including renal, respiratory, and hepatic impairment/disease, and history of seizure) of the ITT Population

4.2 Safety Profile

The safety of Midazolam Multi-Use Vials, intended to be administered IM using a proposed dose of 10 mg/2 mL for patients ≥18 years of age, was supported by data derived from: 5 PK and drug-drug interaction studies; a Phase 1 safety study; the Phase 3 RAMPART clinical study in subjects with SE; and the retrospective review, extraction, and analysis of the medical record data from subjects who participated in RAMPART (Medical Records Project Report). The FDA's prior findings of safety of Versed (NDA 018654), and Midazolam Injection, USP (ANDA 075293) as well as data from the published literature were also used to support the safety of Midazolam Multi-Use Vials for SE.

Phase 1 Studies

The Phase 1clinical data supporting the safety of midazolam included 385 healthy subjects ≥18 years of age who received IM midazolam in 6 Phase 1 studies:

- Five studies (Study 11903 conducted under IND 068432 and sponsored by the OTSG-DA; and Studies K643-08-1001, K643- 08-1002, K643-08-1003 and K643-08-1004 conducted under IND 102540 and sponsored by Meridian); and
- A study (Study K643-08-1005) conducted under IND 102540 and sponsored by Meridian, with extended follow-up to 30 days.

The most common treatment-emergent adverse event (TEAE) was somnolence and most TEAEs occurred <48 hours post-dose. Injection site pain was the other most commonly reported TEAE. Overall, injection site pain was considered to be mild. Twenty one out of 385 subjects experienced intermittent and transient mild episodes of decreased oxygen saturation. Seven subjects fulfilled the definition of respiratory depression (any occurrence of a respiratory rate <10 breaths/minute with an sO2 <90%). No one experienced respiratory arrest or required mechanical ventilation, flumazenil therapy, or other life saving measures. There were no AEs leading to discontinuation or deaths. One subject in Study K643-08-1005 had a serious adverse event (SAE) of moderate thrombocytopenia that was considered possibly related to midazolam. Across all Phase 1 studies, IM midazolam appeared to be well-tolerated, with the incidences of AEs being consistent with the known safety profile of the currently marketed midazolam formulations.

RAMPART

There were 1023 enrollments in RAMPART: 893 unique individual subjects, each with an initial enrollment, plus 130 subsequent re-enrollments. The ITT Population consisted of the first (or only) enrollment for each of the 893 unique subjects: 448 subjects in IM midazolam group (62 subjects assigned to receive 5 mg IM midazolam and 386 subjects assigned to receive 10 mg IM midazolam), and 445 subjects in the IV lorazepam group (59 subjects assigned to receive 2 mg IV lorazepam and 386 subjects assigned to receive 4 mg IV lorazepam).

Overall, IM midazolam appeared to be well-tolerated in the management of status epilepticus, as shown from the analysis of AE data in the ITT Population, i.e., the AE data from the first enrollment of the 893 unique subjects into RAMPART. IM midazolam delivered using the auto-injector and IV lorazepam demonstrated similar safety profiles. The frequency of AEs was actually lower in the IM midazolam group (213 [47.5%] subjects) than in the IV lorazepam group (233 [52.4%] subjects). In total, 192 (49.7%) subjects in the 10 mg IM midazolam group and 21 (33.9%) subjects in the 5 mg IM midazolam group, and 209 (54.1%) subjects in the 4 mg IV lorazepam group and 24 (40.7%) subjects in the 2 mg IV lorazepam group had an AE.

A total of 20 subjects died during the study: 11 (2.5%) subjects in the IM midazolam group (10 subjects in the 10 mg IM midazolam group and 1 subject in the 5 mg IM midazolam group), and 9 (2.0%) subjects in the IV lorazepam group (all in the 4 mg IV lorazepam group). Five of the 20 deaths were felt to possibly be related to study drug: 1 subject in the 10 mg IM midazolam group due to cardiac arrest; 2 subjects in the 10 mg IM midazolam group due to coma; 1 subject in the 10 mg IM midazolam group due to respiratory arrest; and 1 subject in the 4 mg IV lorazepam group due to cardiac arrest, cerebral ischemia, and brain death.

The frequency of SAEs was also lower in the IM midazolam group. Overall, 271 (30.3%) subjects had an SAE: 126 (28.1%) subjects in the IM midazolam group and 145 (32.6%) subjects in the IV lorazepam group. The most frequently reported SAEs were:

- Seizure (64 [7.2%] subjects: 29 [6.5%] in the IM midazolam group and 35 [7.9%] in the IV lorazepam group);
- Respiratory depression (39 [4.4%] subjects: 16 [3.6%] in the IM midazolam group and 23 [5.2%] in the IV lorazepam group);
- Upper airway obstruction (34 [3.8%] subjects: 22 [4.9%] in the IM midazolam group and 12 [2.7%] in the IV lorazepam group);
- Respiratory failure (23 [2.6%] subjects: 7 [1.6%] in the IM midazolam group and 16 [3.6%] in the IV lorazepam group).

The safety data from RAMPART suggest a numerically lower incidence of events in the Acute Central Respiratory Depression MMQ-SMQ (60 [13.4%] subjects in the IM midazolam group versus 71 [16.0%] subjects in the IV lorazepam group) and a slightly lower incidence of hypotension (12 [2.7%] subjects in the IM midazolam group and 18 [4.0%] subjects in the IV lorazepam group).

AEs were analyzed by age, gender, and race subgroups. Among the subgroups evaluated, there were no obvious safety trends related to differences in treatment (IM midazolam versus IV lorazepam). The subgroup of subjects >65 years of age had a higher frequency of AEs overall than younger subjects, and specifically they had a higher frequency of events such as respiratory depression, hypotension, coma, upper airway obstruction, post-ictal state, hypokalemia, acute myocardial infarction, and unresponsive to stimuli compared to the other age subgroups. The frequency of hypotension was higher in females compared to males, and the frequencies of respiratory depression, agitation, and upper airway obstruction were lower in females compared to males. White subjects had a higher frequency of respiratory depression compared with Black/African American subjects or subjects of other races.

Medical Records Project

The RAMPART clinical study database did not allow for some analyses typically provided for other Phase 3 studies due to the inherent difficulties of collecting medical history and follow-up subject information in a pre-hospital emergency setting. To provide additional information, a retrospective collection of relevant data was performed from the medical records of subjects who participated in RAMPART, including the collection of safety events, concomitant medication, and medical history data. Overall, the safety information extracted from the medical records of the subjects who participated in the RAMPART clinical study suggests that IM midazolam and IV lorazepam have similar safety profiles. The data collected and analyzed for the Medical Records Project Report did not identify any previously unrecognized safety concerns with the use of IM midazolam for the targeted indication.

Overall, there were 22 deaths identified in the Medical Records Project Report: 13 in the IM midazolam group and 9 in the IV lorazepam group. There were 2 additional deaths that were identified in the Medical Records Project Report in addition to those reported in the RAMPART study. These 2 additional deaths were early discontinuations from the RAMPART clinical study (withdrew consent), with fatal outcomes present in the medical records after the date of consent withdrawal. Of the 22 deaths, 21 were not attributed to study drug and 1 death was assessed as possibly related to study drug.

An assessment of causality of safety events in the Medical Records Project Report could not be performed in the manner usually done in clinical trials because of the absence of clinical investigators to make the judgments required. The alternative approach used was for the Sponsor to review each of the safety events identified and then make a determination of which events might be considered potentially associated the with RAMPART study drugs, lorazepam and midazolam.

The events thought to be potentially associated with the study drugs were: acute respiratory failure, dyspnea, generalized tonic-clonic seizure, mental status changes, nausea, respiratory failure, and vomiting, some of which could have been due to study drug failure. There was no evidence that the use of midazolam had any increased risk of respiratory depression over that of lorazepam.

4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were no reported cases of misuse, abuse, addiction, diversion, or overdose within any of the midazolam clinical studies supporting this application.

5. Other Relevant Information

None

6. Regulatory Issues and Assessment

The Sponsor proposes that Seizalam remain Schedule IV in the CSA, the same as all midazolam-containing products and benzodiazepines generally.

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/

MARTIN S RUSINOWITZ
08/17/2018

SILVIA N CALDERON
08/17/2018

DOMINIC CHIAPPERINO
08/17/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 15, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209566
Product Name and Strength:	Seizalam (midazolam) injection, 5 mg/mL
Applicant/Sponsor Name:	Meridian Medical Technologies Inc.
FDA Received Date:	August 3, 2018
OSE RCM #:	2017-2445-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

Division of Neurology Products (DNP) requested that we review the revised carton labeling, container label and (b) (4) for Seizalam (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling and container label are unacceptable from a medication error perspective. As currently presented, the expiration date format for the carton labeling and container label is not defined. Additionally, the net quantity statement on the carton labeling should be revised to mitigate the risk of confusion regarding the product strength or dose.

3 RECOMMENDATIONS FOR MERIDIAN MEDICAL TECHNOLOGIES INC.

We recommend the following be implemented prior to approval of this NDA 209566:

[a] Whaley, E. Label and Labeling Review for Seizalam NDA 209566. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 3. RCM No.: 2017-2445.

A. Carton labeling
    1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:
        DDMMMYYYY (e.g., 31JAN2013)
        MMMYYYY (e.g., JAN2013)
        YYYY-MMM-DD (e.g., 2013-JAN-31)
        YYYY-MM-DD (e.g., 2013-01-31)
    2. The carton labeling includes the net quantity statement "10 x 10 mL". We are concerned that the statement might be misinterpreted as the product strength or dose. Therefore, we recommend that the net quantity statement is revised to "10 x 10 mL multiple dose vials" and the words "(b) (4)" are removed. Additionally, you may consider revising the statement below the proposed proprietary name and established name from "(b) (4) for intramuscular use only" to read "for intramuscular use only" to decrease clutter and remove redundancy.
B. Container label
    1. See recommendation A.1. and revise accordingly.

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

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/s/

EBONY A WHALEY
08/15/2018

LOLITA G WHITE
08/15/2018

Clinical Inspection Summary

Date	7/11/2018
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Harold Sano, Regulatory Project Manager Steven Dinsmore, M.D., Medical Officer Division of Neurology Products
NDA #	209566
Applicant	Meridian Medical Technologies
Drug	Midazolam multi-use vials for IM injection
NME	No
Proposed Indication	Treatment of status epilepticus in adults
Consultation Request Date	2/7/2018
Summary Goal Date	7/16/2018
Action Goal Date	9/4/2018
PDUFA Date	9/16/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Hemphill and Welch were inspected in support of this NDA. In general, based on the inspections of the two clinical sites, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication although a regulatory violation was noted at Dr. Hemphill's site (primarily due to discrepancies with study drug accountability). The final compliance classification of the inspection of Dr. Hemphill was Voluntary Action Indicated (VAI) and for that of Dr. Welch was No Action Indicated (NAI).

Of note, at both sites, subjects were enrolled multiple times (as permitted by protocol), each time receiving a different subject number. We recommend that the review division ensure that the statistical plan was followed, which stated that only the first enrollment is used in the efficacy analysis.

Audio recordings were reviewed at the clinical sites and were difficult to decipher. Data listings reviewed for Site #5 (Dr. Welch) indicate that the statement of whether a seizure had terminated was clearly verbalized on the audio recording for only 64% of subjects, for the remaining subjects the statement was unclear, absent, or no data was available in the listing. We recommend that the review division consider the amount of missing data in the evaluation of key secondary efficacy measures obtained from these audio recordings.

II. BACKGROUND

Midazolam for intramuscular (IM) injection is being developed by Meridian Medical Technologies, under NDA 209566 (IND 123,121), for the treatment of status epilepticus in adults.

The applicant has submitted one Phase 3 study, RAMPART (the Rapid Anticonvulsant Medication Prior to ARrival Trial), to support the safety and efficacy of midazolam intramuscular injection for the treatment of status epilepticus. The study was designed and conducted by the Neurological Emergencies Treatment Trials network, funded by the National Institute of Neurological Disorders and Stroke (NINDS) and performed under IND 102,254 (Dr. Silbergleit/University of Michigan). (b) (4)

Protocol RAMPART

Title: A double-blind, randomized clinical trial of the efficacy of intramuscular midazolam versus intravenous lorazepam in the prehospital treatment of status epilepticus by paramedics

Subjects: 893 unique subjects (1023 enrollments)

Sites: 17 sites in the United States

Study Initiation and Completion Dates: 6/15/2009 – 4/10/2011

This was a double-blind, double-dummy, randomized study of the efficacy of IM midazolam (by auto-injector) versus IV (intravenous) lorazepam in the pre-hospital treatment of status epilepticus by paramedics. Included were children (minimum estimated weight 13 kg) and adults experiencing status epilepticus in the pre-hospital setting. Subjects were enrolled if they were having convulsive seizures at the time of treatment by paramedics and were reported by reliable witnesses to have had continuous convulsive seizures for longer than 5 minutes or to have had intermittent seizures for >5 minutes without regaining consciousness.

When paramedics arrived on the scene, they performed an initial assessment and stabilized subjects who were in status epilepticus, according to their local EMS (Emergency Medical Services) protocols. Per protocol, all subjects were to receive, in a blinded fashion, either IM midazolam (by auto-injector) followed by IV placebo or IM placebo followed by IV lorazepam.

Subjects were allocated in an approximate 1:1 randomization to either IM midazolam or IV lorazepam. A study box was carried by the EMS crew who were blinded to the identity of active study medication. When the EMS crew determined that the subject was eligible for the study, the study box was opened. This initiated a timer as well as a voice activated recorder. Paramedics treated subjects first with the IM auto-injector and then immediately obtained IV access followed by treatment with the IV syringe. Paramedics were instructed to verbally indicate when IM treatment

was administered, when IV access was obtained, when IV treatment was administered, when any rescue treatments were given, and when seizures were terminated. Each statement was time-stamped by the study box relative to time zero of study box opening. Paramedics also stated whether the subject was observed to have convulsive seizures upon arrival at the emergency department. Rescue therapy was permitted for subjects still experiencing convulsive seizures 10 minutes after the last study drug was administered. If there was a delay in obtaining IV access and the subject stopped having seizures before the IV study drug could be administered, the IV study drug was not given. If the convulsive seizures resumed during EMS transport, rescue therapy was given.

The *primary efficacy measure* was the determination of whether there was termination of convulsive seizure activity upon arrival to the emergency department after an initial dose of study drug without use of rescue medication. Per protocol, determination of termination of convulsive seizure activity upon arrival at the receiving emergency department is made clinically by the attending emergency department (ED) physician treating the subject. If this determination is missing, then the termination of seizure as determined by the paramedic will be used. *Key secondary efficacy measures* included time from EMS arrival to termination of seizure and time from initiation of treatment to termination of seizure; these data were obtained from the voice recordings.

Rationale for Site Selection

The clinical sites were chosen primarily based on high subject enrollment and prior inspectional history.

III. RESULTS

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection Dates	Compliance Classification
Site #16 **J. Claude Hemphill III, M.D.** San Francisco General Hospital ZSFGH, Bldg 1, Room 101 San Francisco, CA 94110	RAMPART Subjects: 113	11-22 May 2018	VAI
Site #5 **Robert Welch, M.D.** Detroit Receiving Hospital Department of Emergency Medicine 4201 St. Antoine, 6G-UHC Detroit, MD 48201	RAMPART Subjects: 178	15-21 May 2018	NAI

Compliance Classifications
NAI = No Action Indicated, no deviation from regulations.
VAI = Voluntary Action Indicated, deviation(s) from regulations.
OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

1. J. Claude Hemphill, M.D.

At this site for Protocol RAMPART, 113 subjects were randomized and 98 subjects completed the study. Fifteen subjects discontinued the study; five of these discontinuations were due to death and are included in the NDA submission. Deaths occurred in the midazolam IM arm (Subjects (b) (6)) and lorazepam IV arm (Subject (b) (6)). The EIR did not include information about the other 10 discontinuations; reasons provided in data listings include "other reason" for 7 subjects and "consent withdrawn/declined for other reason" for 3 subjects.

Subject enrollment and treatment were performed without prior informed consent using the exception from informed consent requirement for emergency research. Informed consent was sought by study staff after the subject had been enrolled in the study, treated with study medication, had arrived at the hospital, and was able to provide informed consent. If informed consent could not be obtained at the hospital, then the subject was contacted at their residence. Not all subjects were consented.

An audit of the study records of 23 out of 113 (20%) subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, personnel training, IRB/sponsor communications, test article accountability, inclusion/exclusion criteria, audio recordings by paramedics, Rampart Medic Forms, concomitant medications, protocol deviations, ED Arrival Form, and primary efficacy endpoint (termination of seizure). Neurological Emergencies Treatment Trials (NETT) performed clinical monitoring for this protocol.

EMS paramedics notified the study team when a subject had been enrolled. Study staff would attempt to interview the attending physician over the phone and in person once the subject had arrived at the ED. Study staff would also interview paramedics and review documentation. Study staff entered the primary efficacy measure, i.e. whether the subject was having a seizure or not upon arrival to ED (as determined by the ED attending physician), on "scratch paper" or directly into the WebDCU (data capture system) ED Arrival Form fields. Paramedics completed RAMPART Medic Forms, which also included seizure termination information as well as administration of rescue medications.

For the primary efficacy measure, the FDA field investigator reviewed available source documents written by study staff regarding the ED attending physician's determination of seizure on arrival at the ED. No data discrepancies were noted for termination of seizure as determined by the ED attending physician. No discrepancies were noted for administration of rescue medications.

The FDA field investigator did identify discrepancies in three of 23 subject records reviewed between seizure termination upon arrival to ED per ED physician (as recorded on the ED Arrival Form) and the audio recording or RAMPART Medic Forms from the paramedics.

- Subject # (b) (6) (IV lorazepam): ED Arrival Form - no seizure termination; RAMPART Medic Form -seizure termination
- Subject # (b) (6) (IV lorazepam): ED Arrival Form - no seizure termination; audio

recording - seizure termination
- Subject # (b) (6) (IM midazolam): ED Arrival Form - seizure termination; RAMPART Medic Fo no seizure termination

The reasons for these discrepancies are not clear. That said, the protocol specifies that the primary efficacy measure is seizure termination as determined by the ED attending physician.

This protocol allowed subjects to be enrolled more than once, though statistical analyses included only the first enrollment. A new subject number was assigned for each subsequent enrollment. At this site, 12 subjects were enrolled more than once (10 subjects enrolled twice, 1 subject enrolled three times, 1 subject enrolled four times). It should be noted that the subject number for the initial enrollment (second column) is not a sequential number compared to subject numbers for subsequent enrollments. The original WebDCU subject numbers were sequential, when those subject numbers were converted to the subject numbers in the NDA submission, they were no longer sequential.

Table 1. Subjects with Multiple Enrollments (RAMPART) for Site #16

Number of Enrollments	Subject Number	
	Initial Enrollment	Subsequent Enrollments
2	(b) (6)	
2		
2		
2		
2		
2		
2		
2		
2		
2		
3		
4		

A Form FDA 483 was issued at the conclusion of the inspection due to discrepancies in the investigational drug disposition records. Dr. Hemphill acknowledged the documentation errors, which occurred early in the trial as new study forms were being created.

Reviewer Comments: The FDA field investigator noted discrepancies in seizure termination as determined by the ED attending physician compared to seizure termination determined by paramedics for three of 23 subject records reviewed. The protocol specifies that seizure termination was to be determined by the ED attending physician and that, if this information was not available, seizure termination as determined by paramedics would be used. The cause for these discrepancies is not clear. The FDA field investigator was unable to review 100% of subject records at this site to determine the extent of these discrepancies. If deemed important, the review division might consider contacting the applicant to obtain more information regarding the reasons for these discrepancies as well as the extent of the discrepancies in the NDA submission.

Twelve subjects were enrolled multiple times at this site. We recommend that the review division ensure that the statistical plan was followed, which stated that only the first enrollment is used in the efficacy analyses.

2. Robert Welch, M.D.

At this site for Protocol RAMPART, 181 subjects were screened, 178 subjects were randomized, and 166 subjects completed the study. Twelve subjects discontinued the study; four of these discontinuations were due to death and are included in the NDA submission. Deaths occurred in the midazolam IM arm (Subjects (b) (6)) and the lorazepam IV arm (Subjects (b) (6)). The EIR did not include information about the other 8 discontinuations; reasons provided in data listings include "other reason" for 4 subjects and "consent withdrawn/declined for other reason" for 4 subjects.

Subject enrollment and treatment were performed without prior informed consent using the exception from informed consent requirement for emergency research. An audit of the study records of 24 out of 178 (13.5%) subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, personnel training, IRB/sponsor communications, test article accountability, inclusion/exclusion criteria, audio recordings by paramedics, adverse event reports, concomitant medications, protocol deviations, ED Arrival Form, Emergency Medical Service run sheets (completed by paramedics), emergency treatment notes, and primary efficacy endpoint (termination of seizure). Neurological Emergencies Treatment Trials (NETT) performed clinical monitoring for this protocol. Monitoring visits occurred approximately every 2 to 5 months during the study.

EMS paramedics notified the study team when a subject had been enrolled. A study team member went to the ED to retrieve the study box and ask the attending physician if the subject was having a seizure when they arrived at the ED. The study coordinator recorded this response (yes/no) on the ED Arrival Form in WebDCU. The ED Arrival Form also included a yes/no field to record whether a rescue dose of benzodiazepine was administered prior to ED arrival.

The field investigator reviewed the emergency treatment notes (dictated by the ED physician) and EMS Run Sheets (completed by the paramedics) and was able to verify termination of seizure data and whether a rescue medication was administered prior to ED arrival. No data discrepancies were noted. The field investigator also listened to several of the audio recordings. The recordings were difficult to understand due to issues with clarity of statements as well as background noise. Adverse events were also reviewed, with no evidence of under-reporting noted.

This protocol allowed subjects to be enrolled more than once, though statistical analyses included only the first enrollment. A new subject number was assigned for each subsequent enrollment. At this site, 18 subjects were enrolled more than once (12 subjects enrolled twice, 5 subjects enrolled three times, and 1 subject enrolled 14 times)

Table 2. Subjects with Multiple Enrollments (RAMPART) for Site #5

Number of Enrollments	Subject Number	
	Initial Enrollment	Subsequent Enrollments
2	(b) (6)	
2		
2		
2		
2		
2		
2		
2		
2		
2		
2		
2		
3		
3		
3		
3		
3		
14		

Reviewer Comments: The primary efficacy measure, termination of seizure upon ED arrival as determined by ED physician, was verified for a random selection of 13% of subjects enrolled at this site. Use of rescue benzodiazepines prior to ED arrival was also verified.

Key secondary efficacy endpoints, obtained from the audio recordings, included time from EMS arrival to termination of seizure and time from initiation of treatment to termination of seizure. The field investigator listened to several audio recordings and had difficulty deciphering the information. Data Listing h1, Primary Efficacy Parameter (located in Module 5.3.5.4 BIMO, Data Listing Data, BIMO RAMPART Item II Data Listing of the original NDA submission), includes data regarding whether there was a statement in the audio recording whether the seizure had terminated. A "yes" indicates that a clear statement was verbalized, and a "no" indicates that the statement was unclear or absent. For this site, the data listing had a response of "yes" for 63.6% of subjects, and a "no" or no entry for 36.4% of subjects. It would appear that there is a significant amount of missing data for endpoints derived from these audio recordings for this site, and perhaps other sites as well. We recommend that the review division consider the amount of missing data in the evaluation of efficacy for any endpoints obtained from these audio recordings.

Eighteen subjects were enrolled multiple times at this site. We recommend that the review division ensure that the statistical plan was followed which stated that only the first enrollment is used in the efficacy analyses.

{See appended electronic signature page}

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/s/

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07/11/2018

PHILLIP D KRONSTEIN
07/11/2018

KASSA AYALEW
07/11/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 3, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 209566
Product Name and Strength:	Seizalam (midazolam) injection, 5 mg/mL
Total Product Strength	50 mg/10 mL
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Meridian Medical Technologies Inc.
Submission Date:	November 16, 2017; February 13, 2018
OSE RCM #:	2017-2445
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Neurology Products (DNP) has requested the Division of Medication Error Prevention and Analysis review the labels and labeling for NDA 209566 for areas of vulnerability that might lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Seizalam (midazolam) is an injection solution intended for the treatment of status epilepticus in adults. The reference listed drug (RLD) is Versed (midazolam) NDA 18654. Our review of the proposed Prescribing Information, container labels, carton labeling, and (b) (4) for Seizalam (midazolam) identified the following areas of needed improvement that might contribute to medication errors:

Prescribing Information

1. Section 2 Dosage and Administration, specifically subsection 2.1 Dose, contains dosing information which can be simplified to decrease confusion.

Container label

2. The “Rx only” statement does not appear on the principal display panel of the container label.

(b) (4)

We provide recommendations regarding these areas below in Section 4.1 and in Section 4.2 in order to help minimize the potential for medication errors to occur with the use of the product.

In addition, during our review of the submission, we note that Seizalam is intended for intramuscular administration only. We also note there are currently marketed midazolam injection solution products that are indicated for both intramuscular and intravenous administration with the same formulation. As such, we assessed the risk and clinical harm associated with incorrect route of administration medication errors with Seizalam (e.g. if Seizalam is unintentionally administered intravenously due to users being familiar with administering midazolam injection intravenously). In discussion with the medical officer for this product, we learned there are no clinical concerns should the product be given intramuscularly or intravenously. Therefore, we are not concerned with incorrect route of administration errors with Seizalam. We also note the carton labeling and container label clearly state the route the administration is intramuscular.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed Prescribing Information, container label, and (b) (4) where information should be revised or clarified to help ensure safe use of the product. We provide recommendations below in Sections 4.1 and 4.2 to address our concerns. We advise these recommendations be implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Prescribing Information
    a. The dosing information in Section 2 Dosage and Administration lacks clarity and may lead to confusion. Specifically, the instructions in subsection 2.1 Dose contains the statement "(b) (4) (b) (4)]". This statement can be revised to better mitigate risk of confusion. As such, we recommend the sentence is revised to state "(b) (4) (b) (4).

4.2 RECOMMENDATIONS FOR MERIDIAN MEDICAL TECHNOLOGIES INC.

We recommend the following be implemented prior to approval of NDA 209566:

1. Container label
    a. The "Rx only" statement does not appear on the principal display panel (PDP) of the container label as required by Section 503(b)(4)(A) of the Federal Food, Drug, and Cosmetic Act. Relocate the "Rx only" statement so that it appears on the principal display panel.[a] Ensure the "Rx only" statement appears less prominent than other important information (e.g. proprietary name, established name, strength, route of administration) on the PDP. Additionally, consider removal of the (b) (4)" statement to allow space for the "Rx only" statement.
2. (b) (4)

[a] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Seizalam (midazolam) that Meridian Medical Technologies Inc. submitted on November 16, 2017.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Seizalam (midazolam)</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>midazolam</td></tr>
<tr><td>Indication</td><td>the treatment of status epilepticus in adults</td></tr>
<tr><td>Route of Administration</td><td>intramuscular</td></tr>
<tr><td>Dosage Form</td><td>Injection solution</td></tr>
<tr><td>Strength</td><td>5 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td>Adult patients ≥18 years of age: 10 mg administered intramuscularly [2 mL of undiluted Seizalam]</td></tr>
<tr><td>How Supplied</td><td>Each Seizalam (midazolam injection) Multi-Use vial contains 50 mg midazolam in 10 mL sterile solution, equivalent to 5 mg midazolam per mL and is supplied in the following packaging configuration:
<table>
<tr><th>NDC Number</th><th>Container Description</th><th>Fill Volume</th><th>Total Midazolam (per Vial)</th><th>Unit</th></tr>
<tr><td>11704-650-10</td><td>Fliptop Vial</td><td>10 mL</td><td>50 mg</td><td>10 Vials/ Carton</td></tr>
<tr><td>11704-650-01</td><td>Fliptop Vial</td><td>10 mL</td><td>50 mg</td><td>1 Vial</td></tr>
</table></td></tr>
<tr><td>Storage</td><td>Store at 20 °C to 25 °C (68°F to 77°F); excursions permitted between 15 °C and 30 °C [See USP Controlled Room Temperature].</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 15, 2017, we searched DMEPA's previous reviews using the terms, midazolam and IND 123121. Our search did not identify any previous relevant reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Seizalam (midazolam) labels and labeling submitted by Meridian Medical Technologies Inc. on November 16, 2017 and February 13, 2018.

- Container label
- Carton labeling
- (b) (4)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

- Container label

(b) (4)

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

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

EBONY A WHALEY
04/03/2018

LOLITA G WHITE
04/03/2018