CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review

Date	September 13, 2018
From	Philip H. Sheridan, M.D. Nicholas Kozauer, M.D. Eric Bastings, M.D.
Subject	Summary Review
NDA/BLA # and Supplement#	209566
Applicant	Meridian Medical Technologies, Inc.
Date of Submission	November 16, 2017
PDUFA Goal Date	September 16, 2018
Proprietary Name	Seizalam
Established or Proper Name	Midazolam injection
Dosage Form(s)	Multi-use vial for intramuscular injection
Applicant Proposed Indication(s)/Population(s)	Treatment of status epilepticus in adults
Applicant Proposed Dosing Regimen(s)	10 mg midazolam administered by intramuscular injection
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of status epilepticus in adults
Recommended Dosing Regimen(s) (if applicable)	10 mg midazolam administered by intramuscular injection

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

This 505(b)(2) application provides data intended to support the safety and effectiveness of intramuscular (IM) midazolam (Seizalam) for the treatment of status epilepticus (SE) in adults. Midazolam is a benzodiazepine approved for in-hospital sedation and induction of anesthesia in adults and children.

SE is a medical emergency exemplified by continuous tonic-clonic seizure activity, or a series of seizures with no recovery between them, lasting 5 minutes or longer. The incidence of SE varies from 10 to 61 per 100,000 population each year. The frequency of SE is higher in children and the geriatric population, and the overall SE-related mortality is approximately 20%. SE can result from multiple causes, including head injury, febrile seizures, stroke, brain infections, sleep deprivation, withdrawal from alcohol and drugs of abuse, or pre-existing conditions, such as brain tumor, congenital malformations, or Alzheimer's disease.

The RAMPART study (the Rapid Anticonvulsant Medication Prior to ARrival Trial) of the prehospital treatment of SE is the basis for the conclusion of effectiveness. This study enrolled 1023 patients, of whom 85 had 130 repeat enrollments. There were 893 patients in the population used for the primary efficacy analysis (i.e., patients with a first enrollment). There were 448 patients assigned to IM midazolam treatment and 445 assigned to IV lorazepam treatment. A successful outcome was defined as the absence of seizure activity on arrival to the emergency department (ED), as defined by the ED physician, without the use of rescue medication. In the IM midazolam treatment arm, there were 329 (73.4%) patients with a successful outcome, compared to 282 (63.4%) patients in the IV lorazepam treatment arm. There was a statistically significant difference (P=0.002) between groups tested by Fisher's exact test in this superiority analysis.

There is extensive safety experience available from the IV and IM midazolam formulations currently approved for in-hospital sedation and induction of anesthesia. The most common adverse reaction observed in previous clinical trials of midazolam for sedation and anesthetic induction was decreased tidal volume and/or a decrease in respiratory rate; this adverse reaction is manageable when midazolam is administered by trained personnel equipped to intervene if respiratory depression occurs. The extensive experience with other benzodiazepines (IV diazepam and IV lorazepam) which are approved for the treatment of SE provide additional context for the understanding of the efficacy and safety of midazolam for the treatment of SE.

The collection of safety data from the RAMPART trial was limited given the lack of baseline assessment of the subjects prior to enrollment, the lack of a placebo control, the brief duration of the treatment period (less than one hour) following the single dose administered, and the

ambulance setting (which precluded systematic collection of vital signs, laboratory data, or electrocardiographic findings). Respiratory depression was seen in both the midazolam and active control (lorazepam) arms of the RAMPART study, but respiratory depression is a known complication of SE; it is reassuring that less ventilatory compromise was observed in healthy volunteers (evaluated in an early-phase study after a dose of 20 mg IM which is twice the proposed dose of IM midazolam for SE). In order to enhance the limited safety data from the RAMPART trial, a retrospective chart study (Medical Records Project [MRP]) was conducted to collect supplementary safety data from the emergency department charts of patients after they completed the RAMPART study and from the hospital charts of the subset of these patients who required hospitalization. The RAMPART study and MRP study did not reveal any unexpected safety signals.

Overall, the benefit-risk assessment for IM midazolam favors the benefit of the rapid onset and reliable delivery of efficacy for the treatment of SE in adults without identifying any new safety signals. As noted, IM midazolam should be administered by trained medical professionals equipped to intervene if respiratory depression occurs.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Status epilepticus (SE) is a life-threatening neurologic emergency where rapid treatment may avoid neurologic injury and medical complications. SE usually occurs without warning and is therefore an event where patients are generally not near a critical care setting.	SE is a serious emergency requiring rapid treatment to prevent neurological injury and death.
Current Treatment Options	Currently approved therapies for early SE are intravenous (IV) diazepam and IV lorazepam. Neither of these drugs is well suited for IM delivery because of their delayed bioavailability. Diazepam T_{max} following IM delivery is 1.47 hours, while lorazepam reaches peak concentration approximately 3 hours after IM administration. In addition, the injectable formulation of lorazepam requires refrigeration, making it difficult to stock on emergency response vehicles. Delay reaching therapeutic concentration in the setting of SE is a serious limitation.	There is a need for a treatment for SE that can be given rapidly by first responders prior to the patient being transported to an emergency department (ED). A delay in the treatment of SE increases the risk that the SE may become refractory to therapy and also increases the risk of permanent brain damage or death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The effectiveness of IM midazolam for the treatment of SE in adults was established in a multicenter, randomized, double-blind (double-dummy), active-control trial comparing IM midazolam administered via an autoinjector to IV lorazepam. Patients with continuing convulsive seizure activity, defined as continuous or repeated convulsive activity for more than 5 minutes, were eligible for enrollment. The intent-to-treat (ITT) population consisted of 893 patients who were randomized to receive either IM midazolam (N=448) or IV lorazepam (N=445). Following randomization, each adult patient first received 10 mg IM midazolam or IM placebo, followed by the 4 mg IV lorazepam or IV placebo. Study treatments were administered by a healthcare professional (e.g., paramedic) prior to arrival at a hospital. The primary efficacy endpoint was the termination of convulsive seizure activity (without the need for rescue medication) prior to arrival at the ED as determined by the ED attending physician. A statistically significantly higher percentage of midazolam-treated patients met the primary efficacy endpoint (73.4% versus 63.4%; p=0.002).	IM midazolam was shown to be superior to IV lorazepam for the treatment of SE.
Risk and Risk Management	There is extensive experience in the use of midazolam for anesthetic and in-hospital sedation applications. The RAMPART study did not reveal any unexpected safety signals. Respiratory depression was observed but is also a known complication of SE and more limited ventilatory compromise was seen in healthy volunteers at twice the proposed dose of IM midazolam for SE.	Overall, the risks of midazolam are well known. The findings with the current product are consistent with those known risks and support the approval of IM midazolam for the treatment of SE in adults. IM midazolam should be administered by trained medical professionals equipped to intervene if respiratory depression occurs. The risks of treatment with IM midazolam can

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		be minimized by having similar Warnings and Precautions for the IM midazolam product labeling for the treatment of SE in adults as those in the labeling for midazolam formulations currently approved for other indications.

2. Background

This application provides data intended to support the safety and effectiveness of intramuscular (IM) midazolam for the treatment of status epilepticus (SE) in adults.

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 IM dosage formulations 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.

Benzodiazepine drugs are thought to be effective for the treatment of seizures based on their ability to enhance gamma-aminobutyric acid (GABA)-mediated inhibition as GABA is the principal inhibitory neurotransmitter in the cerebral cortex.

The applicant is seeking the approval of midazolam multi-use vials for the treatment of SE in patients 18 years of age or older under the 505(b)(2) pathway relying on information from Versed Injection (NDA 018654), which has been discontinued, as the Listed Drug (LD); and Midazolam Injection, United States Pharmacopeia (USP) vials (ANDA 075293) as a Reference Standard. The applicant suggests that the proposed to-be-marketed product, manufactured by Hospira, is identical to the ANDA 075293 product (Midazolam Injection, 50 mg/10 mL), which is qualitatively and quantitatively the same as Versed Injection.

This application also provides new efficacy and safety data from a randomized, double-blind, active-control trial (the RAMPART trial, discussed in Sections 7 and 8 of this summary memo).

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson. Dr. Wilson's review lists the entire OPQ team that was involved with the review of this application. Refer to the OPQ review for details of the product quality assessment.

See Section 5 of this memo for an integrated discussion of the OPQ findings regarding the comparability of the proposed to-be-marketed formulation of midazolam and the formulation used in the clinical efficacy trial submitted with the application.

Stability and release testing were found to be acceptable. The specified impurity limits were found to be acceptable based on the qualification studies. The microbial quality of the active pharmaceutical ingredient (API) and drug product were found to be adequate. There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

OPQ recommends approval.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review was written by Drs. Edward Fisher and Lois Freed (the supervisory reviewer) and recommends approval of this application.

Dr. Fisher's review notes that this 505(b)(2) application references the nonclinical studies for the listed drug (Versed Injection; NDA 018654) and the Reference Standard (Midazolam Injection; ANDA 075293) and that the nonclinical information contained in those applications provides adequate nonclinical support for the approval of the requested clinical indication (the treatment of status epilepticus in patients age 18 years of age and older).

Dr. Fisher's review also discusses additional animal efficacy studies conducted by the applicant. In her supervisory review, Dr. Freed discusses the shortcomings of the data from these additional animal studies, but notes that there are no nonclinical obstacles to approval for the requested clinical indication.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was written by Drs. Dawei Li and Angela Men (the supervisory reviewer). The final signatory for the OCP review was Dr. Mehul Mehta. OCP recommends approval of this application.

This application proposes to rely on information contained in the applications for the listed drug (Versed Injection; NDA 018654) and the Reference Standard (Midazolam Injection; ANDA 075293). Additionally, the controlled clinical efficacy study (RAMPART) that was submitted with this application used a formulation of midazolam administered via an IM autoinjector. However, the proposed to-

be-marketed formulation is a manual IM injection using multi-use vials. The primary focus of the OCP review was on the following major considerations:

- An evaluation of the adequacy of the bridging between the to-be-marketed formulation of IM midazolam and the midazolam autoinjector used in the RAMPART trial.
- An evaluation of the adequacy of the bridging between the to-be-marketed formulation of IM midazolam and the reference products (outlined above).

The OCP review notes that the acceptability of the comparison between the proposed to-be-marketed product and the autoinjector primarily relies on the conclusion from the OPQ review team that the slight differences in these formulations [including benzyl alcohol content (10 mg/mL versus 10.45 mg/mL in the autoinjector and manual injection, respectively) and target solution pH (3.0 versus 3.3 in the autoinjector and manual injection, respectively)] are not expected to alter the pharmacokinetic (PK) properties of midazolam significantly. The OCP/OPQ reviews conclude that these findings support the granting of a waiver from the need to conduct an in vivo bioavailability study for the to-be-marketed product and the IM autoinjector based on the criteria outlined in 21 CFR 320.22(b)(1)(i).

The OCP review also evaluated cross-study comparisons of midazolam exposures between an open-label Phase 1 pharmacokinetic (PK) study designed to evaluate the safety and dose-linearity of the midazolam autoinjector (Study 11903) and studies obtained from the public domain (the [United States Pharmacopeia] USP for Midazolam Injection and 4 publications) using a manual midazolam IM injection. This analysis demonstrated that dose-normalized midazolam exposures (C_{max} and AUC) were comparable between the IM midazolam autoinjector and the IM midazolam manual injection (including the USP label and the published literature). Additional statistical analyses also demonstrated similar midazolam bioavailability for midazolam when administered via the IM autoinjector and the IM midazolam manual injection.

The OCP also notes that Study 11903 demonstrated that midazolam exhibits dose proportionality after an IM injection using an autoinjector at dosages ranging from 0.10-0.49 mg/kg (or fixed total amount of 5-30 mg).

The OCP review concludes that the application has successfully established the comparability of the proposed to-be-marketed IM product for manual injection to both the autoinjector used in the clinical efficacy trial and the reference products.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Steven Dinsmore was the clinical reviewer for this application. Dr. Jinnan Liu was the biometrics reviewer, and Dr. Kun Jin was the biometrics Team Lead.

Efficacy data in support of this application come from the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study. This multi-center, randomized, double-blind (double-dummy), active-controlled trial was originally designed as a research study (with funding from the National Institute of Health and partial funding from the Department of Defense). It was initially intended to establish the non-inferiority of IM midazolam to IV lorazepam when used in the acute treatment of SE prior to hospital arrival. However, before the initiation of the trial, FDA had indicated to the RAMPART study investigators that efficacy of midazolam should be established based on a superiority analysis, as there are insufficient data to allow for the appropriate determination of a non-inferiority margin (see the clinical review by Dr. Dinsmore for a detailed regulatory history). Therefore, the statistical analysis plan was amended to prespecify a superiority analysis the primary efficacy analysis. IV lorazepam was selected as the active comparator for the trial, based on its indication for the treatment of SE, and on the fact that it is generally accepted as the standard of care in clinical practice.

SE was defined using established International League Against Epilepsy (ILAE) criteria: continuous tonic-clonic seizure activity, or a series of seizures with no recovery between them, lasting 5 minutes or longer. Patients who met this diagnosis after the arrival of paramedics and who had an estimated weight of 13 kg or greater were eligible for enrollment. There were 1023 enrollments in the RAMPART study: 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 and 445 subjects in the IV lorazepam group. Following randomization, each patient received study treatments administered by a healthcare professional (e.g., paramedic) prior to arrival at a hospital. The weight of each pediatric patient was estimated using a study-designed length-measuring tape calibrated for estimated weights. According to the double-dummy design, adult patients (defined in the protocol as 17 years of age and older) and pediatric patients with estimated weights greater than or equal to 40 kg received 10 mg IM midazolam followed by IV placebo or received IM placebo followed by 4 mg IV lorazepam. Pediatric patients with estimated weights

from 13 kg to less than 40 kg received 5 mg IM midazolam followed by IV placebo or received IM placebo followed by 2 mg IV lorazepam.

The primary efficacy endpoint was the termination of convulsive seizure activity (without the need for rescue medication) prior to arrival at the emergency department (ED) as determined by the ED attending physician without the need for rescue medication. A statistically significantly higher percentage of midazolam-treated patients met the primary efficacy endpoint, as shown in Table 1.

Table 1: Primary Efficacy Analysis Results: Seizure Termination (Without Rescue Medication)

	IM Midazolam (n=448)	**IV Lorazepam (n= 445)**
Treatment success (%)	73.4	63.4
p-value [a]	0.002	

[a] Fisher's exact test

The applicant had also proposed to analyze a number of secondary endpoints focused on the rapidity of the drug effect as observed by the paramedics. These analyses planned to rely on audio recordings of the paramedics' voiced observations concerning the patient's seizure activity recorded en route to the ED. However, there were ultimately many quality issues with these audio recordings, with a high percentage of the data either being entirely missing or of unacceptable audio quality. Therefore, the analyses of these secondary endpoints are uninterpretable. The analysis of the primary efficacy endpoint only relied on the ED physician determination of seizure activity on arrival at the ED, and therefore was not dependent on these en route audio recordings.

The median age of the subjects was approximately 46 years, with 12.6% of patients in the pediatric age group (less than 17 years of age). The percentage of females was 44% in the drug group and 47% in the active control group. The majority of patients were either Black/African American (51% and 50%, for drug and active control respectively) or Caucasian (37 and 41%, respectively). Demographic factors were reasonably balanced between the treatment arms.

Analyses for the treatment effect of IM Midazolam versus IV Lorazepam on seizure termination rate across subgroups such as age, gender, and race, were performed. The trends in treatment success were similar across these subgroups.

By design, the assignment of subjects to dose tier (high or low) was based on body weight estimates. The majority of the subjects were estimated as being 40 kg or greater in weight and thus received the high dose. The efficacy in the high-dose subgroup was consistent with the overall efficacy outcome. The sample size in the low-dose subgroup of subjects estimated as being between 13 kg to less than 40 kg in weight (all from the pediatric population) is small, and the result can only be viewed as descriptive. The number of patients in the pediatric age group (113 of the 893 patients in the ITT population being less than 17 years of age) was not sufficient to allow a conclusion of efficacy for pediatric patients.

Efficacy Conclusions

The applicant has provided robustly positive efficacy results from a single randomized, double-blind, active-controlled trial conducted in patients with SE (the RAMPART study) that establish the efficacy of IM midazolam for the treatment of SE in adults. These results have a number of characteristics, cited by FDA's 1998 Guidance "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*," that can provide evidence of effectiveness from a single study. The results of the primary efficacy analysis were highly statistically significant and robust to appropriate sensitivity analyses. These results are even more convincing in consideration of the fact that IM midazolam was found to be superior to an active comparator (IV lorazepam) with established effectiveness for SE. Additionally, the considerable prior clinical experience with other related benzodiazepines already approved for the treatment of SE (IV diazepam and IV lorazepam) supports the mechanistic plausibility of the observed effect.

Importantly, IM midazolam addresses an unmet medical need in that therapeutic levels are achieved rapidly after IM injection and thus can rapidly and effectively be given by paramedics to patients in SE prior to transportation to the ED as shown in the RAMPART trial. Since the responsiveness of SE to treatment and the prevention of irreversible brain damage may depend on effective treatment being initiated as soon as possible, the approval of IM midazolam will be a significant contribution to the therapy of SE.

8. Safety

Dr. Steven Dinsmore conducted the clinical safety review of this application.

The safety of IM midazolam 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 the 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 IM midazolam.

Phase 1 Studies

The Phase 1 clinical data supporting the safety of IM midazolam included 385 healthy subjects 18 years-of-age or older from 6 Phase 1 studies, including:

- Five PK and drug-drug interaction studies (Study 11903 conducted under IND 068432 and sponsored by the Office of the Surgeon General, Department of the Army; and Studies K643-08-1001, K643-08-1002, K643-08-1003, and K643-08-1004, conducted under IND 102540 and sponsored by Meridian).

- A safety study (Study K643-08-1005 conducted under IND 102540 and sponsored by Meridian), with extended follow-up to 30 days. This study is of interest since the volunteers received two autoinjector doses of 10 mg IM midazolam given less than 1 minute apart. This total dose of 20 mg IM is twice the dose shown to be efficacious in the RAMPART study.

The most common treatment-emergent adverse events (TEAE) were somnolence and injection site pain (mostly mild). Most TEAEs occurred less than 48 hours post-dose.

In the safety study giving a high dose of 20 mg IM midazolam as two injections of 10 mg within 1 minute of each other to normal volunteers (Study K643-08-1005), there were 14 (5.6%) unique subjects with adverse events (AEs) of "oxygen saturation decreased" and "respiratory depression." None of these AEs were serious. This is reassuring since the 20 mg IM midazolam dose is twice the 10 mg dose given to the high-dose patients in the RAMPART trial and recommended for the proposed indication. This finding suggests that the respiratory depression occurring in the RAMPART trial (discussed below) is plausibly attributable to the SE rather than to IM midazolam.

There were no AEs in the Phase 1 studies leading to discontinuation or deaths.

Across all Phase 1 studies, IM midazolam was generally well-tolerated, with the incidences of AEs being consistent with the known safety profile of the currently marketed midazolam formulations.

RAMPART Study

Overall, IM midazolam appeared to be well-tolerated, 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 and IV lorazepam (the active control) demonstrated similar safety profiles.

There were a total of 22 deaths in the RAMPART study itself and the follow-up Medical Records Project [MRP] (discussed below): 13 in the IM midazolam treatment group and 9 in the IV lorazepam treatment group. Dr Dinsmore has reviewed these death narratives and concluded that these deaths were not related to either study drug, but were attributable to the patients' pre-existing conditions and/or the SE itself. Dr. Dinsmore further notes that the published literature reports that the frequency of fatal outcome during the severe physiologic challenge of status epilepticus is approximately 20%. Thus, the overall death rate in the IM midazolam arm of 2.5% is low in comparison to the reported fatal outcome of SE in the medical literature and does not constitute a safety signal for IM midazolam treatment.

The frequency of serious adverse events (SAEs) was also lower in the IM midazolam group than in the active control group (IV lorazepam). 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 active control). 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); these seizures should more properly be considered a part of the presentation of SE rather than an adverse effect attributable to either study drug.
- 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).

These findings indicate that the incidence of SAEs observed with IM midazolam treatment is comparable to the current standard of care (IV lorazepam) that was used as the active control. It is likely that a significant portion of the SAEs is attributable to the SE itself, given that the normal volunteer study previously described (Study K643-08-1005) administered twice the dose of IM midazolam given in the RAMPART study and had no SAEs.

The following table summarizes the most common adverse reactions observed in the RAMPART trial:

Table 2: Adverse Reactions in 2% or More of IM Midazolam-Treated Patients and More Frequent than in IV Lorazepam-Treated Patients in Out of Hospital Treatment of Status Epilepticus

Adverse Reaction	IM Midazolam N=448 (%)	IV Lorazepam N=445 (%)
Upper airway obstruction	5	3
Agitation	4	3
Pyrexia	4	3
Mental status changes	3	2
Postictal state	3	2
Acute renal failure	2	1

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 greater than 65 years of age had a higher frequency of AEs overall than younger subjects. This finding most likely reflects a higher burden of pre-existing serious medical conditions in the elderly population and an age-related increased vulnerability to the physiologic stress of SE. Analysis of AE rates by gender and race did not reveal any significant differences. Given that most of these AEs appear related to SE rather than to the study drugs, no dosing adjustments by age, gender, or race are required.

The safety data from the RAMPART trial indicate that IM midazolam has a safety profile that is consistent with the well-established safety profile of midazolam. These data also suggest that IM midazolam may have a slightly reduced risk of respiratory depression when compared to IV lorazepam (the active control for the RAMPART study and the current standard of care for SE), although the limitations of the data preclude any firm conclusions from being made in this respect.

Medical Records Project (MRP)

The safety database from the RAMPART trial was limited given the lack of baseline assessment of the subjects prior to enrollment, the use of an active control rather than of a placebo control due to ethical constraints, the brief duration of the treatment period (less

than one hour) following the single dose administered, and the ambulance setting (which precluded systematic collection of vital signs, laboratory data, or electrocardiographic findings). In an attempt to address these limitations of the RAMPART safety database, the applicant conducted a retrospective collection of relevant data from the medical records of subjects who participated in RAMPART, including the collection of safety events, concomitant medication, clinical laboratory values determined, EKG findings, and previous medical history information (the Medical Records Project [MRP]). These data were all collected after completion of the RAMPART trial (which ended when the patients arrived at the ED) as part of the patients' routine medical care in the ED or (when the patients were hospitalized) in the hospital.

Overall, the safety information extracted from the medical records of these subjects suggests that IM midazolam and IV lorazepam have similar safety profiles. The MRP did not identify any previously unrecognized safety concerns with the use of IM midazolam for the targeted indication.

Safety Conclusions

The safety data provided in this application are consistent with the known safety profile of midazolam. These data support the approval of IM midazolam for the treatment of SE in adults when administered by a medical professional equipped to intervene if respiratory depression occurs.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of IM midazolam is acceptable for the proposed indication.

10. Pediatrics

Because IM midazolam has orphan designation for SE, the Pediatric Research Equity Act (PREA) is not triggered.

11. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP) issues were identified in Dr. Dinsmore's clinical review.

Dr. Dinsmore concludes in his clinical review that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

The Office of Scientific Investigation (OSI) inspected two clinical sites of the RAMPART trial, and no issues impacting trial integrity were identified. Concerns regarding the quality of the audio recordings of the paramedics that were intended to support the analysis of several secondary efficacy endpoints has already been discussed in Section 7 of this memo. These findings do not impact the approvability of the application.

The Controlled Substance Staff (CSS) review concluded that the abuse potential of IM midazolam is well understood and that the application should be approved. IM midazolam should remain a Schedule IV controlled substance under the Controlled Substance Act.

12. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations

No postmarketing requirements (PMRs) are necessary.

14. Recommended Comments to the Applicant

See action letter.

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

/s/

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