CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216359Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	216359
Link to EDR	\\CDSESUB1\evsprod\NDA216359\0001
Submission Date	3/28/2022
Submission Type	Original NDA 505(b)(2)
Product Name	Midazolam Injection
Dosage Form and Strength	Midazolam autoinjector (10 mg/0.7 mL)
Route of Administration	Intramuscular injection
Proposed Indication	Treatment of status epilepticus in adults
Applicant	Rafa Laboratories, Ltd
Associated IND	IND 147559
OCP Primary Reviewer	Dawei Li, Ph.D.
OCP Team Leader	Gopichand Gottipati, Ph.D.

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1. Executive Summary

The applicant submitted the current original New Drug Application, NDA 216359, seeking approval for Midazolam Injection, a drug-device combination product for the treatment of status epilepticus in adults. Midazolam injection is a single-dose (single-strength 10 mg/0.7 mL), emergency-use autoinjector intended for (b) (4) via intramuscular route. The applicant filed this application under the 505(b)(2) pathway and used Seizalam® (midazolam injection) as the listed drug (LD)[1] (NDA 209566), originally approved in 2018. Midazolam Injection and Seizalam® share the same active ingredient, dosage form, route of administration, recommended dose, and indication; but differ in concentrations of the active and inactive ingredients. The current applicant's Midazolam Injection product is more concentrated with 14.3 mg/ml (10 mg/0.7 mL) midazolam compared with 5 mg/mL (50 mg/10 mL) in Seizalam.

The clinical development of Midazolam Single-dose Autoinjector includes a Phase 1 pharmacokinetic (PK)/relative bioavailability study: Study RLM-559-01 is a pivotal bioequivalence study to establish the scientific bridge between Midazolam Injection via autoinjector and Seizalam. In this comparative PK study, the exposure metrics $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} met pre-specified bioequivalence criteria between Midazolam Single-dose Autoinjector and Seizalam®. The reviewer conducted independent analysis and confirmed that the exposures, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}, from the pivotal bioequivalence study were within the pre-specified acceptance limits of 80.00% to 125.00%. Overall, the PK study conducted by the applicant provided an adequate scientific bridge for this application to rely on the relevant labeling information of LD.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study RLM-559-01. OSIS arranged a clinical inspection of study RLM-559-01. After reviewing the study report and the findings in the establishment inspection report, OSIS concluded that the audited study data was reliable (please refer to OSIS review in DARRTS dated 06-23-22 for additional details).

2. Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval of Midazolam autoinjector for the treatment of status epilepticus in adults. This recommendation is based on an adequate PK bridge demonstrated between Midazolam Single-dose Autoinjector and the LD, Seizalam®.

[1] USPI of Seizalam® injection: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209566s001lbl.pdf

3. Background

The applicant is seeking approval of Midazolam Single-dose Autoinjector via the 505(b)(2) pathway using Seizalam® injection as the LD.

On March 16, 2020, the FDA provided Written Responses to the Type B PIND meeting with the applicant's questions on the clinical development program. In the Type B written responses, the FDA provided comments on the eligibility for a waiver of in vivo bioavailability and bioequivalence studies. On May 19, 2020, the Type B Pre-NDA meeting minutes confirmed that if bioequivalence can be established between midazolam autoinjector and Seizalam®, results from the phase 1 study RLM-559-01 could support reliance upon the Agency's previous finding of the safety and effectiveness of Seizalam®.

The current review includes verification the study results, statistical and analytical methods of the pivotal relative BA/BE study.

4. Summary of Pivotal Relative BA/BE Study

Study RLM-559-01

Title: Phase 1, Open-Label, Comparison Study to Evaluate the Safety and PK of a Single Intramuscular Administration of 10 mg Midazolam Using an Auto-Injector vs Marketed Midazolam Vials in Healthy Adults

Primary Objectives: To assess the relative bioavailability between test product (A) and reference product (B) and to monitor the safety of test product (A) and reference product (B) in healthy adult human subjects.

Methodology:

This was a Phase 1, open-label, crossover, comparison study to evaluate the safety and pharmacokinetic (PK) characteristics of a single intramuscular (IM) dose of 10 mg Midazolam Auto-Injector compared with marketed reference drug Seizalam® Midazolam Vial injection.

Number of Subjects (Planned and Analyzed):

40 subjects were enrolled into the study. Data of 36 subjects for pharmacokinetic analysis and 36 subjects for statistical analysis were used.

Note: 4 subjects were excluded from the PK population. Subject (b) (6) had no quantifiable midazolam or 1'-hydroxymidazolam concentrations after receiving midazolam via Auto-Injector. Subjects (b) (6) and (b) (6) did not receive the Marketed Vials treatment. Subject (b) (6) did not receive the Auto-Injector treatment.

Treatments:

Midazolam Injection (10 mg) was administered in one single dose using either Rafa's Auto Injector (n = 20) or the marketed (Seizalam) Midazolam Vial with a 22-gauge, ¾ inch

needle (n = 20) into the anterolateral thigh muscle in Period 1. Subjects who were administered midazolam Auto-Injector in Period 1 received the marketed Midazolam Vial in Period 2, and subjects who received the marketed Midazolam Vial in Period 1 received Midazolam Auto-Injector in Period 2.

Treatment A: (Test) Rafa Laboratories, Ltd.'s Midazolam Injection, 10 mg is a sterile solution for intramuscular injection. The dose administered was 10 mg in 0.7 ml. All Midazolam Injection, 10 mg administrations were from Batch number 701597.

Treatment B: (Reference) Seizalam Midazolam vial is supplied as a 50 mg/10 mL sterile solution. The dose administered was 10 mg in 2 mL. All Seizalam Midazolam vial administrations were from Lot #90-283-DK.

There was a washout period of 14 days between each drug administration.

PK Sampling: Blood samples were collected at pre-dose (1-2 hours) and at 3±1, 6±1, 10±1, 15±1, 20±2, 30±2, 45±2 minutes post-dose, and 1±5, 2±5, 3±5, 4±5, 6±5, 8±5, 12±10, 24±10, and 30 hours ±10 minutes post-dose.

Criteria for PK Comparison:

The following PK parameters were calculated for Midazolam using standard non-compartmental methods: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, K_e, $t_{1/2,}$ CL and Vz. The following standards for relative bioavailability were applied for Midazolam: 90% confidence interval of the geometric least square mean ratio of C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of the test and reference products for Midazolam are completely contained in the range of 80.00 to 125.00 % (limits inclusive) for ln-transformed data.

Results:

Overall, 39 of 40 enrolled subjects received Midazolam using the auto-injector and 38 of 40 enrolled subjects received Midazolam using the marketed vials.

Data of 36 subjects for pharmacokinetic analysis and statistical analysis were used. Plots of the Mean ±SD plasma levels for Midazolam are presented for both Un-transformed and Ln-transformed data in Figure 1. The descriptive statistics for PK parameters of each treatment are shown in Table 1. Table 2 summarized the ratio of PK parameters and confidence intervals (C.I.).

Reviewer's Comments:

Plasma samples (available for PK analysis) of the excluded subject (subject (b) (6), and (b) (6)) were analyzed for Midazolam, and the PK profile of Midazolam of these subjects ((b) (6) received the Marketed Vials treatment; (b) (6) and (b) (6) received midazolam via Auto-Injector) were similar to that of other subjects received the same treatment. Inclusion of the PK data of these subjects did not affect the overall PK results of Midazolam.

Figure 1. Mean ±SD Concentration versus Nominal Time Profiles for Midazolam after a Single Intramuscular Injection of 10 mg Midazolam Administered via Rafa's Midazolam Auto-Injector or 10 mg Seizalam Marketed Vial Administered via Syringe (Linear and Semi-logarithmic) (N = 36)

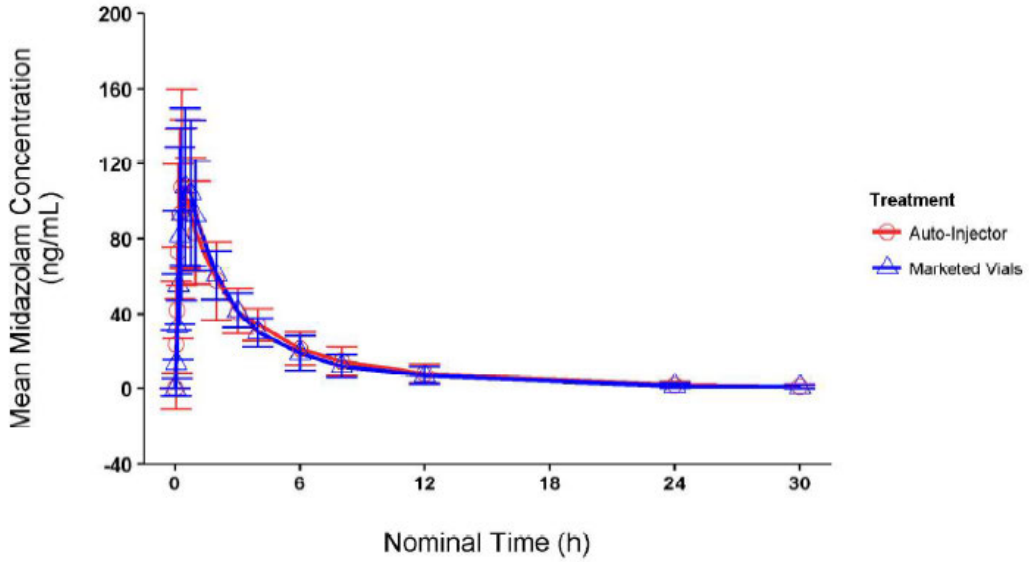

Figure 1 of 2
Auto-Injector N = 36; Marketed Vials N = 36

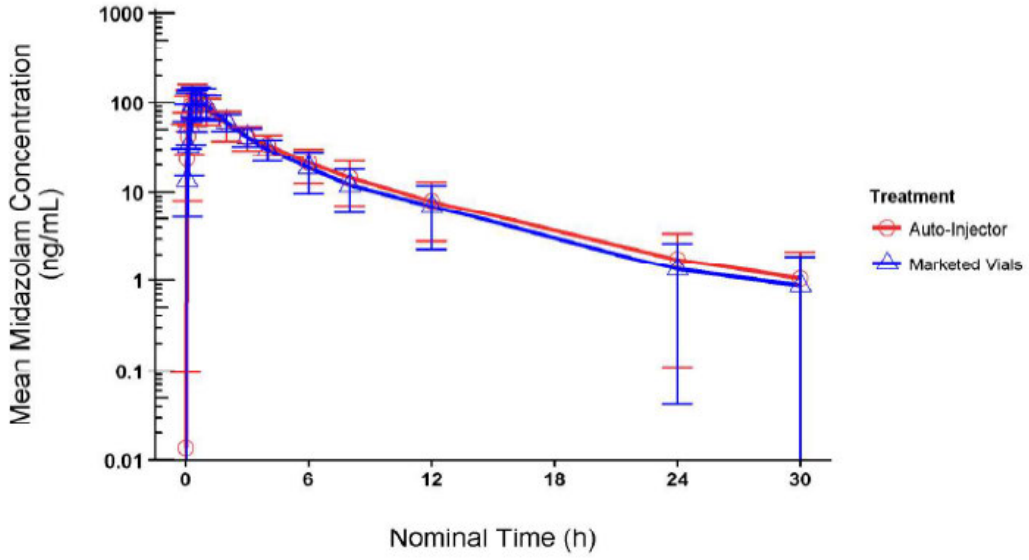

Figure 2 of 2
Auto-Injector N = 36; Marketed Vials N = 36

Source: Clinical Study Report (body 4); Study Number: rlm-559-01, Figure 5-1: Page 23 of 260

Table 1. Summary of Key Pharmacokinetic Parameters for Midazolam by treatment

Treatment/ Number of subjects	$AUC_{0\text{-last}}$ (ng.h /mL)	$AUC_{0\text{-}\infty}$ (ng.h /mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	t_{max} (h)
A (Auto-Injector, n=36)	444±127	454±134	127±47.3	5.16± 1.77	NC
B (Marketed Vials, n=36)	419±105	428±111	123±45.7	4.75±1.65	NC

Source: Clinical Study Report (body 4); Study Number: rlm-559-01, Table 5-4, Page 29 of 260.

Table 2. Ratio of the Least squares Geometric Means of PK parameters and 90% Confidence Intervals

Parameter	Test (A)	N	Reference (B)	N	Ratio %	90% C.I.
AUC0-inf (ng*hr/mL)	437	36	414	36	105.56	100.96 to 110.17
AUC0-last (ng*hr/mL)	428	36	407	36	105.16	100.67 to 109.98
C_{max} (ng/mL)	119	36	114	36	104.39	90.45 to 120.28

Source: Clinical Study Report (body 4); Study Number: rlm-559-01, Table 8-12, Page 60 of 260

Reviewer's Comments:

The overall design of this pivotal BE study, including the dose selection, route of administration, study population, study sample size, PK sampling schedule and washout period, are appropriate. The applicant conducted PK analysis and applied statistical testing criteria are acceptable. The reviewer conducted independent analysis and verified the PK results concluding that the C_{max} $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were within the acceptable limits of 80.00% to 125.00%.

Reviewer's Analysis

Independent NCA analysis was conducted by the reviewer using the raw PK data from study RLM-559-01. The descriptive statistics for PK parameters from the NCA analysis are shown in Table 3. Table 4 summarized the reviewer calculated ratio of the Least squares Geometric Means for PK parameters and confidence intervals (C.I.).

Table 3. Summary of Pharmacokinetic Parameters for Midazolam by treatment (reviewer's analysis)

Treatment/ Number of subjects	**$AUC_{0\text{-last}}$ (ng.h /mL)**	**$AUC_{0\text{-}\infty}$ (ng.h /mL)**	**C_{max} (ng/mL)**	**$t_{1/2}$ (h)**	**t_{max} (h)**
A (Auto-Injector, n=36)	443±126	453±134	127±47.3	5.11±1.83	0.5±0.24
B (Marketed Vials, n=36)	413±100	421±106	121±45.2	4.63±1.65	0.6±0.4

Table 4. Ratio of the Least squares Geometric Means of PK parameters and 90% Confidence Intervals (reviewer's calculation)

Parameter	**Test (A)**	**N**	**Reference (B)**	**N**	**Ratio %**	**90% C.I.**
AUC0-inf (ng*hr/mL)	436	36	414	36	105.30	100.87 to 109.93
AUC0-last (ng*hr/mL)	426	36	406	36	105.06	100.60 to 109.74
C_{max} (ng/mL)	119	36	115	36	103.59	89.66 to 119.69

The reviewer's analysis confirmed that the C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ results were within the acceptable limits of 80.00% to 125.00% for concluding the bioequivalence of the test product to the LD.

5. Bioanalytical Method Validation

A validated liquid chromatographic method was used for determining the Midazolam concentrations in human plasma. The samples were prepared by solid phase extraction and analyzed by liquid chromatography with tandem mass spectrometry detection (LC-MS/MS). The methods met the acceptance criteria for bioanalytical methods according to the Bioanalytical Method Validation Guidance for Industry the FDA Guidance for the Industry. Description of method validation parameters for Midazolam (validation report PF18B-0283) are summarized in Table 5.

Reviewer's Comments: *Method validation and sample analysis are acceptable.*

Table 5 Summary of Bioanalytical Method and Validation Characteristics

Analyte	Midazolam
Internal Standard (IS)	Midazolam-d4
Lower Limit of Quantitation (LLOQ)	0.2 ng/mL
Relative recovery of analyte (%)	QC Low: 100%; QC Med: 92.8%; QC High: 90.1%
Relative recovery of IS (%)	88.3%
Standard curve concentrations (ng/mL)	0.200, 0.400, 1.00, 2.00, 5.00, 10.0, 25.0, 50.0, 100
QC Concentrations (ng/mL)	0.200, 0.600, 8.00, 80.0
Intraday accuracy and precision	Biases: - 13.3 to 9.50%; CV: 0.90% to 8.79%
Inter day accuracy and precision	Biases: 1.13 to 2.33%; CV: 2.93% to 8.95%
Bench-top stability (hrs)	25 hours at room temperature
Long-term storage stability (days)	70 days at -20ºC & -70°C
Processed Sample (hrs)	75 hours 10±5°C
Freeze-thaw stability (cycles)	5 Cycles (-20°C/Room Temperature)
Stock stability	5 years @ -20°C and 6 hours at room temperature

Source: Method validation report PF18B-0283, section 3.1 page 10

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