CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216359Orig1s000

SUMMARY REVIEW

Summary Review

Date	August 8, 2022
From	Philip H. Sheridan, M.D. Nick Kozauer, M.D.
Subject	Summary Review
NDA/BLA # and Supplement#	216359
Applicant	Rafa Laboratories, Ltd.
Date of Submission	March 28, 2022
PDUFA Goal Date	September 28, 2022
Proprietary Name	Midazolam Injection (autoinjector)
Established or Proper Name	Midazolam
Dosage Form(s)	Autoinjector for intramuscular use
Applicant Proposed Indication(s)/Population(s)	Treatment of status epilepticus in adults
Applicant Proposed Dosing Regimen(s)	10 mg midazolam administered by intramuscular injection by single use autoinjector
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 by single use autoinjector

1. Benefit-Risk Assessment

This 505(b)(2) application provides data intended to support the safety and effectiveness of Midazolam Injection (an autoinjector for intramuscular (IM) midazolam administration) for the treatment of status epilepticus (SE) in adults. The listed drug (LD) Seizalam (NDA 209566) is midazolam injection for IM administration by vial and syringe for the same SE indication.

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, nerve agent exposure, 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.

There is a need for a treatment for SE that can be readily available and given rapidly by first responders prior to a patient being transported to a medical facility. 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.

Midazolam Injection (autoinjector) can be given more rapidly as an autoinjector product than the currently approved Seizalam which is administered by vial and syringe. Midazolam Injection (autoinjector) should be administered by trained personnel.

Overall, the benefit-risk assessment for Midazolam Injection (autoinjector) favors the benefit of the rapid onset and reliable delivery of an efficacious treatment of SE in adults.

2. Background and Regulatory History

The applicant, Rafa Laboratories, Ltd., is seeking the approval of the Midazolam Injection (autoinjector) for the treatment of SE in adults under the 505(b)(2) pathway relying on information from the LD Seizalam (NDA 209566).

The applicant has developed this single use 10 mg autoinjector for the treatment of SE in adults. The applicant recently has received FDA approval for atropine injection (NDA 212319; July 2018) that uses a similar autoinjector system to that used by Midazolam Injection.

On March 16, 2020, Type B pre-IND written responses (PIND 147559) were provided to the applicant that discussed product quality, reliability, human factors engineering, and reliance on the LD Seizalam.

On February 9, 2021, May Proceed letter for IND 147559 was issued to allow initiation of the bioequivalence study comparing the pharmacokinetics of Midazolam Injection (autoinjector) and the LD Seizalam.

On May 19, 2021, Type C written responses were provided to the applicant that continued the discussion on product quality and reliability and clarified the Division's non-hold comments included in the February 9, 2021, May Proceed letter.

On August 19, 2021, a pre-NDA teleconference was held to identify any issues regarding filing of the application through the 505(b)(2) regulatory pathway, relying on the safety and effectiveness of the listed drug Seizalam (NDA 209566).

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. The 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.

All components, including the drug substance, are of USP compendial grade. The drug product container closure system consists of an autoinjector filled with 1 mL of drug product, with 0.7 mL of the drug product delivered in a single-use injection. The OPQ review references the CDRH review for further details on the single-use prefilled autoinjector (Section 8 of this summary review).

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.

Reference ID: 5026270

4. Nonclinical Pharmacology/Toxicology

No review was written by the nonclinical pharmacology/toxicology review team since no new nonclinical data were submitted.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was written by Dr. Dawei Li and Dr. Gopichand Gottipati (the supervisory reviewer). OCP recommends approval of this application.

The review notes that Midazolam Injection is a single-dose (single-strength 10 mg/0.7 mL), emergency-use autoinjector intended for (b) (4) via the IM route. Midazolam Injection and the LD 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 Rafa 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 OCP team reviewed the Phase 1 pharmacokinetic (PK)/relative bioavailability study (Study RLM-559-01). Study RLM-559-01 was a pivotal bioequivalence study to establish the scientific bridge between Midazolam Injection (autoinjector) and the LD Seizalam.

Study Description:
This was a Phase 1, open-label, crossover, comparison study to evaluate the safety and PK characteristics from a single IM dose of 10 mg Midazolam Autoinjector (Treatment A) compared to those from the marketed LD Seizalam (Midazolam Injection, syringe and vial) (Treatment B).

Subjects who were administered Tretment A in Period 1 received Tretment B in period 2, and subjects who received Treatment B in Period 1 received Treatment A in Period 2. 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.

Forty healthy adult subjects were enrolled into the study. Data from 36 subjects were used for pharmacokinetic analysis; of the 4 subjects not contributing data: 1 subject did not receive the autoinjector dose, 2 subjects did not receive the Seizalam dose, and 1 subject did not have detectable levels of midazolam after the autoinjector dose. It is not known why the 1 subject did not have detectable levels because there was no apparent procedural error or autoinjector malfunction to account for this result.

Results:

The applicant found that 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 figure below, reproduced from the OCP review and taken from the Study RLM-559-01 study report, shows the Mean Concentration (plus/minus standard deviation) versus the Nominal Time Profiles for Midazolam after a single 10 mg IM injection comparing the Midazolam Injection (autoinjector) to the LD Seizalam (syringe and vial). The first graph is linear and the second semilogarithmic). The data is from 36 healthy adult subjects.

Reference ID: 5026270

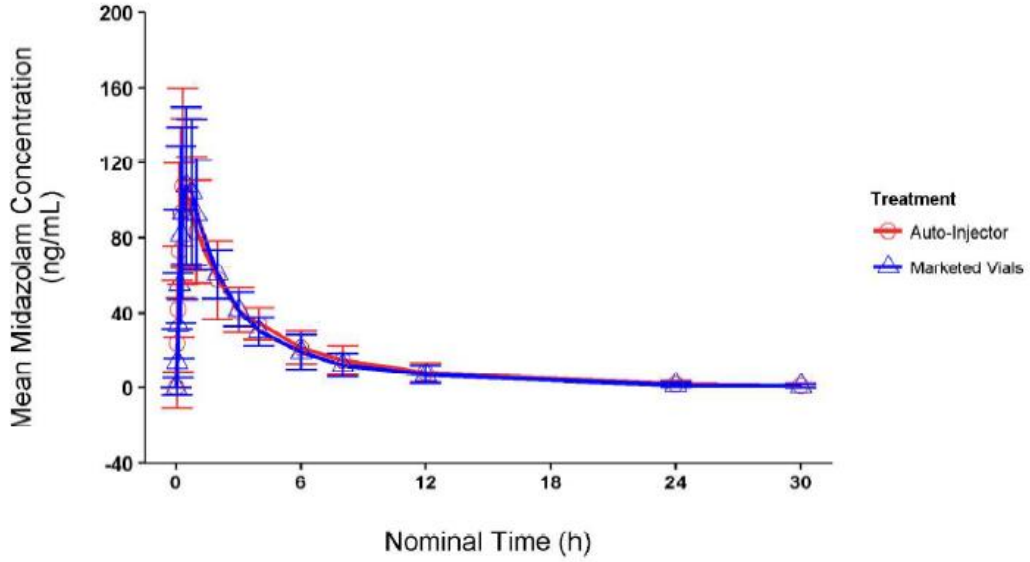

Figure 1 of 2
Auto-Injector N = 36; Marketed Vials N = 36

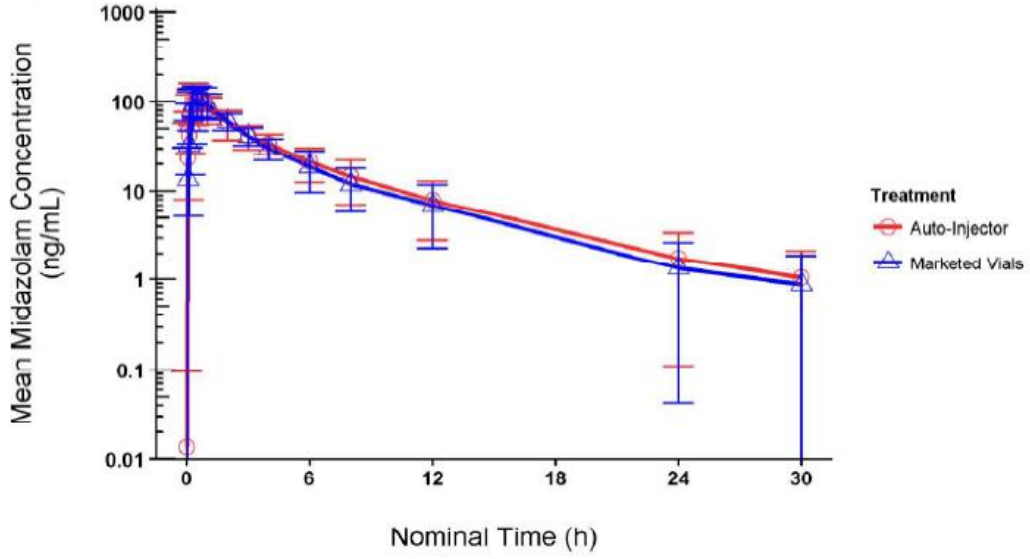

Figure 2 of 2
Auto-Injector N = 36; Marketed Vials N = 36

The OCP reviewer conducted an 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%. The OCP review found that, 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 Seizalam.

The OCP review noted that the Office of Study Integrity and Surveillance (OSIS) conducted clinical and analytical site inspections for the pivotal relative bioavailability study RLM-559-01. After reviewing the study report and the findings in the establishment inspection report, OSIS concluded that the audited study data were reliable.

The OCP review concluded that Study RLM-559-01 was an adequate PK bridge demonstrating bioequivalence between Midazolam Injection (autoinjector) and the LD, Seizalam. Therefore, the OCP review recommends approval.

6. Clinical/Statistical- Efficacy

No review was written by the nonclinical pharmacology/toxicology review team since no new nonclinical data were submitted.

7. Safety

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

The safety population consisted of the 40 normal adult volunteers who received midazolam from one or both of Midazolam Injection (autoinjector) and Seizalam during the bioequivalence study as described in Section 5 of this summary review.

Serious Adverse Events (SAEs) and Treatment Emergent Adverse Events (TEAEs) Leading to Study Medication discontinuation

One subject (2.6%) out of 39 who were administered midazolam via the 10 mg autoinjector experienced an SAE leading to withdrawal. The subject (subject (b) (6)) experienced syncope which was considered by the investigator to be not related to either the

Reference ID: 5026270

drug or the device. Dr. Dinsmore concurs with this determination. He notes that the syncopal event occurred about 32.5 hours after midazolam administration by autoinjector which would be 3.7 x $t_{1/2}$ (given the maximum reported $t_{1/2}$) and 5.8 x $t_{1/2}$ based on the mean $t_{1/2}$; therefore, the syncopal episode did not have a clear temporal relationship to test product treatment. He further notes that the event had clinical characteristics of a syncope of hemodynamic origin with associated epileptiform movements "syncopal seizure". This subject declined to crossover to the vial and syringe treatment period.

No other SAEs were observed.

Treatment Emergent Adverse Events

Dr. Dinsmore compared TEAEs that occurred following the single dose of treatment A (autoinjector) TEAEs that occurred following the single dose of midazolam via needle from vial, treatment B. His analysis reveals there was overlap for only one preferred term from among the two differing treatment administrations: "injection site pain" which 3 (15%) subjects in the Autoinjector administration period and 1 (5%) subject in the needle from vial administration period experienced. From among the remaining 20 preferred terms occurring in the Study RLM-559-01 ADAE (xpt adverse events) dataset, there were none in common between the autoinjector treatment period and the needle from vial treatment period. Dr. Dinsmore concluded that there was no safety signal that represents a significant new risk of midazolam using the autoinjector product compared to the needle from vial administration.

Laboratory Results

Samples for clinical chemistry and hematology laboratory studies were collected 1-2 hours pre-dose and at 7 hours, 30 hours, and 14 days post-Midazolam administration in both treatment periods 1 and 2.

Dr. Dinsmore examined the applicant's presentation of laboratory results from shift tables (summary of results assessed as normal; abnormal, not clinically significant (NCS); and abnormal, clinically significant (CS) as well as individual outliers). He also performed an independent assessment of clinical chemistry and hematology results; he further evaluated results meeting one of the following two conditions: entries identified by the applicant variable "CLINSIG" with a value of "Abnormal, NCS" and a post treatment result that had a greater than or less than 25% change from the baseline (pre-treatment) value. The results of his analysis are available in the clinical review of this submission.

Reference ID: 5026270

Dr. Dinsmore concluded that the frequency of post-baseline laboratory values with an entry of "Abnormal, clinically significant" was low with only 4 entries captured in the autoinjector treatment period. None of these events represents a laboratory safety signal causally linked to the autoinjector product.

Dr. Dinsmore found that his own analysis of the clinical chemistry and hematology values were in alignment with the applicant's reports of clinically significant and non-clinically significant results of the midazolam autoinjector post treatment period. He concluded that there was no evidence of a new or worsening safety signal associated with midazolam treatment with the autoinjector product.

Therefore, Dr. Dinsmore recommended approval of Midazolam Injection (autoinjector).

8. Center for Devices and Radiological Health (CDRH)

The CDRH review by Porsche Bennett, CDRH (secondary review by Courtney Evans and Alan Stevens) assessed the device aspects of the product.

Midazolam Injection (autoinjector) is intended for use by trained personnel for the emergency treatment of SE. This proposed combination product is a disposable, single dose autoinjector that will deliver midazolam injection 10 mg/0.7 mL by IM injection. The immediate container for the drug is a (b) (4) cartridge (b) (4).

The CDRH review finds that the applicant has provided adequate information to support the manufacturing control activities for the essential performance requirements of this combination product.

The CDRH review states that the device component is similar to that of the applicant's previously approved atropine autoinjector. The applicant has utilized historical data from the atropine autoinjector to assess and determine the overall reliability of the midazolam autoinjector. The differences between atropine and midazolam products are the drug product and the safety pin and injector cap colors.

The CDRH review states that the applicant's approach to leveraging atropine autoinjector reliability data is reasonably applicable, but an adequate assessment of the reliability of the midazolam autoinjector independent of the atropine autoinjector should also be performed. The CDRH review notes that device performance is an essential performance requirement for emergency use products;

however, the CDRH review observes that there is an urgent need for the approval of this product. The CDRH review thus concludes that it is reasonable for the applicant to perform some of the reliability studies specific to the midazolam autoinjector under a postmarketing requirement (PMR) because the benefit of having this product available outweighs any remaining residual risk due to residual device reliability issues. The details of the PMR are discussed in Section 13 of this summary review.

With respect to device quality, the CDRH review recommends approval of the Midazolam Injection (autoinjector) with this PMR.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of Midazolam Injection (autoinjector) is acceptable for the proposed indication.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which include new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because these criteria do not apply, Midazolam Injector (autoinjector) is exempt from this PREA requirement.

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 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. The labeling sections relevant to abuse and dependence for the Midazolam Injection autoinjector will align with those in the labeling of the LD Seizalam.

The Division of Medication Error Prevention and Analysis (DMEPA) review team determined (based on its review of the use-related risk analysis, comparative analyses (to the Rafa atropine autoinjector), and justifications submitted by the applicant) that the applicant did not need to submit the results of a Human Factors (HF) validation study for the Midazolam Injection autoinjector. DMEPA also evaluated the proposed label, labeling, and Instructions For Use (IFU); its recommendations were addressed in negotiations with the applicant.

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. These changes include the new class safety labeling changes (SLC) being required for the labelings of all benzodiazepine products to address pregnancy- and lactation-related risks and overdosage risks.

13. Postmarketing Recommendations

The approval letter includes one PMR to further characterize the reliability of the autoinjector as discussed in the CDRH review.

> 4319-1 Provide an updated Fault Tree Analysis and the associated reliability requirements and specifications to demonstrate that Midazolam Injection autoinjector will provide successful injection with at least 99.999% reliability at the 95% confidence interval. The fault tree analysis must include information from your combination product's design and manufacturing methods by identifying all basic failure modes anticipated.
>
> Final Protocol Submission: 01/2023
> Study Completion: 04/2023
> Final Report Submission: 05/2023

Reference ID: 5026270

14. Recommended Comments to the Applicant

See action letter.

Reference ID: 5026270

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/s/

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08/08/2022 09:48:05 AM

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