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APPLICATION NUMBER:

211635Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	January 10, 2020
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Memorandum
NDA/BLA # and Supplement#	211635
Applicant	Neurelis
Date of Submission	December 12, 2018
PDUFA Goal Date	October 10, 2019 (Extended by major amendment to January 10, 2020)
Proprietary Name	Valtoco
Established or Proper Name	Diazepam
Dosage Form(s)	Single use drug-device product for nasal inhalation
Applicant Proposed Indication(s)/Population(s)	Patients age 6 years and older with acute repetitive seizures, seizure clusters, (b) (4)
Applicant Proposed Dosing Regimen(s)	5, 10, 15, or 20 mg intranasally (IN); may be repeated once after 4 hours if needed
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.
Recommended Dosing Regimen(s) (if applicable)	5, 10, 15, or 20 mg IN; may be repeated once after 4 hours if needed

1. Benefit-Risk Assessment

Diazepam nasal spray (Valtoco) is a new formulation of an already approved drug substance (diazepam). Valtoco is an intranasal (IN) combination drug-device product intended for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.

This submission is a 505(b)(2) application using Diastat (diazepam rectal gel, NDA 20648) as the listed drug (LD). The application relies on the previous finding of safety and effectiveness for the LD, and on the determination of the comparative bioavailability of Valtoco to the LD.

The overall benefit-risk analysis of Valtoco is acceptable. Valtoco has been shown to have comparative bioavailability to the LD, Diastat, in a pivotal comparative bioavailability study in healthy volunteers. Additionally, exposures in a PK study conducted in epilepsy patients were similar between the ictal/peri-ictal and interictal states. The LD has been marketed in the United States since 1997 for intermittent use to control bouts of increased seizure activity and has a well characterized safety profile. No new or unexpected adverse events were discovered in the course of the development program of Valtoco in healthy adults and patients with epilepsy 6 years of age and older. There are no clinical safety issues impeding the approval of the proposed product.

2. Background

This application provides data intended to support the safety and effectiveness of Valtoco for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.

Diazepam, the active ingredient, is a short-acting benzodiazepine, initially approved in the United States for management of anxiety in 1963 under the trade name Valium (NDA 013263). It is currently marketed as a generic drug in the US in intravenous (IV), intramuscular (IM), and oral formulations for adults and children for treatment of anxiety, symptomatic treatment of acute alcohol withdrawal, relief of skeletal muscle spasm, and as adjunctive treatment of seizures. Diastat, the LD (NDA 20648), is approved for management of increased seizure activity (i.e., acute repetitive seizures) in patients with epilepsy.

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

Valtoco is a diazepam single-use drug-device product for nasal inhalation in the outpatient setting. The applicant proposes treatment with 5, 7.5, or 10 mg single-use vials, administered as one IN spray (5 or 10 mg dose) or 2 IN sprays (15 or 20 mg dose), with the allowance of repeat dosing after 4-12 hours, if needed. The product is intended to be utilized on a chronic, intermittent basis, as it will likely be given as needed for each seizure cluster or episode of acute repetitive seizures. The delivery device is packaged as a single-use vial with aspirator and includes 2 or 4 vials (depending on dose).

As discussed in Section 3 of this summary memorandum (Product Quality), the review goal date was extended to January 10, 2020, after submission of a major amendment by the applicant on September 26, 2019, in response to a Discipline Review (DR) letter from the Office of Product Quality (OPQ) review team.

3. Product Quality

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

The OPQ review team initially concluded that, despite several amendments in response to Agency information requests, there was not adequate information to ensure that the applicant could consistently manufacture a product that was suitable for patient use. The identified drug product and manufacturing deficiencies identified during the review were communicated to the applicant via a Discipline Review (DR) letter (September 6, 2019), discussed below.

In response to the approvability issues described in the DR letter, the applicant provided additional information on September 26, 2019, intended to address the listed deficiencies; since this additional information appeared to be capable of potentially satisfying these deficiencies, pending a detailed review, the Division accepted it as a major amendment, extending the review goal date from October 10, 2019, to January 10, 2020.

The OPQ addendum review, dated January 8, 2020, assessed this additional information and two subsequent related submissions and found the amended application adequate for approval.

The key issues, copied from the September 6, 2019, OPQ DR letter, and their subsequent resolution are summarized as follows:

1. Commercially viable shelf-life(s) cannot be assigned due to inadequate data to qualify the proposed limit of NMT (b) (4)% for USP Related Compound B and significant increases in this degradant in long-term stability studies exceeding the ICH Q3B qualification threshold of NMT 0.5%.

   Resolution: The RCA and RCB limits have been lowered to NMT 0.5% each and Total Related Substances to NMT (b) (4)%. The applicant also provided data to support the correction of key stability results and statistical analyses supporting a 6-month shelf-life for the 50 and 75 mg/mL strengths and 9 months for 100 mg/mL.

2. In section 3.2.P.5.3 Validation of Analytical Procedures, Accuracy of related substances was not performed for USP Related Compounds A and B, the major degradation products for this drug product. Additionally, the spiking level for precision samples is stated to be (b) (4)% for all 3 impurities, but the results for USP Related Compound A are more consistent with a spiking level of (b) (4)%.

   Resolution: The applicant provided accuracy and precision results for RCA and RCB which meet the acceptance criteria.

3. In section 3.2.P.5.1, testing of actuation force should be included in the specification for both release and stability testing or adequate justification provided including stability data.

   Resolution: The applicant added actuation force to the specification, with acceptance criteria based on batch release/stability data, although all of the requested data were not provided. However, the OPQ review team determined that that submission of the actuation force data will not be required as a condition for recommendation of approvability.

4. In section 3.2.P.2, identification of leachables is incomplete.

   Resolution: The applicant provided additional identification information and justification that the remaining unidentified compounds are unlikely to be leachables.

In summary, 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 Dr. Edward Fisher, with Dr. Lois Freed (the supervisory reviewer) writing an addendum to Dr. Fisher's review. The nonclinical review recommends approval of this application.

The nonclinical review team notes that this 505(b)(2) application references the nonclinical studies for the LD (Diastat, which is approved for use in children down to age 2 years) and requests approval for the proposed indication for use in children down to 6 years of age. However, Valtoco also contains the functional excipient dodecyl maltoside (DDM) which is not present in the LD. The primary concerns, from a nonclinical standpoint, were the local (nasal) toxicity of the clinical formulation (diazepam and DDM) and the potential systemic effects of the excipient, DDM. The need for nonclinical studies of the excipient itself would be based on the extent of systemic exposure in humans resulting from intranasal administration. In the pre-NDA meeting for this application, the applicant was informed that if DDM did not circulate in humans at clinically relevant doses, then reproductive and developmental (including juvenile animal) toxicity and carcinogenicity studies of the excipient would not be needed. The applicant provided pharmacokinetic (PK) data demonstrating minimal systemic exposure to the excipient; therefore, nonclinical studies of the excipient alone were not required.

The applicant also did not conduct a local toxicity study in juvenile animals to assess potential differences between juvenile and adult animals in sensitivity of the nasal mucosa to diazepam nasal spray (i.e., diazepam and DDM). Based on this, Dr. Fisher concluded the nonclinical data support approval in adult, but not pediatric, patients. However, as Dr. Freed notes in her memorandum, the clinical team has determined that the safety data from clinical studies of diazepam nasal spray in pediatric patients, which included careful examination of the nasal passages, are adequate to support approval in children 6 years of age and older. See the discussion of the clinical safety data in Section 8 of this summary memorandum.

Therefore, in the context of adequate pediatric and adult clinical safety data, the nonclinical review team concludes that there is no need for a juvenile animal toxicology study to support approval of Valtoco for the intended patient population (6 years of age and above).

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was conducted by Dr. Jagan Parapelly and Dr. Angela Men (the supervisory reviewer).

The clinical development program includes four Phase 1 studies, described below (Studies 01, 02, 03, and 04). An open-label, long-term safety and usability study (Study 05) is discussed in Section 8 of this review.

Study 01 was an open-label, randomized, three-treatment, three-period, six-sequence crossover study in healthy volunteers under fasted conditions to evaluate the PK properties of diazepam after administration of an IN aqueous suspension (NRL-1.A), 10 mg, or an IN nonaqueous solution (NRL-1.B), 10 mg, compared to 5 mg administered IV.

Table 1, and the subsequent text, summarize the key results from Study 01.

Table 1: Observed PK Parameters from Study 01

	Diazepam Nasal Spray (10 mg/100µL)				Diazepam Injection	
	NRL-1.A Suspension		NRL-1.B Solution		5 mg/mL IV	
Parameter [a]	n	Mean (SD) [b]	n	Mean (SD) [b]	n	Mean (SD) [b]
C_{max} (ng/mL)	24	221 (78.6)	24	272 (100)	24	555 (316)
T_{max} (h)	24	1.00 (0.6, 2.0)	24	1.50 (0.8, 4.0)	24	0.03 (0.03, 0.50)
AUC_{0-t} (h×ng/mL)	24	5229 (1463)	24	7340 (1882)	24	3832 (1150)
$AUC_{0-\infty}$ (h×ng/mL)	20	5381 (1409)	20	7338 (2072)	24	4104 (1318)
λz (h^{-1})	20	0.0142 (0.0053)	20	0.0155 (0.0046)	24	0.0142 (0.0055)
$t_{½}$ (h)	20	56.2 (23.0)	20	49.2 (16.9)	24	56.2 (21.0)

a: Mean values are presented as arithmetic means.
b: Median (min, max) reported for T_{max}

- The mean elimination t½ of diazepam of about 50 hours was comparable across all treatment groups (IN or IV)

- The nonaqueous solution (NRL-1.B) was chosen for commercial development and was used in Studies 02, 03, 04, and 05. It has subsequently been referred to as NRL-1 (Valtoco).

Study 02 was a PK and dose proportionality study of Valtoco (NRL-1) in healthy volunteers. The following are the key results from Study 02.

- Diazepam and nordiazepam exposure increased essentially proportionally with increasing doses of 5 mg, 10 mg, and 20 mg.

- All PK parameters were similar across the three dosing cohorts and did not exhibit dose-dependent changes.

Study 03 was the pivotal relative bioavailability study in healthy subjects that established the bridge between Valtoco and the LD, Diastat. Study 03 was an open-label, randomized, single-dose, three-treatment, three-period, six-sequence crossover study of the bioavailability and PK properties of diazepam after administration of Valtoco, Diastat, and oral diazepam (Valium) in 48 healthy adult subjects. Diazepam C_{max} and AUC were evaluated following 15 mg and 20 mg doses using Valtoco and Diastat. Body-weight based dosing was taken into consideration per Diastat prescribing information for the 15 and 20 mg cohorts. The key comparison for this application in Study 03 was between Valtoco and Diastat.

The data from Study 03 show that the mean relative bioavailability of diazepam from Valtoco was approximately 118% and 100% for C_{max} and AUC, respectively, compared to those from Diastat at a 20 mg dose as shown in the Table 2 below. The OCP review concludes that the range of individual diazepam PK parameters following administration of Valtoco was well within the range seen with Diastat.

Table 2: Comparison of Diazepam Cmax and AUC between 20 mg Valtoco and 20 mg Diastat

Wt Group	Dependent	Ratio %Ref	CI 90 Lower	CI 90 Upper
High (N=28)	$Ln(C_{max})$	118	69	202
	$Ln(AUC_{0-\infty})$	100	65	152

CI = confidence interval, Ref = reference, Wt = weight

For the 15 mg dose, the mean relative bioavailability of diazepam from Valtoco was approximately 85% for C_{max} and 74% for AUC when compared to Diastat (Table 3). The OCP review notes that the decreased mean relative bioavailability for the 15 mg cohort may be a function of the lesser number of subjects (n=17) in this group.

Table 3: Comparison of Diazepam Cmax and AUC between 15 mg Valtoco and 15 mg Diastat

Wt Group	Dependent	Ratio %Ref	CI 90 Lower	CI 90 Upper
Low (N=17)	Ln(Cmax)	85	57	126
	Ln(AUC0-∞)	74	53	102

CI = confidence interval, Ref = reference, Wt = weight

The T_{max} was 1.25 hours following Valtoco 15 mg and 20 mg administration. This is comparable to a median T_{max} of 1 and 1.25 hours for Diastat 15 mg and 20 mg, but slightly delayed compared to oral Valium.

The OCP review further observes that the diazepam PK parameters were less variable for Valtoco by 2 to 4-fold, and well within the range of those seen with Diastat. This observation is critical in the determination of the comparative bioavailability of Valtoco to the LD. Although conventional BE parameters (i.e., the 90% confidence intervals of the relative mean for both C_{max} and AUC of the test drug to the LD should be within 80-125%) were not met, Valtoco was still found to be BE to Diastat based on the acceptable approximation of the mean values for these parameters, as well as the noted significantly reduced exposure variability of Valtoco relative to the LD, both in in terms of the overall data, as well as the individual subject data. Therefore, the OCP review concludes that Valtoco is BE to Diastat.

Potential for a Food Effect

The OCP review also notes that for drug products administered by IN or rectal routes of administration, FDA generally does not require the food effect studies required for orally administered products that are absorbed from the gastrointestinal tract and thus subject to first-pass metabolism. Additionally, each 5 mg or 10 mg dose of Valtoco is delivered in 100 µl of solution per nostril. Any potential swallowing of a portion of the Valtoco dose is minimized by the low volume administered per dose. Moreover, the median T_{max} for Valtoco is similar to the median T_{max} for rectally absorbed Diastat (the LD), indicating that Valtoco is not being absorbed from the gastrointestinal tract. Therefore, the OCP review concludes that diazepam from Valtoco would not be expected to be absorbed through the gastrointestinal tract given the low volume of the dose administered and the observed median T_{max}. As a result, a food effect study with Valtoco is not required.

Exposures in Patients

The Division has been concerned that IN administered anticonvulsants for the treatment of ARS will often be given to epileptic patients during or shortly after a seizure at a time when their respiratory patterns and level of alertness may interfere with their ability to tolerate and absorb an IN dose as readily as an alert normal volunteer would. To address this concern, the sponsor was required to conduct an additional PK study in epileptic patients to demonstrate that dosing of the patients in the ictal/peri-ictal period results in diazepam exposures equivalent to the exposures following dosing in the interictal period. The results of such a study also allow for a

cross-study comparison with the exposures obtained in the pivotal comparative bioavailability study in normal volunteers. The applicant conducted Study 04 to address these issues.

Study 04 was an open-label, repeat dose PK study of Valtoco in epilepsy patients in the ictal/peri-ictal and interictal states. The OCP review makes the following conclusions based on the results of this study.

- The mean PK profiles were similar with a large overlap following IN administration of Valtoco in patients during the ictal/peri-ictal and interictal states.

- A cross-study comparison of the interictal state PK profiles of the epileptic patients in Study 04 to those of normal healthy volunteers from Study 03 indicated that patients with epilepsy had lower levels of diazepam (~25% to 33% lower AUC and ~34% to 42% lower C_{max}) compared to healthy subjects. The OCP review suggests that these differences are potentially attributable to the use of concomitant inducers.

Recommended Dosing

The proposed dosing of Valtoco is 5-20 mg. The 5 mg and 10 mg doses are administered as a single spray intranasally into one nostril. The 15 mg and 20 mg doses require two nasal spray devices (7.5 mg and 10 mg, respectively), with one spray into each nostril. The OCP review agrees with the applicant's proposal that the dosing of Valtoco should be based on weight, as summarized in Table 4 below. Of note, there are fewer dose groups with Valtoco dosing (4) than with Diastat (7), because of lower variability in PK of diazepam when administered intranasally as compared to rectally.

Table 4: Proposed Weight-based Dosing Categories

6 - 11 years (0.3mg/kg)		≥12 years (0.2mg/kg)	
Weight (kg)	**Dose (mg)**	**Weight (kg)**	**Dose (mg)**
10 - 18	5	14 - 27	5
19 - 37	10	28 - 50	10
38 - 55	15	51 - 75	15
56 - 74	20	76 and up	20

OCP Recommendation

The OCP reviewers conclude that the results of Study 03 establish that Valtoco has comparative bioavailability to the LD, Diastat. Additionally, the results of Study 04 establish that the PK of Valtoco in epilepsy patients is similar when dosing in the ictal/peri-ictal state is compared to the interictal state. Therefore, OCP recommends approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy data were submitted since the application relies on the previous finding of effectiveness for the LD, Diastat, and on the determination of the comparative bioavailability of Valtoco to Diastat (discussed in section 5 of this review).

8. Safety

Dr. Natalie Getzoff conducted the clinical safety review of this application.

The application relies on the previous finding of safety for the LD, Diastat.

Additional clinical safety data were generated in Studies 04 and 05. For the purpose of her review, Dr Getzoff combined these data into a single dataset. The data from these two studies constitute the safety database and provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, nasal toxicity, and vital signs. This safety database includes a total of 164 patients who were exposed to at least one dose of Valtoco in Studies 04 and 05 prior to the data submission cutoff dates for each study. There were no placebo-treated patients in these trials.

As noted, the primary safety data were primarily generated from:

- Study 04: Multicenter, open-label, PK and safety study of Valtoco in adult and pediatric patients (ages 6-16 years) during ictal/peri-ictal and interictal periods.
- Study 05: Multicenter, open-label, single-arm chronic safety study of Valtoco in adult and pediatric epilepsy patients (ages 6-16 years) who used Valtoco as needed to control bouts of uncontrolled seizures (seizure clusters or ARS) over at least a 6-month period.

Out of the 164 patients in the pooled primary safety database, 26 (15.9%) were 6-11 years of age, 22 (13.4%) were 12-17 years of age, and 116 (70.7%) were 18 years or older. About half (51%) were female. The majority of the patients were White (81.1%).

Table 5: Patient Demographics, Pooled Studies 04 and 05

Category	Study 04 N = 50	Study 05 N = 122	Pooled N=164
Age (years)			
Mean (SD)	30.6 (14.7)	27.3 (15.2)	28.3 (15.0)
Min, Max	6, 59	6, 65	6, 65
Age groups (years) n (%)			
6-11	7 (14)	21 (17.2)	26 (15.9)
12-17	4 (8)	18 (14.8)	22 (13.4)
Adults (≥18)	39 (78)	83 (68)	116 (70.7)
Adolescents and Adults (≥12)	43 (86)	101 (82.8)	138 (84.1)
Sex, n (%)			
Female	26 (52)	63 (51.6)	84 (51.2)
Male	24 (48)	59 (48.4)	80 (48.8)
Ethnicity, n (%)			
Not Hispanic/Latino	36 (72)	110 (90.2)	141 (86)
Hispanic/Latino	14 (28)	12 (9.8)	23 (14)
Race, n (%)			
White	39 (78)	100 (90.0)	133 (81.1)
Black	5 (10)	11 (9.0)	16 (9.8)
Asian	0	3 (2.5)	3 (1.8)
Pacific Islander	1 (2)	5 (4.1)	6 (3.7)
Other	5 (10)	3 (2.5)	6 (3.7)

Pediatric Chronic Safety Data

In the March 30, 2018, preNDA meeting minutes, the Division recommended that the applicant attempt to submit safety data in 50 adult patients and 50 pediatric patients receiving three or more doses of drug over a 12-month period to support the applicant's proposed age range (age 6 years and above); alternatively, the Division commented that 6 months of safety data in 100 adults might be found sufficient to support an adult indication.

During Studies 04 and 05 (having a pooled total of 164 adult and pediatric patients), 26 pediatric patients less than 12 years of age (and an additional 22 pediatric patients 12 to less than 18 years of age) received at least one dose of Valtoco. There were 9 pediatric patients less than 12 years old (in the original NDA submission) with at least 3 doses over at least 6 months in Study 05 (not including dosing in the rollover patients from Study 04). When data from the 120-day safety update was considered, 58 pediatric patients (34 of whom were below 12 years of age) had been enrolled into either Study 04 or 05. A total of 32 pediatric patients (17 of whom were below 12 years of age) received at least 3 doses of Valtoco over a period of at least 6 months in the cumulative dataset.

Although this number of pediatric patients is somewhat less than the number recommended in the preNDA minutes (50 pediatric patients receiving three or more doses of drug over a 12 month period), the preNDA recommendation was based on a conservative estimate of how many

pediatric patients might be needed to characterize any new safety signal that might be detected with regard to local nasal mucosal toxicity or from the functional excipient DDM (the safety of diazepam having already been established by reliance on the LD for pediatric patients down to 2 years of age). However, as discussed below, the safety findings from Studies 04 and 05 for both pediatric and adult patients did not reveal any new safety signals (including no evidence of local nasal or olfactory toxicity). In light of the total safety data and the absence of a safety signal for local toxcity in either adults or children, the pediatric chronic safety data are sufficient to support approval of Valtoco down to age 6 years.

Deaths

There were no deaths that occurred during Valtoco drug development in any study.

Serious Adverse Events

A total of 39 treatment-emergent serious adverse events (SAEs) were reported in 24 patients (14.6%) in the pooled patient safety database for Studies 04 and 05, primarily in patients in Study 05 (23/24, 96%). The majority of these events occurred during Study 05 (n=36), as compared to Study 04 (n=2). Seizures were the most frequent SAE, occurring in 13 patients (7.9%). The only other SAE to occur in more than 1 patient was pneumonia, which occurred in 2 patients (1.2%). The rest of the SAEs occurred in only 1 patient each. Although an evaluation of any dose effect is limited by the small number of patients in the 5 mg treatment arm, there was no clear dose effect on SAEs. No SAEs were reported in Studies 01, 02, or03. The incidence of SAEs was greatest in the 6-11-year age group (23.1%), as compared to that in patients 12-17 years (13.6%) and adults (12.9%).

Dropouts and/or Discontinuations Due to Adverse Effects

No patients discontinued participation in Study 04 due to adverse events. One patient discontinued participation in Study 05 due to the SAE of suicidal ideation. This patient had a prior history of depression, and a causal relationship to Valtoco could not be established.

All anticonvulsant labelings include a class warning for suicidal behavior and ideation. This class warning will be part of the Valtoco labeling.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) occurred in 94/164 (57.3%) of patients in the pooled safety database; 28% and 49% of patients in Studies 04 and 05, respectively. A summary of the percentages of patients with TEAEs that occurred in at least 2% of patients overall are presented in Table 6, below.

The most frequent TEAEs in Studies 04 and 05 were seizures (any) and respiratory tract

infection, which occurred in 11% and 6.1% of patients, respectively. As seen in Table 6, TEAEs that occurred in at least 5% of patients in the pooled dataset from Studies 04 and 05 were seizures, somnolence/sedation/fatigue/lethargy, nasal discomfort, headache (including migraine), and upper respiratory tract infections.

In general, other than those related to potential local effects of the IN administration, the frequently reported TEAEs are consistent both with commonly observed events in this population as well as the TEAEs observed in the controlled trials of Diastat. See below for a discussion of local effects of Valtoco.

Table 6: TEAEs in at least 2% of Patients by Treatment Arm, Studies 04 and 05

TEAE (preferred term)	DZP NS 5 mg N=3		DZP NS 10 mg N=38		DZP NS 15 mg N=52		DZP NS 20 mg N=72		DZP NS Total N=164	
	n	%	n	%	n	%	n	%	n	%
Any adverse event	***2***	***66.7%***	***22***	***57.9%***	***32***	***61.5%***	***38***	***52.8%***	***94***	***57.3%***
ANY LOCAL NASAL SYMPTOM (Excl Infections)	1	33.3%	3	7.9%	11	21.2%	8	11.1%	23	14.0%
Nasal Discomfort	0		0		5	9.6%	5	6.9%	10	6.1%
Nasal Congestion	0		1	2.6%	3	5.8%	1	1.4%	5	3.0%
Epistaxis	0		3	7.9%	2	3.8%	0		5	3.0%
Rhinorrhea	1	33.3%	0		1	1.9%	1	1.4%	3	1.8%
Nasal Pruritus	0		0		0		1	1.4%	1	0.6%
Nasal Ulcer	0		0		0		1	1.4%	1	0.6%
SEIZURE (Any)	0		7	18.4%	8	15.4%	3	0.4%	18	11.0%
Status Epilepticus	0		2	5.3%	1	1.9%	0		3	1.8%
Somnolence/Sedation/Fatigue/Lethargy	1	33.3%	2	5.3%	5	9.6%	2	2.8%	10	6.1%
Headache (Incl Migraine)	0		0		4	7.7%	6	8.3%	10	6.1%
Upper Respiratory Tract Infection (Incl Viral)	0		2	5.3%	3	5.8%	5	6.9%	10	6.1%
Nasopharyngitis	1	33.3%	3	7.9%	1	1.9%	3	4.2%	8	4.9%
Nausea/Vomiting	0		2	5.3%	3	5.8%	2	2.8%	7	4.3%
Dizziness	0		0		2	3.8%	4	5.6%	6	3.7%
Pyrexia	1	33.3%	4	10.5%	0		1	1.4%	6	3.7%
Influenza	0		1	2.6%	3	5.8%	1	1.4%	5	3.0%
Ataxia/Gait Disturbance/Balance Disorder	0		0		0		5	6.9%	5	3.0%
Gastroenteritis	1	33.3%	3	7.9%	1	1.9%	0		5	3.0%
Contusion	0		0		3	5.8%	1	1.4%	4	2.4%
Dysgeusia	0		0		3	5.8%	1	1.4%	4	2.4%
Fall	0		2	5.3%	1	1.9%	1	1.4%	4	2.4%
Pneumonia	0		3	7.9%	0		1	1.4%	4	2.4%
Urinary Tract Infection	0		2	5.3%	2	3.8%	0		4	2.4%
Depression	0		0		2	3.8%	2	2.8%	4	2.4%

Source: ADAE (ISS), verified in JMP

Nasal and Olfactory Toxicity

Nasal and Olfactory toxicity were among the AEs of special interest for this application. Among all studies, there were no reported TEAEs indicative of olfactory toxicity or nasal toxicity. Nasal examinations revealed no nasal abnormalities recorded as clinically significant at any visit.

No clinically meaningful changes or findings were observed in the prospective assessments of olfaction and nasal toxicity in either Study 04 or Study 05. Overall, local adverse events related to nasal administration occurred in more than 18% of patients in the pooled Studies 04 and 05 dataset; however, all of these events were characterized as mild in severity and none led to discontinuation or dose adjustment. There was no overall correlation of local AEs to dose or age group. Based on the safety data from Studies 04 and 05, there is no safety signal

for local nasal toxicity with Valtoco, when used in a chronic intermittent fashion in patients with ARS.

Laboratory Findings

There were no clinically meaningful changes from baseline in hematology and serum chemistry laboratory tests.

Vital Signs

There were no clinically meaningful changes from baseline in vital signs.

Electrocardiograms (ECGs)

There were no clinically meaningful changes from baseline in ECG results including no QT prolongation.

Integrated Assessment of Safety

This memo summarizes the safety data collected primarily from 164 patients with epilepsy exposed to diazepam nasal spray in one comparative bioavailability study and one open-label, long-term safety study. The clinical safety tests conducted in the studies were appropriate and capable of identifying major safety signals. Overall, the safety findings from this submission are consistent with data from the original NDA submission for Diastat. Although there is a class risk of acute respiratory depression with benzodiazepine use, no deaths or related SAEs were observed in the Valtoco development program. No new safety signals were identified in either Study 04 or Study 05, or in the rest of this product's development program. No evidence of local nasal or olfactory toxicity was identified in Studies 04 and 05.

These safety data support the approval of Valtoco for the treatment of acute repetitive seizures in patients age 6 years and above when administered by an appropriately trained caregiver in the outpatient setting.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application because efficacy has been established through comparative bioavailability to the LD (Diastat), the clinical trials were acceptable, the safety findings were clear, and the safety profile was similar to the LD.

10. Pediatrics

Because Valtoco has orphan designation for the acute treatment of acute repetitive seizures, the Pediatric Research Equity Act (PREA) is not triggered.

11. Other Relevant Regulatory Issues

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

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

The Center for Devices and Radiological Health (CDRH) review team concluded that the device constituent of Valtoco (a combination product) is approvable for the proposed indication.

The Division of Medication Error Prevention and Analysis (DMEPA) concluded that the results of the human factors validation study report submitted with respect to the use of the proposed drug-device product were adequate. DMEPA also evaluted the proposed label, labeling, and Instructions For Use (IFU); their recommendations were addressed in negotiations with the applicant.

The Office of Scientific Investigation (OSI) was consulted for inspections of the clinical and analytical sites for the pivotal relative bioavailability study (Study 03). Given the records of a recent previous inspection of these study sites, OSI concluded that another inspection was not required.

The Controlled Substance Staff (CSS) review recommends approval of this application, noting that diazepam is 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/

PHILIP H SHERIDAN
01/10/2020 11:19:21 AM

NICHOLAS A KOZAUER
01/10/2020 11:31:55 AM