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Brian J. Malkin
Counsel
202.857.6240 DIRECT
202.857.6395 FAX
brian.malkin@arentfox.com

VIA ELECTRONIC DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION AND PETITION FOR STAY OF ACTION

Arent Fox LLP submits this 505(q) petition on behalf of Aquestive Therapeutics, Inc. ("Aquestive") under the Federal Food, Drug and Cosmetic Act, § 505, Chapter V, Subchapter B (known as the "Orphan Drug Act"), and related regulations 21 C.F.R. Parts 314, 316 and §§ 10.30, 10.31 and associated provisions. Aquestive requests that the Commissioner of Food and Drugs (the "Commissioner") to stay approval of Neurelis, Inc.'s ("Neurelis's") 505(b)(2) new drug application ("NDA") for Valtoco® (diazepam intranasal solution) until additional clinical studies have been conducted that would allow for adequate labeling as requested in this petition. The additional requested studies include a bridging study comparing Valtoco to Diastat® (diazepam rectal gel, held by Bausch Health US, LLC), in patients taking anti-epileptic drugs demonstrating comparable exposure, and a food effect study for Valtoco in patients. Aquestive also requests that, unless the additional clinical studies demonstrate otherwise, the U.S. Food and Drug Administration (FDA) must determine Valtoco does not offer a major contribution to patient care under the Orphan Drug Act.

The current clinical development program for Valtoco (diazepam intranasal solution) is insufficient to support approval as a 505(b)(2) NDA referencing Diastat (diazepam rectal gel). Neurelis should conduct a bridging study in patients comparing the pharmacokinetics between Valtoco to Diastat consistent with their desired indication. The existing clinical studies for Valtoco demonstrate considerable pharmacokinetic ("PK") variability and do not support the development of robust and adequate labeling for the product.

In addition, FDA should require Neurelis to conduct a food effect study for Valtoco (diazepam intranasal solution) because unlike Diastat, which does not undergo first pass metabolism effect ("GI effect"), Valtoco's nasal drug formulation has the potential for swallowing if not fully absorbed in the nasal cavity. Moreover, Valtoco has a curiously-delayed T_{max} up to five times longer than even Valium® (diazepam oral tablets). Neurelis's T_{max} data for Valtoco strongly suggests that, instead of being absorbed from the nasal mucosa, the product is being swallowed and undergoes gastrointestinal absorption. Understanding whether Valtoco has a food-

effect is therefore important for adequate labeling and prescribing considerations for healthcare professionals.

As a related matter, Aquestive requests that the Commissioner determine that Valtoco is not clinically superior to nor offers a "major contribution to patient care" when compared to Diastat primarily, because several critical clinical studies for Valtoco excluded patients with epilepsy who concomitantly suffer from allergies and may present blocked nasal passages. Given that a significant number of potential Valtoco users may also present with allergies and blocked nasal passages, many sufferers may also need to carry Diastat in the absence of Neurelis conducting appropriate bridging studies in nasally-compromised patients; and therefore, Valtoco cannot be considered a major contribution to the patient care. Moreover, Valtoco data appears to show a significantly-delayed T_{max} and a lower C_{max} compared to Diastat. Furthermore, Aquestive requests that the FDA stay approval for Valtoco until these requested actions are taken. Aquestive believes these actions are necessary to ensure patient welfare and would not impact current patient choices for seizure treatment, which include Diastat and Nayzilam® (midazolam nasal spray) for the same indication.

ACTIONS REQUESTED

Aquestive respectfully requests the Commissioner take the following actions:

(1) The FDA should require Neurelis to conduct a bridging study comparing Valtoco to Diastat in patients, demonstrating comparable exposure to support approval of its 505(b)(2) NDA.

(2) The FDA should require Neurelis to conduct a food effect study for Valtoco that will allow for adequate labeling to address the curiously-delayed T_{max} that suggests the product is primarily swallowed and absorbed through the GI tract, not nasally.

(3) The FDA should determine that Valtoco is not clinically superior to nor offers a major contribution to patient care when compared to Diastat.

STATEMENT OF GROUNDS

I. Factual Background

A. Background

During development of Libervant™[1] (buccal oral film) for seizure clusters, Aquestive learned that Neurelis was in the process of developing a nasal diazepam product. Both Libervant and Valtoco have proposed indications for patients with epilepsy who experience bouts of increased seizure activity while on a stable regimen of daily antiepileptic medication(s) (often referred to as "cluster seizures" or acute repetitive seizures ("ARS")). While Aquestive conducted a patient crossover study of Libervant to Diastat to assure an adequate bridge to its reference, as well as food effect studies that will allow for adequate labeling, Neurelis has avoided conducting such studies. Aquestive believes that Neurelis should conduct such studies to fully characterize the risk of Valtoco and assure that adequate labeling be developed that will allow for safe use of the product in its intended patient population.

B. Valtoco

According to Neurelis, Valtoco uses a "unique" Intravail® formulation that "helps overcome common challenges encountered with intranasal administration of benzodiazepines."[2] Neurelis does not elaborate on these "common challenges," but Intravail is purported to provide increased bioavailability, safety (odorless, tasteless, non-toxic, non-mutagenic, and non-irritating), solubility in water and oils, and can be used for a wide range of molecules—presumably these may be some of the challenges encountered.[3] According to one study comparing two intranasal solution formulations for diazepam and midazolam, transient pain was reported for the first 30 minutes and post nasal drainage and watery eyes was reported by all subjects. For both formulations, the mean bioavailability was 50.4 +/- 23.3% compared to intravenous solutions of the same active ingredient with T_{max} at 18 +/- 11 minutes (5 mg dose for both intranasal and IV formulations) in healthy volunteers. These common adverse events coupled with low bioavailability, therefore, may be the "common challenges" Neurelis referenced.[4] Neurelis has also described Intravail as a "permeation enhancer excipient" and further stated that a "vitamin E-based solution" was also included in Valtoco, suggesting that

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[1] Aquestive has received conditional acceptance of the use of this trade name for its buccal diazepam product and is subject to final FDA review and acceptance.
[2] *Our Pipeline, VALTOCO™ (diazepam nasal spray)*, Neurelis, https://www.neurelis.com/our-pipeline/valtoco-nasal-spray (last visited Nov. 1, 2019).
[3] *Our Technologies*, Neurelis, https://www.neurelis.com/our-technologies (last visited Nov. 1, 2019).
[4] *Our Pipeline, VALTOCO™ (diazepam nasal spray)*, Neurelis.

Valtoco's formulation was expected to have better bioavailability, possibly with lower side effects and greater patient tolerability from vitamin E,[5] than this earlier diazepam nasal solution.[6]

C. Clinical Program for Valtoco

Aquestive is aware of three clinical trials that Neurelis has reported in www.ClinicalTrials.gov that appear to include Valtoco, as well as another phase 1 study. Based on Aquestive's analysis of the publicly available information from these studies, Aquestive believes that this clinical program does not provide sufficient information for regulatory review, labeling, and approval.

To date, Neurelis appears to have conducted: (1) two Phase I BA/BE studies in healthy subjects focusing on PK values, (2) one PK and (3) one 12-month safety study in patients with repeat doses. The studies and interim or final result are summarized below:

1) NCT01364558, *A Study of Diazepam After Intranasal and Intravenous Administration by Healthy Volunteers*[7] ("the '558 study"). This study was first posted June 2011 with last update June 2014.

   - Suresh K. Agarwal et al., *A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers*, 105 Epilepsy Research 362, 362-67 (2013), Exhibit 1.
   - Phase 1: 24 healthy subjects, open-label, 3-way crossover, 10 mg doses of two investigational intranasal formulations (suspension and solution (identified by Lubrizol as Valtoco), both supplied by Neurelis) (Valtoco is described by Lubrizol as a solubilized diazepam using a "benign vehicle that is compatible with nasal

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[5] *Neurelis News, Neurelis Announces Two Poster Presentations At The Annual Meeting Of The American Academy of Neurology*, Neurelis (Apr. 29, 2019), https://www.neurelis.com/neurelis-announces-two-poster-presentations-annual-meeting-american-academy-neurology; Ursula Pieper-Fürst et al., *Alpha-tocopherol acetate nasal spray in the treatment of pollen-induced allergic rhinitis*, 28 Allergo Journal International 152, 153-54 (2019), https://link.springer.com/article/10.1007/s40629-018-0086-7 (noting that alpha-tocopherol acetate (vitamin E) in a nasal spray forms a protective barrier on the nasal mucosa to help restore natural hydration).

[6] *Neurelis News, Neurelis Announces Completion Of Senior Management Team Buildout To Support The Anticipated Commercial Launch Of Valtoco™*, Neurelis (Apr. 22, 2019), https://www.neurelis.com/neurelis-news/neurelis-announces-completion-senior-management-team-buildout-support-anticipated-commercial-launch.

[7] *See* study results at https://clinicaltrials.gov/ct2/show/results/NCT01364558?intr=diazepam&spons=neurelis&draw=1&rank=1 (last visited Nov. 1, 2019); Press Release, Lubrizol, Proprietary Nasal Delivery Formulation of Diazepam Developed by Particle Sciences' Reaches NDA (Nov. 5, 2018), https://newscenter.lubrizol.com/news-releases/news-release-details/proprietary-nasal-delivery-formulation-diazepam-developed?ID=2375274&c=250972&p=irol-newsArticle ("Press Release, Lubrizol").

delivery" using technology from Particle Sciences, which is a part of Lubrizol.)[8] and a 5 mg IV dose diazepam injectable.

- The study excluded subjects with a known history of severe seasonal or non-seasonal allergies, having nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration.
- Suspension: Mean C_{max} 221 +/- 78.6 ng/mL, mean T_{max} 1.00 hr [0.6-2.0 range], mean $AUC_{(0\text{-inf})}$[9] 5381 +/- 1409 ng·hr/ mL and absolute bioavailability at 67% compared to IV diazepam v. Solution (Valtoco): mean C_{max} 272 +/- 100 ng/mL, mean T_{max} 1.5 hr [0.8-4.0 hr range], AUC 7338 +/- 2072 ng h/mL and absolute bioavailability at 97% compared to IV diazepam with AUC 4104 +/- 1318 ng h/mL. [Note: Since the doses of intranasal and IV were different, these values are dose-normalized.]

2) Robert E. Hogan et al., *Bioavailability and Safety of NRL-1 (Diazepam Intranasal Solution) Compared to Oral and Rectal Diazepam* ("the Hogan study").[10] Robert E. Hogan et al., *Bioavailability and Safety of Valtoco™ (diazepam intranasal solution) Compared to Oral and Rectal Diazepam*, Exhibit 2.

- Phase 1: 48 healthy subjects / 44 completed
- The study excluded subjects if contraindicated for diazepam or other "typical" reasons for Phase 1 studies (listed reasons included comorbid diseases and concomitant medications, or unlikely to adhere to study practice).
- Single-dose, three treatments, three periods comparing Valtoco to Diastat and Valtoco to oral diazepam tablets (Valium®).
- Based on the poster, calculated Valtoco bioavailability relative to oral diazepam (using $AUC_{(0\text{-inf})}$ and normalizing for dose): 56% for low weight group (51-75 kg) (15 mg dose) and 51% for the high weight group (76-111 kg) (20 mg dose). Calculated Diastat bioavailability relative to diazepam IV solution: 80% for the low weight group and 50% for the high weight group. Since oral diazepam cannot be more bioavailable than IV diazepam, this result demonstrates that the bioavailability observed in this study is far lower than the 97% bioavailability for the solution formulation reported in the '558 study (both healthy subjects). The Diastat bioavailability and C_{max} reported here are lower than in the labeling, which

[8] *See* Press Release, Lubrizol.
[9] AUC is Area Under the Curve, the definite integral in a plot of drug concentration in blood plasma versus time, i.e., total drug exposure over a period of time.
[10] *See Annual Meeting Abstracts: View* (2018), https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/500481.

indicates 90% bioavailability to IV diazepam and a C_{max} at 400 ng/mL for a 15 mg dose.[11]

- In this study, C_{max} for Valtoco is lower than Diastat especially in the low weight group, and T_{max} for Valtoco appears to be longer than for Diastat.
- PK chart values from the poster are reproduced below:

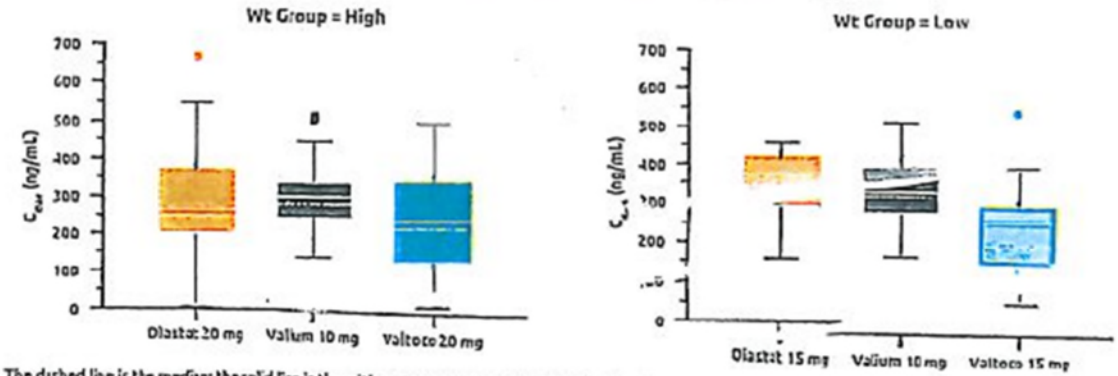
Table 2: Pharmacokinetic Measures

	Valtoco		Diastat		Valium	
	15 mg	20 mg	15 mg	20 mg	10 mg - Low	10 mg - High
C_{max} (ng/mL)						
N	17	28	17	27	17	28
Geometric Mean	225.66	185.53	280.28	163.63	338.36	286.15
CV% Geometric Mean	60	84	109	229	25	30
t_{max} (hr)						
N	17	28	17	27	17	28
Min	0.75	0.5	0.33	0.17	0.33	0.5
Median	1.25	1.25	1.25	1	1	0.75
Max	4	12	8	4	4	2
$AUC_{0-\infty}$ (hr*ng/mL)						
N	17	28	17	27	17	28
Geometric Mean	6999	8069	9953	7855	8268	7850
CV% Geometric Mean	44	81	83	170	31	38

Abbreviations: CV = coefficient of variation, Geo = geometric, Max = maximum, Min = minimum, N = number, NA = not applicable, SD = standard deviation, Wt = weight.

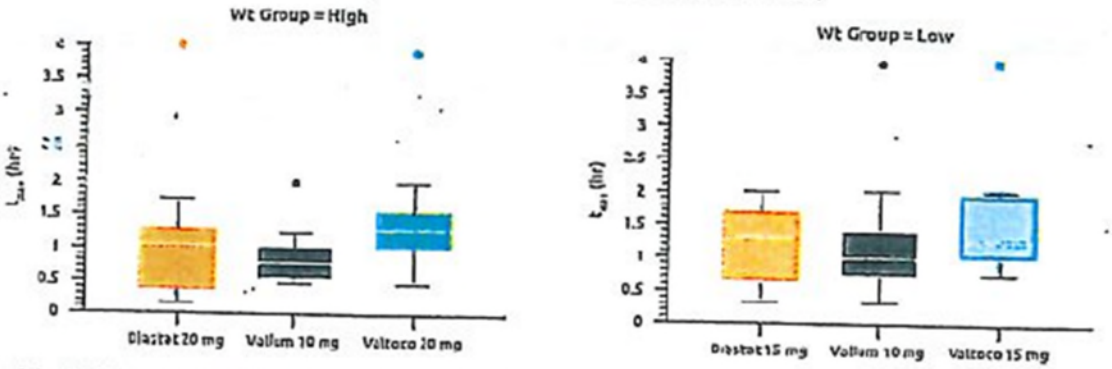
[11] Prescribing Information, Diastat Label, Pharmacokinetics, U.S. Food and Drug Administration at 16, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020648s014lbl.pdf (last visited Nov. 1, 2019) ("Diastat Label").

Figure 4: Comparative Pharmacokinetic Measures: Box plots: C_{max}



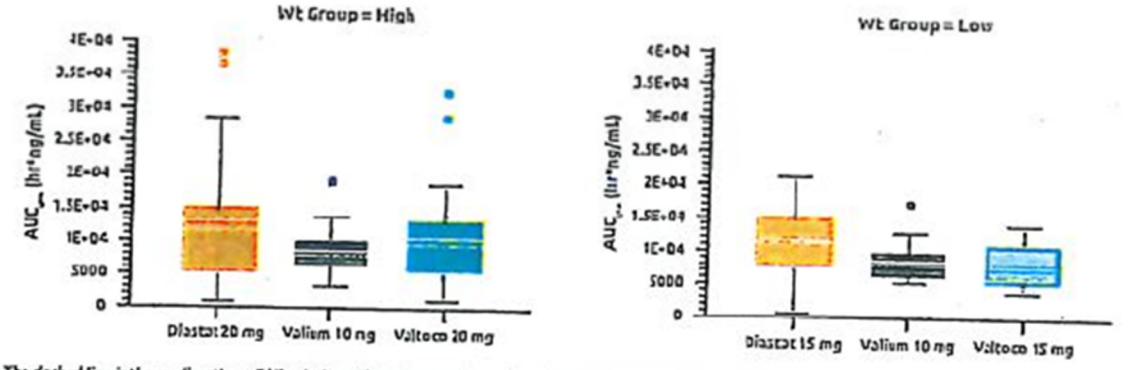
The dashed line is the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles.

Figure 5: Comparative Pharmacokinetic Measures: Box plots: t_{max}



The dashed line is the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. Data values that do not fall between the whiskers are plotted as outliers (markers outside of the whiskers).

Figure 6: Comparative Pharmacokinetic Measures: Box plots: $AUC_{0-\infty}$



The dashed line is the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. Data values that do not fall between the whiskers are plotted as outliers (markers outside of the whiskers).

3) NCT02724423, *Repeat-Dose Pharmacokinetics Study of NRL-1 in Epilepsy Subjects*. ("the '423 study").[12] This study was first posted March 2016 with last update March 2019 (ClinicalTrials.gov has no posted results.). Robert E. Hogan et al., *Pharmacokinetic Study of Valtoco™ (NRL-1; diazepam nasal spray) in Patients with Epilepsy Under Ictal and Inter-ictal Conditions–Interim Report*[13], Exhibit 3.

- 50 patients enrolled (including 10 pediatric)
- The study excluded patients if they had the flu, rhinitis or any other nasal condition that would impact absorption of intranasal diazepam, or if they had used nasal decongestants or nasal steroids within seven days prior to the screening visit or during the study.
- Interim results for 34 patients (including 6 pediatric)
- First dose ictal/periictal (seizure condition) and second dose interictally (non-seizure) with minimum 14-day inter-period interval, reporting, respectively, (mean values and standard error of mean (SEM)) AUC 518 +/- 30 hr·ng/mL v. 566 +/- 33 hr·ng/mL and C_{max} 156 +/- 17 ng/mL (ictal/peri-ictal) v. 179 +/- 18 ng/mL, T_{max} 3.31 +/- 2.10 hr v. 2.79 +/- 1.89 hr [15 mg or 20 mg adult dose based on weight]. When standard error of the mean (SEM) is converted to standard deviation, the coefficient of variation (CV) is ~60% for C_{max} and 34% for $AUC_{(0\text{-}6\ hr)}$.
- Poster Fig. 3 shows 25% of the non-seizure patients had a C_{max} less than 80 ng/mL and 25% seizure patients had a C_{max} less than 100 ng/mL. The generally accepted value for a therapeutic concentration of diazepam for ARS is 120-130 ng/mL. Thus, it appears that a substantial portion of subjects did not reach a therapeutic level for diazepam, leading to a lack of efficacy and possible repeat doses or overdoses.[14]
- The poster reporting the interim results does not provide $AUC_{(0\text{-}inf),}$ because sampling went out only to 6 hours (i.e., partial AUC values). However, geometric mean C_{max} values were reported as 145 ng/mL and 127 ng/mL in the non-seizure and seizure state, respectively, which is lower than what was reported for healthy subjects (the '558 reported C_{max} at 272 ng/mL (10 mg dose) and the Hogan study reported C_{max} at 225.66 ng/mL (15 mg dose) and 185 ng/mL (20 mg dose)).

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[12] *See* study results at https://clinicaltrials.gov/ct2/show/NCT02724423 (last visited Nov. 1, 2019).
[13] Robert E. Hogan et al., *Pharmacokinetic Study of Valtoco™ (NRL-1; diazepam nasal spray) in Patients with Epilepsy Under Ictal and Inter-ictal Conditions–Interim Report (P3.5-009)*, 92 (15 Supplement) Neurology (2019) (Article reporting interim results), https://n.neurology.org/content/92/15_Supplement/P3.5-009.
[14] *See* Ashish Dhir et al., *Determination of minimal steady-state plasma level of diazepam causing seizure threshold elevation in rats*, 59 Epilepsia 935 (2018), https://onlinelibrary.wiley.com/doi/epdf/10.1111/epi.14069 (providing an estimate of the minimum diazepam plasma level under steady-state conditions to elevate the anti-seizure effects between 120-130 ng/mL) ("Dhir et al.").

4) NCT02721069, *Repeat Dose Safety Study of NRL-1 in Epilepsy Subjects* ("the '069 study"). This study was first posted March 2016 with last update August 2018.[15]

- Interim results of this study were reported in an abstract and poster.[16]
- Long-term (12-month) safety study in 121 patients with 109 reported in interim analysis (14 <12 years old) / 1,585 seizure episodes each 1 to > 40 doses.
- Unlike the '558 study and the '423 study, this study did not appear to exclude patients if they had a history or current nasal obstructions or congestion that may impact nasal absorption.
- Single dose was reported as "adequate" for seizure control for 92% (1,457 seizure episodes) with no further information, but no PK data was reported. Because "adequate" is uncontrolled and not explained, such results appear meaningless.
- Adverse events – 7 patients, 6.45 % had nasal discomfort.

II. Discussion

Aquestive's review of these studies indicate that:

- Valtoco has a delayed T_{max} of 2.79 or 3.31 hours in patients with bioavailability closer to 50%, based on the 2018 poster results calculated at 56% for low weight group (51-75 kg) (15 mg dose) and 51% for the high weight group (76-111 kg) (20 mg dose). Since a diazepam tablet (Valium) cannot be more bioavailable than IV diazepam, this means that the absolute bioavailability of Valtoco is therefore lower than these values and nowhere near the 97% absolute bioavailability claimed in the '558 study. Valtoco, therefore, is more likely closer to the 50.4% bioavailability determined in the earlier midazolam and diazepam intranasal study that compared similar dosed intranasal diazepam formulations to IV.[17]
- Perhaps more importantly for a drug used for ARS and seizure control is Valtoco's patient-data mean T_{max} of 2.79 or 3.31 hours, which is not consistent with what would be expected for an intranasal formulation (i.e., T_{max} less than 20 minutes) and is more delayed than Diastat and oral Valium, which are both reported at a median 1.5 hours (Valium has a delayed Tmax of 2.5 hours in the

[15] *See* study results at https://clinicaltrials.gov/ct2/show/NCT02721069 (last visited Nov. 1, 2019).
[16] Michael Sperling et al., *Abstract, A 12-month, open-label, repeat-dose safety study of Valtoco™ (NRL-1, diazepam nasal spray) in patients with epilepsy: Interim report (P1.5-028)*, 92 (15 Supplement) Neurology (2019) (presented at the 2019 American Academy of Neurology meeting), https://n.neurology.org/content/92/15_Supplement/P1.5-028.
[17] *See* V.D. Ivaturi et al., *Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers*, 120 Acta Neurologica Scandinavica 353, 356 (2009) https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1600-0404.2009.01170.x ("Ivaturi et al.").

presence of food.).[18] Valtoco's C_{max} is also low in relation to Diastat in patients, which is 375 ng/mL at 45 minutes with a second peak of 400 ng/mL at 70 minutes, versus Valtoco's C_{max} of 180 ng/mL or less (mean value) (and even less when reported as a geometric mean at 145 ng/mL (non-seizure) and 125 ng/mL (seizure) in the '423 study. Diastat reaches a therapeutic 120-130 ng/mL diazepam concentration between 20-25 minutes.[19]

- Two of the four studies, the '558 study (healthy subjects/intranasal solutions compared to IV diazepam) and the '423 study (repeat dose Valtoco in patients) both expressly excluded nasally-compromised patients; it is unclear if the Hogan study included a similar restriction, and the '069 study did not appear to include a similar restriction. Nasal spray formulations are limited by the small capacity/volume for the nasal cavity (approximately 200 µL per adult nostril), which may be lost due to respiration or swallowing drug product or reduced due to mucus congestion.[20]
- The combination of a delayed T_{max} with a lower C_{max} to Diastat and the possibility for nasal congestion or obstructions to further restrict drug delivery makes Valtoco a poor choice as a rescue medication and not a major contribution to patient care for treating seizure clusters or ARS, when Diastat and Nayzilam are already available for the same indication.

Given this data, Valtoco's nasal spray diazepam requires additional clinical testing to support its proposed use for cluster seizures or ARS. Valtoco's clinical data thus far demonstrates a delayed T_{max} and low C_{max} compared with Diastat. Neurelis has not conducted sufficient bridging studies in patients comparing Valtoco with Diastat to overcome this data. Moreover, Neurelis has not conducted a food effect study, the results of which should inform adequate product labeling, because the curiously-delayed T_{max} suggests that drug product is primarily swallowed and absorbed through the GI tract.[21] Finally, Valtoco is not clinically

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[18] Both nasal formulations had bioavailability from 50.4 +/- 23.3% with T_{max} at 18 +/- 11 minutes. *See* Ivaturi et al., at 356; Diastat Label at 2 (Diastat's T_{max} is 1.5 hours with 90% bioavailability compared to diazepam IV, reporting 62% responders compared to 20% placebo); and Prescribing Information, VALIUM® (DIAZEPAM) Label, U.S. Food and Drug Administration at 2, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/013263s094lbl.pdf (last visited Nov. 1, 2019) (Valium (diazepam tablets) tablets reaches C_{max} at an average of 1-1.5 hours with a range from 0.25 to 2.5 hours with a food effect showing an average time of 1.25 fasted compared to 2.5 hours fed) ("VALIUM® (DIAZEPAM) Label")

[19] Diastat Label at 2-3 (Figure 1: Plasma Concentrations of Diazepam and Desmethyldiazepam Following Diastat or IV Diazepam).

[20] *See* Mark Anderson, *Buccal midazolam for pediatric convulsive seizures: efficacy, safety, and patient acceptability*, 7 Patient Preference and Adherence 27, 28 (2013), Exhibit 4 ("Anderson").

[21] A review of the ClinicalTrials.gov website, which is supposed to list all clinical studies conducted in the US and worldwide failed to locate a crossover study for Valtoco (also referenced as "NRL-1" compared to Diastat or a food effect study conducted for Valtoco. *See, e.g.*, search results available at:

superior to nor offers a major contribution to patient care when compared to Diastat, because Valtoco has limited utility in patients with epilepsy who may concomitantly suffer from allergies or are otherwise nasally compromised, and will therefore still need to carry Diastat.

A. The FDA Should Require Neurelis to a Study Bridging Valtoco to Diastat in Patients, Demonstrating Comparable Exposure to Support its 505(b)(2) NDA.

Neurelis filed a 505(b)(2) NDA for Valtoco in 2018 referencing Diastat but has not conducted appropriate bridging studies in patients sufficient to support approval. If a product is pharmaceutically equivalent but not bioequivalent, the FDA said it would be appropriate to file a 505(b)(2) if:

1. The proposed product is at least as bioavailable as the approved pharmaceutically equivalent product (unless it has some other advantage, such as a smaller peak/trough ratio); or

2. The pattern of release of the proposed product, although different, is at least as favorable as the approved pharmaceutically equivalent product. [22]

When it comes to nasal absorption, a key factor for whether the drug will have rapid or poor transport across the nasal membrane is whether the drug is lipophilic or polar. With lipophilic drugs, including diazepam and all other benzodiazepines, nasal penetration is rapid and efficient with similar PK values to those obtained with IV injection (i.e., 1-5 minutes) with bioavailabilities approaching 100%.[23] For a nasal formulation containing diazepam, therefore, a rapid absorption and bioavailability (i.e., T_{max} less than 20 minutes) and bioavailability approaching IV injection (i.e., near 100%) would be expected, as was seen at least with Nayzilam's T_{max} (median T_{max} = 17.3 minutes)[24] and earlier studies with nasal solutions for midazolam and diazepam with mean T_{max} at 18 minutes.[25] Neurelis's marketing suggests that its

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https://www.clinicaltrials.gov/ct2/show/NCT01364558?intr=diazepam&spons=neurelis&rank=1 (None of Neurelis's three clinical studies compared Valtoco to Diastat in patients nor involved a food effect study element.).

[22] FDA Guidance for Industry: Applications Covered by Section 505(b)(2), at 5-6 (Oct. 1999), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applications-covered-section-505b2.

[23] Lisbeth Illum, *Nasal drug delivery: new developments and strategies*, 7 Drug Discovery Today, 1184, 1185 (2002), Exhibit 5 (supports nasal absorption is rapid for lipophilic drugs) ("Illum"); Diazepam, Drugs.com, https://www.drugs.com/monograph/diazepam.html (last visited Nov. 1, 2019) (supports diazepam and benzodiazepines generally are lipophilic and diazepam IV absorption rates are 1-5 minutes).

[24] Prescribing Information, Nayzilam Label, Pharmacokinetics, U.S. Food and Drug Administration at 15, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211321s000lbl.pdf (last visited Nov. 1, 2019) ("Nayzilam Label").

[25] Ivaturi et al., at 356.

Intravail technology, coupled with Lubrizol's Particle Sciences's technology to solubilize diazepam, should provide increased bioavailability, but this is also not supported.[26]

Valtoco's single bridging study—the Hogan study conducted in healthy subjects—not patients—demonstrated significantly delayed T_{max}, indicating bridging studies should be conducted in patients comparing Valtoco to Diastat to rule out whether there are other factors beyond induction resulting in poor bioavailability. As noted above, the FDA has stated that bridging studies may be used in lieu of full safety and efficacy studies for 505(b)(2) NDAs seeking the same indication as the reference drug. According to a press release from Lubrizol, as noted above, the only bridging study conducted by Neurelis demonstrated only 80% bioavailability to Diastat in the low weight group (51-75 kg, 15 mg dose) and only 50% for the high weight group (76-111 kg, 20 mg dose). These data suggest even lower bioavailability compared to IV diazepam, not even close to 97%, calling the '558 study's initial BA/BE data compared to IV diazepam into question. The Hogan study also demonstrated a delayed T_{max} at 1.25 hours for both doses versus Diastat (1.25 hours (15 mg) and 1.0 hours (20 mg)) and Valium tablets (1 hr (15 mg) and 0.75 hr (20 mg)). In addition, the Hogan study's Valtoco C_{max} was lower at both doses with 225.66 ng/mL (15 mg) and 185.53 ng/mL (20 mg) versus Diastat with 280.28 ng/mL (15 mg) and 163.63 ng/mL (20 ng/mL) and lower than Valium tablets at 338.36 ng/mL (low dose) and 285.16 ng/mL (high dose). Because the Valtoco patient C_{max} values in the '423 study were lower than the C_{max} values in healthy subject volunteer studies and not explained, a bridging study in patients comparing Valtoco to Diastat should be performed to ensure that Valtoco and Diastat exposures are the intended sufferer population.

Such abnormal PK values for a nasal diazepam formulation are well below other similar nasal solutions such as Nayzilam and other diazepam nasal solutions whose development programs were subsequently discontinued.[27] The lower C_{max} may be consistent with lower expected bioavailability for such dosage forms, where the tradeoff is usually lower T_{max} values with lower C_{max} values reflecting drug products that are incompletely absorbed through the nasal membranes.[28] Based on the combination of significantly lower bioavailability in healthy subjects compared to Diastat and Valium (the Hogan study) and the significant delay of T_{max} and low C_{max} in patients (the '423 study), Neurelis should be required to conduct PK studies in patients comparing Valtoco to Diastat.

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[26] *Our Pipeline, VALTOCO™ (diazepam nasal spray)*, Neurelis, ("Epilepsy Patients Have Limited On-Hand Rescue Treatment Options"); Press Release, Lubrizol.
[27] *See* Nayzilam Label; Ivaturi et al., at 356; the '558 study (lower bioavailability solution).
[28] Illum at 1186, Exhibit 5 (noting that some nasal dosage forms may still be indicated when absorption is lower because some or most of the product is swallowed but T_{max} is considerably shorter; in this case absorption is lower AND T_{max} is slower).

B. The FDA Should Require Neurelis to Conduct a Food Effect Study for Valtoco and Include Appropriate Labeling to Address its Results, Because the Delayed T_{max} Suggests the Product Is Primarily Swallowed and Absorbed Through the GI Tract.

The FDA should require Neurelis to conduct a food effect study for Valtoco and include appropriate labeling to address its results. In general, food effect studies should be conducted for all orally-administered drug products, regardless of the differences in products compared in a 505(b)(2) NDA.[29] As described in Section II.A above, the Hogan study comparing Valtoco to Diastat in healthy subjects indicated significantly lower bioavailability compared to Diastat (and Valium tablets) than initially suggested by the '558 study, also in healthy subjects. Additionally, Valtoco's studies in patients demonstrated a delayed T_{max} versus expected nasal T_{max} at under 20 minutes or less based on Nayzilam and earlier diazepam and midazolam nasal solutions. And, Valtoco's T_{max} values do not offer any benefit over Diastat's T_{max} at 1.5 hours,[30] or Valium tablet's T_{max} at 1.25 hours (2.5 hours with food, a delayed T_{max} absorption).[31] Valtoco's absorption, therefore, does not match other benzodiazepine nasal solutions, particularly in patients. One likely explanation is that some or a significant portion of Valtoco is swallowed rather than absorbed within the nasal cavity, which a food effect study could determine.[32] Therefore, Neurelis should conduct a food effect study or another comparable study to determine whether some or most of the diazepam from Valtoco is absorbed in the GI tract and include such results in its product labeling.[33]

C. The FDA Should Determine that Valtoco Is Not Clinically Superior to nor Offers a Major Contribution to Patient Care when Compared to Diastat.

The FDA should also conclude that Valtoco is not clinically superior to, or does not provide a major contribution to patient care over, Diastat—the first diazepam orphan drug approved for cluster seizures or ARS. Under the Orphan Drug Act, Food, Drug and Cosmetic Act § 527(c), a second same active ingredient (drug) can obtain orphan drug exclusivity (seven

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[29] *See, e.g.*, Ingrid Freije et al., *Review of Drugs Approved via the 505(b)(2) Pathway: Uncovering Drug Development Trends and Regulatory Requirements*, Therapeutic Innovation & Regulatory Science 1, 5 (2019), https://journals.sagepub.com/doi/full/10.1177/2168479018811889 ("Freije et al.,")

[30] Diastat Label, Pharmacokinetics at 2.

[31] VALIUM® (DIAZEPAM) Label at 2; Ivaturi et al., at 355.

[32] *See, e.g.*, Illum at 1186, Exhibit 5 (indicating that when only a minor part of a nasally-administered formulation is absorbed from the nasal cavity, it may be that the reported bioavailability [and, in the case of Valtoco, delayed T_{max}] is a result of the drug being swallowed).

[33] *See* Freije et al., at 5.

years) for the same orphan indication only if it is clinically superior or provides a major contribution to patient care.

FDA's implemented regulations in 21 C.F.R. § 316.3(b)(3) clarify when a drug is considered "clinically superior" for the purposes of orphan drug exclusivity:

> Clinically superior means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:
>
> (i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or
>
> (ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or
>
> (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

And the FDA clarifies in the preamble to these regulations that, for the purposes of orphan drug exclusivity, "major contribution to patient care" is defined as follows:

> The following factors, when applicable to severe or life-threatening diseases, may in appropriate cases be taken into consideration when determining whether a drug makes a major contribution to patient care: convenient treatment location; duration of treatment; patient comfort; reduced treatment burden; advances in ease and comfort of drug administration; longer periods between doses; and potential for self-administration. FDA declines to add "increased quality of life" to this list because many factors already on the list may be viewed as increasing quality of life, such as increased patient comfort and longer periods between doses. FDA also declines to add "improved patient compliance" to

> the list of factors potentially informing whether a drug provides a major contribution to patient care, because FDA would expect improved patient compliance to be reflected in other factors already on this list (e.g., increased patient comfort, reduced treatment burden, etc.), if not otherwise reflected in greater safety or greater effectiveness showings for the drug.[34]

While Valtoco may offer a more convenient dosage form than Diastat, its limited use in patients with epilepsy who are nasally compromised coupled with a delayed T_{max} and lower C_{max} would make it a poor choice for outpatients with epilepsy experiencing bouts of refractory seizures. Valtoco's expected treatment in sufferers is not a major contribution to patient care, since its C_{max} was subtherapeutic in the '423 study in a substantial number of patients, specifically 25% of the non-seizure patients had C_{max} less than 80 ng/mL and 25% seizure patients had C_{max} less than 100 ng/mL versus a generally-accepted therapeutic level of at least 120-130 ng/mL.[35] In comparison, Diastat reached those therapeutic levels of 120-130 ng/mL within 20-25 minutes and a first T_{max} at 45 minutes (375 ng/mL).[36] If subtherapeutic, Valtoco could require repeat treatments, as is indicated for Nayzilam, if relief is not observed within 10 minutes.[37] At this point it is unknown how long a patient would need to wait until repeat treatment would be indicated for Valtoco, but the need for possible repeat treatments and possible resultant overdoses given the delayed T_{max} also would not be a major contribution to patient care compared to Diastat. Therefore, Valtoco's current formulation does not appear to offer a major contribution to patient care for its indicated use.

Valtoco may also have more limited use when prescribed in nasally-compromised patients.[38] For example, a number of Valtoco clinical studies excluded patients who were nasally compromised, suggesting that its use may be less effective or different for epilepsy patients who are congested or have nasal issues.[39] Without knowing how many healthy subjects in the Hogan study (Valtoco compared to Diastat and Valium tablets) or patients in the '069 study (long-term repeat dose Valtoco), it is difficult to draw conclusions. Nasal spray formulations in general are limited by the small capacity/volume for the nasal cavity (approximately 200 µL per adult nostril), which may be lost due to respiration or swallowing drug product or have reduced

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[34] Orphan Drug Regulations, 78 Fed. Reg. 35,117, 35,125 (June 12, 2013) (codified at 21 C.F.R. pt. 316).
[35] *See* Dhir et al.
[36] *See* Diastat Label, Pharmacokinetics at 3.
[37] *See* Nayzilam Label, Dosage and Administration at 2.
[38] *See, e.g.*, Anderson at 28 (noting that nasal congestion may affect absorption), Exhibit 4.
[39] Specifically for the'558 study (healthy subjects/intranasal solutions compared to IV diazepam) and the '423 study (repeat dose Valtoco in patients), as noted in section I.C. for each Valtoco study and II. Introduction.

absorption due to mucus congestion.[40] Therefore, Valtoco's use for patients with cluster seizures or ARS would be limited if a patient was nasally compromised.

Furthermore, Valtoco's reported 92% efficacy rate (the '069 study) is uncontrolled and meaningless. Such efficacy appears high in view of Diastat's reported efficacy at 62% and Valtoco's delayed T_{max} compared to Diastat. Valtoco's $AUC_{(0\text{-}6h)}$ values and C_{max} for the same respective test conditions are low compared to labeled values for Diastat, further calling into question the uncontrolled and essentially meaningless 92% response rate and the '069 study results.

III. Conclusion

For the reasons cited above, the FDA should require Neurelis to conduct BA/BE studies comparing Valtoco to Diastat in patients and a food effect study. If such BA /BE studies in patients do not support relying on Diastat's safety and efficacy, the FDA should require Neurelis to conduct efficacy studies to support its indication. At a minimum, the FDA should determine that Valtoco is not eligible for orphan drug exclusivity based on the currently available clinical data, because these data do not support a conclusion Valtoco is not clinically superior to, or provides a major contribution to patient care over Diastat.

IV. Environmental Impact

Petitioner claims categorical exclusion under 21 C.F.R. §§ 25.30, 25.31, 25.32, 25.33, or § 25.34 or an environmental assessment under § 25.4.

V. Economic Impact

Economic Impact information will be submitted at the request of the Commissioner.

[40] *See* Anderson at 28, Exhibit 4.

VI. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 17, 2019 (American Epilepsy Foundation Annual Meeting (November 30, 2018), Poster, the Hogan study, reviewed by Aquestive on April 17, 2019); May 4, 2019 (American Academy of Neurology Annual Meeting, Poster, the '423 study); May 17, 2019 (FDA approval, Nayzilam); and August 6, 2019 (Aquestive announces topline results from Libervant crossover study comparing Libervant to Diastat). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Aquestive. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

Brian J. Malkin, Esq.
Arent Fox LLP
1717 K Street NW
Washington, DC 20006-5344
(202) 857-6240
brian.malkin@arentfox.com