U.S. FOOD & DRUG ADMINISTRATION

JAN 10 2020

Brian J. Malkin, Esq.
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Washington, DC 20006-5344

Re: Docket No. FDA-2019-P-5121

Dear Mr. Malkin:

This letter responds to your citizen petition received on November 1, 2019 (Petition), requesting that the Food and Drug Administration (FDA, the Agency, or we) deny approval of a new drug application (NDA) for Valtoco (diazepam nasal spray)[1] submitted by Neurelis, Inc. (Neurelis), until additional clinical studies are conducted. The Petition further requests that FDA determine that Valtoco is not eligible for orphan-drug exclusivity. Specifically, the Petition requests that FDA 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 Tmax 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.

Petition at 2.[2]

You also submitted a supplement to the citizen petition received on December 4, 2019 (Supplement), requesting that FDA take the following actions:

1) The FDA should require Neurelis to reformulate Valtoco to remove vitamin E or conduct a study to determine whether the vitamin E-containing nanoparticles in Valtoco's nasal

[1] Today, we have approved NDA 211635 for Valtoco (diazepam nasal spray).

[2] The Petition asks FDA "to stay approval" of the NDA for Valtoco (Petition at 1). A request that an administrative action be stayed must be submitted in accordance with 21 CFR 10.20 and in the form specified in 21 CFR 10.35. Because the Petition was not otherwise styled as a petition for stay of action, and because NDA 211635 was still pending when the Petition was submitted, we have interpreted your Petition as asking FDA to refuse to approve Valtoco unless the bridging study and food effect study described in your petition are submitted and support approval.

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spray are of respirable size and, therefore, whether they have the potential to reach the alveoli of an indicated patient's lungs.

2) If Valtoco's vitamin E has the potential to reach the alveoli of an indicated patient's lungs, the FDA further should require Neurelis to quantify the amount reaching the alveoli, as well as the potential for its vitamin E to affect normal lung functioning in all indicated age groups by interfering with pulmonary surfactant.

3) The FDA should require Neurelis to include appropriate labeling for Valtoco based on the above-requested studies, given the concern for vitamin E and its effects on an individual's lungs when inhaled in an aerosolized form.

Supplement at 2.[3]

We have carefully considered your Petition, the Supplement, comments submitted to the Docket, and other information available to the Agency. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Valtoco

[3] Neurelis urges FDA to summarily deny this Petition, characterizing it as, among other things, an "ill-disguised attempt to delay approval of a competing product." Neurelis Comment at 3 (Nov. 22, 2019). According to Neurelis, the timing of the submission of the Petition in November 2019, "shortly before an expected FDA determination on the [Valtoco NDA]," warrants "summary denial consistent with the applicable statute and FDA guidance" because, among other things, the Petition appears to be based on "Neurelis's public disclosure of interim data . . . at various points from 2016 to 2018." Id. In its second comment, Neurelis also points out "Aquestive's complete lack of . . . care in researching and constructing its supplemental argument," and asserts that the deposition of nasally administered sprays is well characterized and understood, and published literature contradicts Aquestive's argument regarding the potential introduction of Vitamin E into the lungs. Neurelis Comment at 1-2 (Dec. 5, 2019).

"Submission of a petition close in time to a known, first date upon which . . . a 505(b)(2) application . . . could be approved" is one of the factors that may suggest that a Petition was submitted for the primary purpose of delaying approval of that application. FDA's guidance for industry, *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, at 16 (September 2019). We agree that this appears to be the case here. In addition, we agree with Neurelis that there is publicly available information on the general characteristics of nasal spray products that would show it is unlikely that droplets generated by a nasal spray product would reach the alveoli of the lungs, and that such information was not included or cited in the Supplement. "Submission of a petition with little or no data or information in support of the scientific positions set forth in the petition" is another factor that may suggest that a petition was submitted with the primary purpose of delaying approval. Id. At the same time, section 505(q)(1)(E) of the FD&C Act allows summary denial of a petition that was submitted with the primary purpose of delay *and* does not on its face raise valid scientific or regulatory issues. Because we are unable to conclude that the petition does not, on its face, raise valid scientific or regulatory issues, the conditions for summary denial under the FD&C Act are not met. Thus, though we agree with Neurelis that there appears to be at least some grounds to surmise that the Petition was submitted with the primary purpose of delaying the approval of Valtoco, we are unable to summarily deny it.

Valtoco's NDA was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). It proposed, among other things, a new dosage form (nasal spray) and new route of administration (intranasal) compared to the listed drug (LD) relied upon, Diastat (diazepam rectal gel) (NDA 20648). The 505(b)(2) NDA for Valtoco relied on the Agency's previous findings of safety and effectiveness for Diastat.

Valtoco is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures (ARS)) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older. Valtoco is a nonaqueous solution for intranasal administration available in 5 milligrams (mg), 7.5 mg, or 10 mg in 100 microliters (μL) of solution. The 15 mg and 20 mg doses may be administered by using two 7.5 mg or 10 mg unit dose devices, respectively. A second dose may be given, as needed, 4 to 12 hours after the first dose. Although the exact mechanism of action for diazepam is not fully understood, it is thought to involve potentiation of gamma-aminobutyric acid (GABA) neurotransmission (i.e., affecting the neurotransmitter GABA) resulting from binding at the benzodiazepine site of the GABAA (γ-aminobuyric acid type A) receptor. GABA, the major inhibitory neurotransmitter in the central nervous system, acts at this receptor to open the membrane channel allowing chloride ions to flow into neurons. Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials.

On October 9, 2012, and prior to the submission of the 505(b)(2) NDA, FDA received a request from Neurelis for orphan-drug designation for Valtoco for the management of ARS.[4] Because the active moiety diazepam had already been approved for management of ARS under the brand name Diastat, in order to be eligible for orphan-drug designation, Neurelis had to provide a plausible hypothesis supporting that its product is clinically superior to Diastat for management of ARS.[5] On November 16, 2015, FDA granted Neurelis orphan-drug designation for intranasal diazepam for "management of ARS" based on a plausible hypothesis that Neurelis's product's route of administration may provide a major contribution to patient care compared to Diastat's.

B. 505(b)(2) NDAs

Section 505(b)(2) of the FD&C Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments). Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c). As such, it must satisfy the same statutory requirements for safety and effectiveness as a stand-alone NDA. For a 505(b)(2) NDA, however, some of the information required for approval comes from studies not conducted by or for the applicant and

[4] The designation request initially asked for designation for "management of selected patients with refractory epilepsy, on stable regimens of antiepileptic drugs (AEDs), who require intermittent use of diazepam to control bouts of increased seizure activity." FDA subsequently determined that this described a distinct disease called ARS.

[5] 21 CFR 316.20(a) ("a sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug.").

for which the applicant has not obtained a right of reference or use.[6] For instance, a 505(b)(2) NDA may rely on FDA's previous finding that a listed drug is safe and effective as evidence in support of the proposed product's safety and effectiveness.

A 505(b)(2) NDA can describe a drug with differences from the listed drug it references.[7] These differences may include, for example, a different active ingredient or a new indication, dosage form, strength, formulation, and/or route of administration.[8] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a listed drug, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant is expected to establish a bridge[9] between its proposed product and the listed drug by submitting, for example, a study that measures the relative bioavailability[10] of the two products or other appropriate scientific information. An acceptable scientific bridge enables the applicant to rely on the Agency's previous finding of safety and effectiveness for the listed drug. To the extent that the listed drug and the drug proposed in the 505(b)(2) NDA differ, the 505(b)(2) NDA must include sufficient data to support these differences.[11]

C. Orphan-Drug Exclusivity and Clinical Superiority

Congress enacted the Orphan Drug Act[12] in 1983 to provide incentives for the development of drugs for rare diseases or conditions that would presumably not otherwise be developed due to the small patient population and an assumed lack of profitability of such drugs. Section 526 of the FD&C Act defines a "rare disease or condition," in part, as any disease or condition that

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[6] Specifically, section 505(b)(2) of the FD&C Act contemplates:

> An application [may be] submitted under [section 505(b)(1)] for a drug for which the [safety and effectiveness] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

[7] See, e.g., FDA's draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[8] There is no statutory requirement for a 505(b)(2) applicant to demonstrate bioequivalence of its proposed product to another product. A drug product in a 505(b)(2) application may not necessarily be bioequivalent, pharmaceutically equivalent, and/or therapeutically equivalent to the listed drug relied upon.

[9] A *bridge* in a 505(b)(2) NDA is information to demonstrate sufficient similarity between the proposed product and the listed drug to justify reliance scientifically on certain existing information for approval of the 505(b)(2) NDA.

[10] "Bioavailability" means "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action." 21 CFR 314.3; see also 21 CFR 320.1. Bioavailability data provide an estimate of the fraction of the drug absorbed, as well as provide information related to the pharmacokinetics of the drug. See, e.g., FDA's draft guidance for industry *Bioavailability Studies Submitted in NDAs or INDs—General Considerations* (February 2019). When final, this guidance will represent FDA's current thinking on this topic.

[11] 21 CFR 314.54(a).

[12] Pub. L. No. 97-414, 96 Stat. 2049 (1983).

affects less than 200,000 persons in the United States.[13] To be eligible to receive orphan-drug designation incentives, the sponsor of a drug must request orphan-drug designation for a rare disease or condition under section 526 of the FD&C Act, and FDA must grant the orphan-drug designation. FDA's regulations at 21 CFR part 316 lay out the requirements for an orphan-drug designation submission.[14] Once designated, an orphan-drug becomes eligible for certain incentives, including tax credits for qualified clinical testing, exemption from the application user fee, and, potentially, orphan-drug exclusivity.

Clinical superiority is evaluated at both the designation and drug approval phase, and has implications for both orphan-drug designation and exclusivity where a drug containing the same active moiety[15] for the same use or indication has already been approved. A sponsor may obtain orphan-drug designation for a drug that has the same active moiety as a drug already approved for the same rare disease or condition if the sponsor submits (and FDA accepts) a plausible hypothesis that its drug may be clinically superior to the previously approved drug.[16] When FDA approves a drug product that has the same active moiety as a drug product already approved for the same use or indication, the newly approved drug product may be eligible for orphan-drug exclusivity if the sponsor can demonstrate that its product is clinically superior to every previously approved drug product that contains the same active moiety for the same use or indication.[17]

Section 527 of the FD&C Act defines "clinically superior" to mean "the drug provides a significant therapeutic advantage over and above an already approved or licensed drug in terms of greater efficacy, greater safety, or by providing a major contribution to patient care."[18] The orphan-drug regulations elaborate on the definition of "clinically superior" as follows:

> *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:
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> (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
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> (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

[13] See section 526(a)(2) of the FD&C Act.

[14] See 21 CFR 316.20-21.

[15] See 21 CFR 316.3(b)(14) for the definition of *same drug*; see also 21 CFR 316.3(b)(2) for the definition of *active* moiety.

[16] 21 CFR 316.20(a); see also 21 CFR 316.20(b)(5).

[17] See section 527(c)(1) of the FD&C Act and 21 CFR 316.34(c).

[18] Section 527(c)(2) of the FD&C Act.

> 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.[19]

Because of the diverse ways in which drugs may qualify as clinically superior under these criteria, FDA evaluates clinical superiority on a case by case basis.[20] Specifically, with respect to the major contribution to patient care prong of the clinical superiority definition, the Agency has stated:

> There is no way to quantify such superiority in a general way. The amount and kind of superiority needed would vary depending on many factors, including the nature and severity of the disease or condition, the quality of the evidence presented, and diverse other factors;[21]

and:

> 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.[22]

II. DISCUSSION

A. An Additional Bridging Study in Patients Is Not Necessary

The Petition asserts that the clinical studies supporting Valtoco's 505(b)(2) NDA "demonstrated significantly delayed T_{max}"[23] and that Valtoco has "abnormal [pharmacokinetic (PK)] values for a nasal diazepam formulation" (Petition at 12). The Petition further states that "[t]he 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,

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[19] 21 CFR 316.3(b)(3).

[20] See FDA's "Orphan Drug Regulations" proposed rule (56 FR 3338, 3340, January 29, 1991) (1991 Proposed Rule) ("The content of this evidence [needed for a demonstration of clinical superiority] will depend on the nature of the superiority claimed."); see also FDA's "Orphan Drug Regulations" final rule (57 FR 62076, 62079, December 29, 1992) (rejecting a comment which challenged the clinical superiority concept as insufficiently clear).

[21] Id. at 62078.

[22] See "Orphan Drug Regulations" final rule, 78 FR 35117, 35125 (June 12, 2013).

[23] T_{max} refers to the time at which maximum drug concentration is reached in an area of the body (e.g., in plasma) following administration of one dose.

20 mg dose)" and suggests that as a result of this study, an additional bridging study in patients is necessary (Petition at 12). We do not agree that an additional bridging study in patients is necessary.

To establish a bridge, a 505(b)(2) applicant may conduct a relative bioavailability study between the proposed drug and the listed drug relied upon. A relative bioavailability study measures the rate and extent of absorption of the proposed drug compared to the listed drug. Generally, a relative bioavailability study is conducted in healthy volunteers to provide a sensitive measure of differences in the exposures of the drugs.[24] The relevant pharmacokinetic parameters calculated from these data include the area under the concentration-time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$). This parameter represents the extent of absorption (i.e., how much of the drug in the given dose was absorbed). The other relevant pharmacokinetic parameters are the maximum or peak drug concentration (C_{max}) and the time required to reach the peak drug concentration after administration (T_{max}), which reflect the rate of absorption.

Neurelis conducted Study DIAZ.001.03,[25] a relative bioavailability study in healthy subjects, to establish the bridge from its proposed product, Valtoco (diazepam nasal spray) to the relied upon listed drug, Diastat (diazepam rectal gel). In this study, the applicant compared the relative bioavailability of diazepam following administration of Valtoco and Diastat (LD) in healthy volunteers under fasted conditions.[26] Body weight-based dosing was taken into consideration per Diastat prescribing information for the 15 and 20 mg cohorts. The labeling for Diastat addresses body weight dosing and recommends "acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose."[27] This labeling statement reflects the variability of Diastat. Contrary to the assertions in the Petition[28] and given Diastat's wide pharmacokinetic variability, when the same diazepam dose for Valtoco and Diastat is administered based on body weight, the AUC and C_{max} values for

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[24] See, e.g., FDA's draft guidance for industry *Bioavailability Studies Submitted in NDAs or INDs—General Considerations* (February 2019) ("In general, BA studies should be conducted in healthy subjects 18 years of age or older who are capable of giving informed consent."). When final, this guidance will represent FDA's current thinking on this topic.

[25] The Petition refers to the studies conducted by Neurelis as "the '558 study," "the Hogan study," "the '423 study," and "the '069 study." Because the NDA refers to these studies differently, in this letter, we will refer to the study names used in the NDA. For ease of reference the '558 study will be referenced as DIAZ.001.01, the Hogan study will be referenced as DIAZ.001.03, the '423 study will be referenced as DIAZ.001.04, and the '069 study will be referenced as DIAZ.001.05.

[26] This study was a randomized, single-center, single-dose, three-treatment, three-period, six-sequence, crossover study comparing the relative bioavailability of Valtoco to Diastat and Valium in 48 healthy adult male and female subjects. Valtoco and Diastat were dosed by weight categories with subjects 51 to 75 kg of weight receiving 15 mg of diazepam and subjects 76 to 111 kg of weight receiving 20 mg of diazepam. Dosing in the Valium (diazepam tablets) arm was 10 mg as an internal reference.

[27] See Diastat (diazepam rectal gel) labeling (December 16, 2016), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020648s014lbl.pdf.

[28] See, e.g., Petition at 12.

Valtoco were comparable to those for Diastat. For example, in the 20 mg dose cohort, the mean relative bioavailability of diazepam from Valtoco was approximately 118% for C_{max} and 100% for $AUC_{0-\infty}$ compared to those from Diastat. The confidence intervals for both C_{max} and AUC were very wide due to the large variability in diazepam PK in this study, and more generally, as reflected in Diastat's labeling statement acknowledging that patients will receive between 90 percent and 180 percent of the calculated recommended dose. Also, the range of diazepam pharmacokinetic parameters for individual subjects following Valtoco administration was well within the range (minimum to maximum) of pharmacokinetic parameters seen with individual subjects given Diastat in Study DIAZ.001.03. The intersubject variability for Diastat's bioavailability was much greater than the variability of Valtoco. For the 15 mg dose cohort, the mean relative bioavailability of diazepam from Valtoco was approximately 85% for C_{max} and 74% for $AUC_{0-\infty}$ when compared to Diastat. The $AUC_{0-\infty}$ values at the 15 mg dose for Valtoco were slightly lower than that of Diastat, compared to FDA's general bioequivalence criteria of 80-125%. The lower AUC values may have been skewed due to the small population size studied for the 15 mg group (n=17). We found these lower values to be less concerning given that the diazepam pharmacokinetic parameters were less variable for Valtoco (2 to 4-fold lower) and well within the range of those seen with Diastat for individual subjects. Moreover, the median T_{max} was 1.25 hours following Valtoco 15 mg and 20 mg administration.[29] This is comparable to a median T_{max} of 1 and 1.25 hours for Diastat 15 mg and 20 mg. FDA determined that the pharmacokinetic data from Study DIAZ.001.03 demonstrated comparable C_{max}, $AUC_{0-\infty}$, and T_{max} values between Valtoco and Diastat. FDA concluded that this comparable pharmacokinetic data in healthy subjects was adequate to establish a bridge between Valtoco and Diastat, therefore justifying reliance on FDA's finding of safety and effectiveness for Diastat.

Neurelis conducted several other bioavailability studies to support and characterize the pharmacokinetic profile of Valtoco. For instance, Neurelis conducted an absolute bioavailability study, Study DIAZ.001.01, that assessed the pharmacokinetics of diazepam after administration of Valtoco and intravenous (IV) diazepam to healthy volunteers under fasted conditions.[30] The study demonstrated that diazepam was extensively absorbed after intranasal administration of Valtoco with an absolute bioavailability of 97% and a median T_{max} of 1.5 hours.

The Petition rejects the finding in Study DIAZ.001.01 that the absolute bioavailability for Valtoco is 97% (see Petition at 5). The Petition instead, uses information from "the poster" submitted as an attachment to the Petition, in an attempt to calculate Valtoco's bioavailability using data on Valium and diazepam IV solution to conclude that "[s]ince 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 . . ." (Petition at 5). This conclusion is flawed because it is not based on source data found in the NDA, and the Petition's assertions are unsupported. The Petition further hypothesizes that the bioavailability of Valtoco "is more likely

[29] We note that FDA considers T_{max} when evaluating the comparative bioavailability of two drug products but does not analyze T_{max} using the statistical parameters for C_{max} and AUC.

[30] This study was an open-label, randomized, three-treatment, three-period, six-sequence crossover study of 24 healthy subjects assessing the pharmacokinetics of diazepam after administration of Valtoco, IV diazepam, and an earlier suspension formulation of Valtoco.

closer to the 50.4% bioavailability determined in the earlier midazolam and diazepam intranasal study that compared similar dosed intranasal diazepam formulations to IV" (Petition at 9).[31] The results of Neurelis's Study DIAZ.001.01 do not support the Petition's claim. Moreover, the literature the Petition cited does not describe the intranasal diazepam formulation, and therefore we do not know if the study was conducted with Valtoco. We further question the validity of the study results because of the small sample size (n=3) used.

We reject the Petition's claim that Valtoco has a mean T_{max} of 2.79 or 3.31 hours in patients (Petition at 9). The Petitioner extrapolates from abbreviated information found in "the 2018 poster results" and not on the full data submitted to FDA as part of Neurelis's 505(b)(2) application. Notably, the 2018 poster does not state that the mean T_{max} for Valtoco is 2.79 or 3.31 hours. As explained above, the applicant's relative bioavailability study, Study DIAZ.001.03, showed that T_{max} was 1.25 hours following 15 mg and 20 mg administration of Valtoco, which is comparable to the median T_{max} of 1 and 1.25 hours for Diastat 15 mg and 20 mg.[32] Moreover, the absolute bioavailability study, Study DIAZ.001.01, showed a median T_{max} of 1.5 hours following administration of Valtoco. Only in one other study was the T_{max} for Valtoco slightly delayed. In Study DIAZ.001.04, a study conducted in epilepsy patients in which only Valtoco was used, the T_{max} was 2 hours following Valtoco administration. We do not believe that a difference in 45 minutes was significant given that Study DIAZ.001.03 showed comparable T_{max} of Valtoco to Diastat. We generally consider bioavailability testing in healthy subjects to be more sensitive than studies in patients for showing differences in the bioavailability of different formulations because there are fewer confounding factors such as concomitant medications and the effects of the disease state. We further note that none of the Valtoco studies resulted in the median T_{max} values of 2.79 or 3.31 hours stated in your Petition.

The Petition also claims that "[b]ecause the Valtoco patient C_{max} values in the '423 study [Study DIAZ.001.04] 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 . . . ." (Petition at 12). Study DIAZ.001.04 was an open-label, repeat dose PK and safety study of Valtoco in epileptic patients under seizure and normal conditions. In Study DIAZ.001.04, as noted by the Petitioner, the C_{max} values for patients taking Valtoco were lower than the C_{max} values for healthy subjects. However, it is not unusual for C_{max} values to be lower in patients because epileptic patients would likely be on one or more concomitant medications, which can affect the PK due to drug-drug interactions.

We do not agree that it is necessary for Neurelis to conduct an additional bridging study in patients. As with many relative bioavailability studies submitted in 505(b)(2) applications generally, the bridging study for Valtoco, Study DIAZ.001.03, was conducted in healthy subjects (not patients) comparing Valtoco to Diastat. As explained above, healthy subjects are more sensitive than patients for showing differences in the bioavailability of different formulations and

[31] V.D. Ivaturi, J.R. Riss, R.L. Kriel, and J.C. Cloyd, Pharmacokinetics and tolerability of intranasal diazepam and midazolam in healthy adult volunteers, Acta Neurol Scand (2009), available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/j.1600-0404.2009.01170.x.

[32] The Petition also compares the T_{max} values for Valtoco and Nayzilam, noting that the median T_{max} for Nayzilam is 17.3 minutes (Petition at 11). This comparison is not informative because Nayzilam (midazolam) is composed of an entirely different drug substance.

are generally recommended. If there is a concern over differences in the pharmacokinetic profile between the proposed drug product and the listed drug, the Agency may recommend additional studies in patients. However, that concern was not present in the case of Valtoco. Study DIAZ.001.03 demonstrated comparable C_{max}, $AUC_{0-\infty}$, and T_{max} between Valtoco and Diastat.

In sum, adequate data from Study DIAZ.001.03 were included in Valtoco's 505(b)(2) application that show comparable pharmacokinetic parameters between Valtoco and Diastat to establish a bridge and support approval of the application. We do not agree that an additional bridging study in patients is necessary.[33]

B. A Food-Effect Study Is Not Necessary

The Petition states that Neurelis should "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" (Petition at 1). The Petition further claims that "Valtoco has a curiously-delayed Tmax" and that "Neurelis's Tmax data for Valtoco strongly suggests that, instead of being absorbed from the nasal mucosa, the product is being swallowed and undergoes gastrointestinal absorption" (Petition at 1).[34]

The Agency recommends that sponsors conduct food-effect studies for orally administered drug products.[35] Food-drug interactions can have a significant impact on the safety and efficacy of a drug. For example, in some cases, co-administration of an orally-administered drug with food can increase the systemic exposure of the drug, leading to improved efficacy or higher rates of adverse reactions. In other cases, administration of a drug with food can lower the systemic absorption of a drug, reducing its effectiveness. Food-effect studies can inform how, when, and why drugs should or should not be administered with food. Although the concerns about food-effects are generally focused on orally-administered drugs, food-effect studies may be recommended for non-orally administered products if there is reason to believe that a proportion of the drug product will be swallowed, and thus, subject to a food-effect and first-pass metabolism. FDA determines whether a food-effect study is necessary for non-orally administered drug products on a case-by-case basis.

We have determined that it is unnecessary for Valtoco to undergo a food-effect study. Nasal spray formulations typically deliver 100 µl (25–200 µl) per spray. Each 5 mg or 10 mg dose of Valtoco nasal spray is delivered in 100 µl solution per nostril. Any potential swallowing of a portion of the Valtoco dose is minimized by the low volume administered per dose. It does not

[33] The Petition asserts that "Aquestive conducted a patient crossover study of Libervant to Diastat" (Petition at 3). FDA does not comment on development programs for drugs that have not been approved. See 21 CFR 314.430.

[34] As described in section II.A above, we reject the Petitioner's assertion that Valtoco has a significantly delayed T_{max}. Valtoco's median T_{max} is comparable to Diastat's.

[35] See, e.g., FDA's draft guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs—Clinical Pharmacology Considerations* (February 2019). When final, this guidance will represent the FDA's current thinking on this topic.

appear that the diazepam from Valtoco (diazepam nasal spray) is absorbed through the gastrointestinal tract given the low volume of the dose administered. Contrary to the Petition's claim, T_{max} for Valtoco is not "curiously-delayed" as the median T_{max} for Valtoco is similar to the median T_{max} for Diastat, which indicates that the Tmax for Valtoco is not the result of gastrointestinal absorption. Thus, we did not have concerns about Valtoco being absorbed in the gastrointestinal tract.[36]

C. Vitamin E in Valtoco Does Not Pose a Public Health Concern

The Supplement claims that "Valtoco nasal spray poses a potential public health risk due to its use of high-concentration vitamin E of potentially respirable particle size capable of reaching the alveoli of the lungs and interfering with the function of the surfactant at the air-water interface" (Supplement at 5). The Supplement further claims that "Valtoco has the potential to be used over the course of a patient's lifetime from child to adult, leading to possible cumulative pulmonary effects and distress from periods of chronic, intermittent use" (Supplement at 5). The Supplement concludes that "[a]s with e-cigarette and vaping products utilizing vitamin E, Neurelis's Valtoco nasal spray poses a potential public health risk . . ." (Petition at 5). We do not agree with the Petition's claims.

The vitamin E used in Valtoco and its potential to reach the alveoli of the lung is not comparable to vaping products[37] because nasal spray products differ markedly from vaping products in terms of the size of the respirable particle/droplet fraction generated by the formulation/delivery device, product daily exposure as well as dosing frequency. The droplets generated during administration of Valtoco are unlikely to reach the lung alveoli because the respirable particle/droplet fraction size will be much too large to do so. The devices used in nasal spray products, like the Valtoco product, are designed to deliver the drug to the nasal cavity through spray producing (e.g., orifice, nozzle, jet) pump mechanisms and generate a low percentage of droplets small enough (i.e., $\leq$10 μm) to be able to exit the nasal cavity and reach the upper respiratory tract. The typical respirable particle/droplet fraction of nasal spray products, such as Valtoco, is small, with greater than 95% of the droplets being larger than 10 μm, making it unlikely for such droplets to exit the nasal cavity and even reach the upper lung.[38] Also, due to Valtoco's high viscosity, droplet sizes for Valtoco are generally larger than droplet sizes from aqueous solutions that are typically used in other nasal spray products.

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[36] The Petition asserts that Aquestive conducted "food effect studies that will allow for adequate labeling" (Petition at 3). FDA does not comment on development programs for drugs that have not been approved. See 21 CFR 314.430.

[37] The Supplement discusses both "e-cigarettes and vaping" and also refers to the Center for Disease Control and Prevention (CDC) website titled *Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products*. Because the Supplement's referenced website treats e-cigarettes and vaping products synonymously (see Key Facts about Use of E-Cigarette, or Vaping, Products), we interpret the Supplement's reference to e-cigarettes and vaping products to be synonymous. FDA also views "e-cigarettes" as a type of "vaping product" and as a part of the larger category of electronic nicotine delivery systems (ENDS).

[38] See FDA's guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls* (July 2002).

By contrast, the average particle size generated by commercial vaping products is markedly smaller than those generated by nasal spray devices like Valtoco. For vaping devices, an "e-liquid" containing nicotine or tetrahydrocannabinol and other ingredients is heated to create an aerosol consisting of very small particles or droplets for the user to inhale directly to the lungs. In a recent study on commercial vaping products conducted by FDA's Center for Drug Evaluation and Research using widely used aerosol measurement technology, high levels of respirable particle fraction (more than 99% of all particle counts, or 44-58% of total particle mass, are less than 5 μm) and high particle concentration in submicron range (up to $7.2\times10^{8}/cm^{3}$) were observed.[39] Given these differences, the likelihood of a nasal spray device, such as Valtoco, generating the same level of respirable particles capable of reaching lung alveoli is unsubstantiated; indeed, as noted above, the droplets generated during administration of Valtoco are unlikely to reach the lung alveoli due to their size.

Daily exposure and dosing frequency are also important factors to consider when comparing Valtoco and vaping products. Valtoco is indicated for short-term emergency use in patients 6 years of age and older to treat intermittent, stereotypic episodes of frequent seizure activity. The maximum dose of Valtoco nasal spray is 20 mg per treatment. Typical dosing frequency for Valtoco is a single spray per nostril, and should not be used more than twice for a single episode (a second dose may be administered 4 to 12 hours after the initial dose), more than every 5 days, or more than 5 times per month. Given these limitations, the natural turnover of surfactant in the lungs should reasonably recover its function, reducing the risk of potential long-term damage, in the unlikely event that any particle reaches the alveoli. Although these are the dosing limitations for Valtoco, most patients likely will not need to use the product with such frequency. Conversely, vaping products are often used multiple times a day for indefinite periods of time.[40]

Moreover, the applicant for Valtoco conducted a safety and pharmacokinetics study in patients in the ictal and interictal states and a chronic safety study in which patients with ARS used Valtoco as needed over a prolonged period of time. Out of the 164 patients enrolled in these studies, 91 were exposed to at least 3 doses of Valtoco over at least 6 months, 76 of whom used at least 2 doses/month on average. In these studies, there were no reported adverse events suggestive of lung injury similar to that reported with the use of vaping products.

For these reasons, we do not agree with the Petition that the vitamin E in Valtoco has the potential to a pose a public health risk similar to the recent concerns raised over vaping products. Thus, we deny your request to require the reformulation of Valtoco and other nasal spray drug products to remove vitamin E or to conduct vitamin E penetration/effect studies on the alveoli of the lungs, to require the quantification of the amount of vitamin E reaching the alveoli, or to include labeling on vitamin E penetration/effect studies.

D. Valtoco is Clinically Superior to Diastat

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[39] See report of FY20-033-DPA-T: Vaping Marketplace Assessment – Particle Size Distribution (December 5, 2019).

[40] See, e.g., E-cigarette Use, or Vaping, Practices and Characteristics Among Persons with Associated Lung Injury – Utah, April-October 2019, Morbidity and Mortality Weekly Report, CDC webpage, available at https://www.cdc.gov/mmwr/volumes/68/wr/mm6842e1.htm.

The Petition states 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" (Petition at 13). We do not agree with the Petition's claims and have found that Valtoco provides a major contribution to patient care, and is thus, clinically superior to Diastat.[41] Additionally, we have determined that Valtoco is eligible for orphan-drug exclusivity.[42]

As discussed above, the definition of "clinically superior" states "where neither greater safety nor greater effectiveness has been shown," a drug may be clinically superior if it "makes a major contribution to patient care." Valtoco does not meet either the greater safety or the greater efficacy prongs of the clinical superiority definition.[43] The Agency did not identify any significant differences in the safety or effectiveness of Valtoco in comparison to Diastat. Nevertheless, the Agency has determined that the intranasal route of administration provides a major contribution to patient care over the rectal route of administration by providing a significantly improved ease of use. FDA expects it to be easier to administer the drug intranasally rather than rectally to a patient experiencing a seizure. Rectal administration is inherently invasive for the patient and difficult to administer, whereas it is inherently more comfortable for the patient to receive the drug intranasally than rectally. This is especially so when a patient experiences a seizure in a public place.

The Petition claims that Valtoco has "limited use in patients with epilepsy who are nasally compromised coupled with a delayed Tmax and lower Cmax" (Petition at 15). We disagree. Neurelis has conducted a chronic safety study of Valtoco in which neither nasal allergies nor nasal blockage were reported as a barrier to administration.

The Petition also claims that "the need for possible repeat treatments and possible resultant overdoses given the delayed Tmax also would not be a major contribution to patient care compared to Diastat" (Petition at 15). The Petition's claim that a patient would need repeat doses of Valtoco is based on the premise that Valtoco has a delayed C_{max} and T_{max} relative to Diastat (Petition at 15). We have already stated above that the pharmacokinetic parameters (C_{max} and T_{max}) for Valtoco are comparable to those of Diastat. The efficacy determination and dosing recommendations for Valtoco rely on previous findings for Diastat as the listed drug. The recommended labeling dose of diazepam for Valtoco is very similar to that of Diastat to attain similar drug exposure. Therefore, we do not agree with the Petition's statement that Valtoco may require multiple repeat treatments resulting in possible overdosing.

The Petition further states that "Valtoco's reported 92% efficacy rate (the '069 study) [DIAZ.001.05] is uncontrolled and meaningless . . . [s]uch efficacy appears high in view of Diastat's reported efficacy at 62% and Valtoco's delayed Tmax compared to Diastat" and that "[s]uch efficacy appears high in view of Diastat's reported efficacy at 62% and Valtoco's low AUC(0-6h) values and Cmax for the same respective test conditions compared to labeled values

[41] See Section 527(c) of the FD&C Act.

[42] See id.

[43] See Section 527(c)(2) of the FD&C Act; 21 CFR 316.3(b)(3).

for Diastat" (Petition at 16). As mentioned above, the Agency's finding that Valtoco is clinically superior to Diastat is not based on Valtoco's greater efficacy over Diastat. Moreover, the study that the Petition references was an open-label, uncontrolled study only intended to evaluate long-term safety of Valtoco when used in a chronic intermittent fashion. The study was not designed to assess efficacy. Thus, no definitive conclusions about efficacy can be drawn or were intended to be drawn from this study. Accordingly, the Agency is not relying on this study to support its determination that Valtoco makes a major contribution to patient care over Diastat.

III. CONCLUSION

In sum, we deny your request to require Neurelis to conduct additional bridging and food-effect studies. We also deny your request to require Neurelis and other sponsors of nasal spray products that include vitamin E to reformulate their products or to require vitamin E penetration/effect studies on the alveoli of the lungs. We further deny your request that FDA find Valtoco is not clinically superior to Diastat and that FDA determine that Valtoco is not eligible for orphan-drug exclusivity.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research