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December 18, 2024

Re: Docket No. FDA-2024-P-3563

Dear Ms. Koblitz and Mr. Karst:

This letter responds to the citizen petition dated July 29, 2024 (Petition), which you filed on behalf of your client, Aquestive Therapeutics, Inc. (Petitioner). The Petition requests that the Food and Drug Administration (FDA or Agency) take the following actions:

(1) Refuse to approve any application for a nasal spray drug product that omits studies characterizing food effects if the active moiety, when separately approved for oral use, has a demonstrated food effect; and

(2) Investigate complaints documented in the FDA Adverse Event Reporting System (FAERS) regarding lack of efficacy for such FDA-approved nasal spray drug products and determine whether such complaints arise due to an unknown food effect.

FDA has carefully considered your Petition and the submissions to docket FDA-2024-P-3563,[1] as well as other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, the Petition is denied as to your first request. Regarding your second request, FDA has conducted the requested investigation; the results of that investigation are described in section II.B below.

## I. BACKGROUND

### A. Factual Background

Neurelis, Inc. (Neurelis) is the sponsor of a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[2] for an intranasal form of diazepam:

[1] Neurelis, Inc. submitted a comment dated September 20, 2024 (Neurelis Comment), arguing, among other things, that FDA should summarily deny the Petition under FD&C Act section 505(q)(1)(E), or alternatively find that the Petition shall not block or delay approval of its supplemental new drug application for Valtoco. Neurelis also requests that FDA report Aquestive to the Federal Trade Commission. Neurelis, Inc., Sept 20, 2024 (FDA-2024-P-3563-0004).

[2] 21 U.S.C. 355(b)(2).

Valtoco (diazepam) nasal spray (NDA 211635). This 505(b)(2) NDA relies on FDA's previous finding of safety and effectiveness for Diastat (diazepam) rectal gel (NDA 020648), the listed drug. On January 10, 2020, FDA approved 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 (hereinafter, "ARS") in patients with epilepsy 6 years of age and older.[3] Neurelis was not required to submit food-effect studies as part of its 505(b)(2) NDA for Valtoco. Subsequently, Neurelis submitted a supplemental NDA (sNDA 211635-10) seeking a labeling change that would expand Valtoco's indication to the acute treatment of ARS in patients with epilepsy 2 years of age and older.

Petitioner is the sponsor of two 505(b)(2) NDAs for an oral dosage form of diazepam: Libervant (diazepam) buccal film (NDA 212641 and NDA 218623). As with Valtoco, both NDAs rely on FDA's previous finding of safety and effectiveness for Diastat. On August 30, 2022, FDA tentatively approved NDA 212641, noting that the NDA may not be fully approved for marketing before Valtoco's 7-year period of orphan-drug exclusivity expires.[4] As part of this application for Libervant (NDA 212641), Petitioner was required to submit a food-effect bioavailability study assessing the effects of food on the rate and extent of absorption of its orally dosed drug. On April 26, 2024, FDA approved NDA 218623 for the acute treatment of ARS in patients with epilepsy 2 to 5 years of age.[5]

This is the second citizen petition filed by Petitioner advocating that FDA require a food-effect study for Valtoco.[6] In November 2019, shortly before Valtoco was approved, Petitioner submitted a citizen petition[7] asking FDA to, among other things, require a food-effect study for Valtoco. FDA denied Petitioner's 2019 citizen petition, explaining that a food-effect study was unnecessary for Valtoco because "[a]ny potential swallowing of a portion of the Valtoco dose is minimized by the low volume administered per dose" and because "[i]t does not appear that the

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[3] Valtoco prescribing information (PI) (Jan 10, 2020), section 1, INDICATIONS AND USAGE, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211635.

[4] See Libervant (NDA 212641) approval letter at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212641.

[5] Libervant (NDA 218623) PI, section 1, INDICATIONS AND USAGE, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=218623.

[6] In a comment to this citizen petition's docket, Neurelis urges FDA to summarily deny this Petition in accordance with section 505(q)(1)(E) of the FD&C Act on the grounds that it was submitted with the primary purpose of delaying the approval of an application and does not on its face raise valid scientific or regulatory issues (Neurelis Comment at 1–3). According to Neurelis, the Petition is clearly intended to delay the Valtoco sNDA because it satisfies several considerations that FDA views as suggesting that a citizen petition was submitted for the primary purpose of delay (Neurelis Comment at 2–3). Such considerations include submission of multiple or serial citizen petitions raising issues that reasonably could have been known to the petitioner at the time of submission of an earlier petition; submission of a citizen petition close in time to the first date upon which an application could be approved, and submission of a citizen petition raising the same or substantially similar issues as a prior petition to which FDA has already substantively responded. (FDA, guidance for industry *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act* (September 2019) at 16. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.) Neurelis further argues that the Petition does not, on its face, raise valid scientific or regulatory issues because it relies on flawed or inapplicable literature (Neurelis Comment at 3). We are not able to conclude that the Petition *on its face* does not raise valid scientific or regulatory issues.

[7] Citizen petition, Docket No. FDA-2019-P-5121 (Nov 1, 2019).

drug is absorbed through the gastrointestinal tract given the low volume of the dose administered."[8]

## B. Legal and Regulatory Framework

Under section 505(b) of the FD&C Act (21 U.S.C. 355(b)), applicants seeking to market a new drug generally must first submit an application to FDA for approval. 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,[9] a 505(b)(2) NDA is submitted under section 505(b)(l) of the FD&C Act and approved under section 505(c) of the FD&C Act. As such, a 505(b)(2) NDA 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 for which the applicant has not obtained a right of reference or use.[10] For instance, a 505(b)(2) NDA may rely, in part, on FDA's previous finding that a listed drug is safe and effective as evidence in support of the proposed drug product's safety and effectiveness.

A 505(b)(2) NDA can describe a drug product with differences from the listed drug it references.[11] These differences may include, for example, a different active ingredient or a new indication, dosage form, strength, formulation, and/or route of administration.[12] When a 505(b)(2) NDA applicant seeks to rely on a finding of safety and/or effectiveness for one or more listed drugs, the applicant must demonstrate that reliance on the listed drug(s) is scientifically justified.[13] A 505(b)(2) NDA applicant is expected to establish a bridge[14] between its proposed drug product and each listed drug to demonstrate that reliance on the listed drug(s) is scientifically justified.[15] For example, an applicant may establish a bridge by using comparative

[8] FDA citizen petition response letter from J Woodcock, Director, Center for Drug Evaluation and Research, to BJ Malkin, FDA-2019-P-5121-0011 (Jan 10, 2020) at 10–11.

[9] A *stand-alone NDA* is an application submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use. FDA, guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019) at 2.

[10] 21 U.S.C. 355(b)(2).

[11] See, e.g., 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.

[12] There is no statutory requirement for a 505(b)(2) NDA applicant to demonstrate bioequivalence of its proposed drug product to another drug product. A drug product in a 505(b)(2) NDA may not necessarily be bioequivalent, pharmaceutically equivalent, and/or therapeutically equivalent to the listed drug relied upon. However, to the extent that the drug product in a 505(b)(2) application differs from the listed drug, the 505(b)(2) application must include sufficient data to support those differences. See 21 CFR 314.54(a).

[13] FDA, guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019) at 4.

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

[15] FDA, guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019) at 4.

bioavailability data between the proposed product and listed drug(s).[16] An acceptable scientific bridge enables the applicant to rely on the Agency's previous finding of safety and effectiveness for the listed drug.

The Agency recommends that sponsors conduct food-effect studies for new orally administered drug products.[17] Food-drug interactions can have a significant impact on the safety and efficacy of orally administered drug products.[18] Administration of an oral drug product with food can increase or decrease the systemic exposure of the drug, thereby impacting the safety and/or efficacy of the drug product.[19] Food-effect studies can inform how, when, and why drug products should or should not be administered with food.[20] Assessing the effect of food on the absorption of an orally administered drug product contributes to the optimization of the safety and efficacy of the drug product and helps provide adequate instructions for use of the drug product.[21]

Although the concerns about food effects are generally focused on orally administered drug products, FDA may recommend food-effect studies for nonorally administered drug products if there is reason to believe that a clinically significant proportion of the drug product will be swallowed and, thus, subject to a food effect and first-pass metabolism.[22] FDA determines whether a food-effect study is necessary for nonorally administered drug products on a case-by-case basis.[23]

## II. DISCUSSION

### A. There Is Insufficient Evidence to Require Food-Effect Studies for Low-Volume Nasal Spray Drug Products

Nasal administration of medications is a useful and expedient method of delivering medication. The nasal cavity possesses a rich vascular network that provides a direct route to the blood stream. Nasal absorption is accomplished by distributing a drug solution as a mist, rather than as larger droplets that may run off either into the throat (*nasal drippage*) or out the nostril. Nasal

[16] Id. *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 drug action" (21 CFR 314.3); see also 21 CFR 320.1. Bioavailability data provide an estimate of the amount of the drug absorbed as well as information related to the pharmacokinetics of the drug, the effects of food on the absorption of the drug, and dose proportionality or linearity in the pharmacokinetics of the active moieties. See, e.g., FDA, guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (April 2022).
[17] See, e.g., FDA, guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations* (June 2022) at 3.
[18] Id. at 2.
[19] Id.
[20] Id.
[21] Id.
[22] Citizen petition response, FDA-2019-P-5121-0011 (Jan 10, 2020) at 10.
[23] Id.

administration avoids drug loss that typically occurs with oral administration due to interaction with gastric enzymes and hepatic first-pass metabolism.

The Petition argues that intranasally administered drug products, including Valtoco, are swallowed more often and in a greater amount than FDA has presumed (Petition at 7-12). As evidence, the Petition points to the frequency of oral and gastrointestinal adverse events cited in the literature, such as dysgeusia (altered sense of taste), throat irritation, and nausea, among others (Petition at 7-12). The Petition further states that to the extent such drugs are swallowed, they are absorbed systemically through the gastrointestinal tract, which affects the pharmacokinetics of the drug and, in turn, the bioavailability and efficacy of the drug (Petition at 6–11). According to the Petition, this potential for reduced bioavailability and efficacy of an intranasally administered drug product is of particular concern if the active moiety has a known food effect (Petition at 7). Accordingly, the Petition urges FDA to require food-effect studies for nasally administered drug products whose active moiety, in an oral dosage form, has a known food effect.

As explained below, we are not persuaded that food-effect studies should be required for all such nasally administered drug products or for Valtoco in particular. The Petitioner argues that oral and gastrointestinal adverse events reported for nasal spray drug products occur as a result of swallowing a significant portion of the drug substance, which is not necessarily true. To the extent that a low volume nasal spray drug is swallowed, the amount swallowed is typically negligible and does not impact efficacy.

*1. Oral and Gastrointestinal Adverse Events Do Not Constitute Evidence That More Than Trace Amounts of Nasal Spray Drug Products Are Swallowed and Enterally Absorbed*

The Petition asserts that the likelihood of gastrointestinal exposure to intranasally administered drugs is higher than FDA presumes, as evidenced by certain adverse events such as nausea/vomiting and dysgeusia reported with nasal drug products like Imitrex (sumatriptan), Nayzilam (midazolam), Valtoco (diazepam), and epinephrine nasal spray (Petition at 7–8, 10-11). However, these adverse events do not necessarily indicate that a drug substance has been swallowed or that more than trace amounts of the drug substance have been absorbed in the gastrointestinal tract. To the best of our knowledge, there is no established correlation between these adverse events and the amount of drug substance absorbed in the gastrointestinal system.

The sense of taste is a complex sensory experience that relies on signals from the tongue and olfactory tract, which is responsible for the sense of smell.[24] The tongue's sensation of different tastes varies within and between individuals, so it is not scientifically possible to use taste alone to quantify an amount of a drug substance reaching the tongue.[25] Importantly, the contribution of the olfactory system to taste is more significant than the tongue's. Only a minority (5 percent) of

[24] Witt M, 2019, Chapter 10 – Anatomy and Development of the Human Taste System. In: RL Doty, editor, Handbook of Clinical Neurology, Cambridge: Elsevier, 164:147–171.

[25] Spence C, 2022, The Tongue Map and the Spatial Modulation of Taste Perception, Curr Res Food Sci, 5:598–610; see also Webb J, Bolhuis DP, Cicerale S et al., 2015, The Relationships Between Common Measurements of Taste Function, Chemosens Percept, 8(1):11-18, doi: 10.1007/s12078-015-9183-x.

individuals who report a problem tasting food have a primary problem with the sense of taste; the rest have experienced a loss of olfactory sensation.[26] Thus, when patients taking therapies such as Imitrex (sumatriptan), Nayzilam (midazolam), and Valtoco (diazepam) via the nasal route report dysgeusia or bad/unusual taste, it may simply reflect the proximity of the drug product to the olfactory system.

Nausea and vomiting are triggered by many stimuli, some of which are received systemically. Thus, it is not clear if patients who report nausea after intranasal administration of Imitrex (sumatriptan), Nayzilam (midazolam), and Valtoco (diazepam) are reporting nausea because of exposure to the drug via absorption in the nasal epithelium or absorption in the gastrointestinal tract. Indeed, there is evidence indicating that nausea and vomiting are not always caused by absorption in the gastrointestinal tract. For example, the labeling for Imitrex (sumatriptan) nasal spray indicates similar rates of nausea reported for placebo (11.3 percent) and intranasal sumatriptan (11 to 13.5 percent) exposures, both of which are markedly higher than the rate of treatment-associated nausea for oral sumatriptan (not reported on approved labeling and therefore less than 2 percent).[27] If nausea associated with intranasal sumatriptan administration is attributable to gastrointestinal absorption, the rate of nausea with oral administration should be greater than that of intranasally administered sumatriptan, not substantially lower.

Moreover, nausea and vomiting can be triggered by exposure to a drug substance that enters circulation without any absorption in the gastrointestinal tract (e.g., intravenously administered chemotherapeutic agents). Finally, although the Petition claims that vomiting associated with epinephrine nasal spray is linked to swallowing some portion of the nasal dose (Petition at 10–11), nausea and vomiting are common adverse events associated with intramuscular and intravenous dosage forms of epinephrine.[28] In addition, orally administered epinephrine is so quickly metabolized that absorption in the gastrointestinal tract is negligible and its oral bioavailability is extremely low.[29] Thus, to the extent that a portion of nasally administered epinephrine is swallowed, there should be no significant absorption in the gastrointestinal tract.

Accordingly, we do not interpret reports of dysgeusia, nausea, or vomiting as evidence that low-volume nasal spray drug products have been swallowed in a significant amount or that more than trace amounts of such drugs are being absorbed in the gastrointestinal tract.

*2. Literature Cited by Petition Does Not Establish That Low-Volume Nasal Spray Drug Products Are Frequently Swallowed in Significant Amounts*

The Petitioner discusses various studies to support its theory that swallowing of intranasally administered diazepam and other drugs occurs often, thereby resulting in a significant amount of the drug being absorbed in the gastrointestinal tract and potentially subject to food effects that

[26] Risso D, Drayna D, and Morini G, 2020, Alteration, Reduction and Taste Loss: Main Causes and Potential Implications on Dietary Habits, Nutrients, 12(11):3284.
[27] Imitrex (sumatriptan) nasal spray (NDA 020626) PI, subsection 6.1, *Clinical Trials Experience*; Imitrex (sumatriptan succinate) tablets (NDA 020132) PI, available at available at https://www.accessdata.fda.gov/scripts/cder/daf/.
[28] See, e.g., Adrenalin (epinephrine) injection (NDA 204200) PI, section 6, ADVERSE REACTIONS, available at https://www.accessdata.fda.gov/scripts/cder/daf/.
[29] Menninger WC, 1927, The Oral Administration of Epinephrine, Arch Intern Med (Chic), 40(5):701–714.

may reduce bioavailability and efficacy (Petition at 9–11). The cited literature does not offer support for Petitioner's theory because the studies did not account for various factors that can contribute to differences in nasal drippage.[30] Experiences with one nasal spray drug product cannot be generalized to other nasal spray drug products or even to other formulations of the same drug product.

Many factors affect drug absorption and bioavailability, including the physical and chemical properties of the drug, its formulation, and its route of administration. In the case of a nasal spray drug product, drug absorption can be affected by several factors, including excipients and a combination of formulation-drug-device characteristics. Formulation characteristics (e.g., viscosity, density) are important considerations that affect the selection and performance of the delivery device and, ultimately, the performance of the drug itself.[31] How a product is administered (i.e., intranasal spray versus intranasal drop) also plays an important role in the absorption of the active moiety and can contribute to differences in nasal drippage.[32]

The studies cited by Petitioner regarding intranasally administered diazepam either did not evaluate the same formulation as Valtoco nasal spray or do not include sufficient information to ascertain whether the formulation evaluated was the same formulation as Valtoco nasal spray. For example, the Petition cites two studies evaluating intranasal diazepam in 8 and 12 subjects, respectively, in which all subjects reported swallowing a portion of the intranasal dose.[33] The study with 8 subjects did not evaluate the Valtoco formulation or administer the product the same way as Valtoco. Instead, the study evaluated a liquid diazepam formulation administered intranasally using a syringe with the subject lying in the supine position. The 12-subject study evaluated two strengths of an investigational diazepam nasal spray formulation. According to the Neurelis's comment submitted to the docket for this Petition (Neurelis Comment), the formulation of diazepam nasal spray used in this study was more likely than Valtoco to run out of the nose or down the back of the throat due to its low viscosity and use of organic solvents (Neurelis Comment at 12–13).[34] We note that the authors of the 12-subject study reported "technical difficulties with administration"[35] that may also limit the reliability of the study findings. Thus, the results of these two studies cannot be extrapolated to Valtoco or other low-volume nasal spray drug products generally.

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[30] See generally guidance for industry *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* (July 2002) (2002 Nasal Spray Guidance); see also Pires A et al., 2009, Intranasal Drug Delivery: How, Why and What For? J Pharm Pharm Sci, 12(3):288–311. doi: 10.18433/j3nc79 (Pires et al. 2009).

[31] 2002 Nasal Spray Guidance at 22.

[32] See, generally, 2002 Nasal Spray Guidance; see also Pires et al. 2009.

[33] Petition at 9-10 (Discussing Ivaturi VD et al., 2009, Bioavailability and Tolerability of Intranasal Diazepam in Healthy Adult Volunteers, Epilepsy Res, 84(2–3):120–126. doi:10.1016/j.eplepsyres.2009.01.001.; Ivaturi V et al., 2013, Bioavailability of Intranasal Vs. Rectal Diazepam. Epilepsy Res, 103(2–3):254–261. doi: 10.1016/j.eplepsyres.2012.07.018).

[34] The Neurelis Comment states that the Valtoco formulation uses a different primary solubilization vehicle (tocopherol), resulting in a more viscous formulation that "naturally confines to the site of administration and minimizes any potential run-off." Neurelis Comment at 12–-13. We are unable to confirm the accuracy of this statement, but it is plausible.

[35] Ivaturi V et al., 2013, Bioavailability of Intranasal Vs. Rectal Diazepam, Epilepsy Res, 103(2–3):254–261 at 260. doi: 10.1016/j.eplepsyres.2012.07.018.

The Petition also cites a study comparing intranasal diazepam to rectally administered diazepam in 24 subjects, noting that dysgeusia, dry throat, and throat irritation were reported in the nasal administration group.[36] Two concentrations of intranasal diazepam were administered as a microemulsion using a Pfeiffer nasal spray device. In contrast, Valtoco is a liquid solution, not a microemulsion. It appears that the same microemulsion formulation was evaluated in another study cited by Petitioner regarding the prevalence of oral and gastrointestinal side effects after administration of a diazepam nasal spray.[37] In both studies, the nasal drug product formulation, excipients and delivery device could have contributed to the reported side effects. In addition, for the reasons discussed above in section II.A.1, gastrointestinal adverse events do not necessarily indicate that a drug substance has been swallowed.

In summary, none of the diazepam studies cited by the Petitioner establish that swallowing diazepam administered in a low volume nasal spray occurs frequently and in significant amounts. The instances of drug swallowing reported by study subjects are not necessarily applicable to a low volume nasal spray,[38] and none of the studies were designed to quantitatively characterize the amount of diazepam lost by nasal drippage into the gastrointestinal tract. Moreover, the Petition overlooked a study evaluating a diazepam nasal spray supplied by Neurelis.[39] The authors noted that "prior studies with diazepam and midazolam reported dual peaks reflecting oral absorption in which the first peak representing nasal absorption occurs within 20-30min and a second peak presumably due to enteral absorption occurs around 1-2h after intranasal drug administration" and concluded that "[s]econd diazepam peak concentrations were not observed" in the current study.[40] Even if this study evaluated a different formulation of Valtoco from what is currently marketed, it nevertheless substantiates the importance of the drug formulation and administration on the pharmacokinetics for a particular product.

Regarding other low-volume nasal spray drug products, the Petition asserts that Imitrex (sumatriptan) nasal spray has an absorption profile consistent with the product being swallowed: an early peak of the drug in plasma levels likely related to intranasal absorption, followed by a

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[36] Petition at 10 (discussing H. Henney III et al., 2014, Assessment of Pharmacokinetics and Tolerability of Intranasal Diazepam Relative to Rectal Gel in Healthy Adults, Epilepsy Res, 108(7):1204–1211. doi: 10.1016/j.eplepsyres.2014.04.007) (Henney study).

[37] See Sperling MR et al., 2014, Dosing Feasibility and Tolerability of Intranasal Diazepam in Adults With Epilepsy, Epilepsia, 55(10):1544–1550 at 1545 (Sperling study). Although the Sperling study did not provide specific information on the nature of the formulation that was evaluated, it appears that it was a diazepam nasal spray under development by Acorda Therapeutics, Inc. (Acorda). Both the Sperling study and the Henney study were funded by Neuronex, Inc., a wholly owned subsidiary of Acorda, and both studies disclose that they were authored by individuals who were employed by, or engaged as consultants to, Acorda or Neuronex, Inc. Acorda ultimately discontinued development of the drug product. See Press Release, May 20, 2016, available at https://www.businesswire.com/news/home/20160520005142/en/.

[38] Although some subjects reported swallowing a portion of the nasal spray drug product, the sensation of swallowing following an intranasal administration of a drug product could reflect swallowing a bolus of drug product, a bolus of nasopharyngeal secretions, or a combination of the two. Thus, it is not clear what exactly the subjects swallowed and what quantities of diazepam, if any, were contained in what patients perceived themselves to have swallowed.

[39] Agarwal SK et al., 2013, A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration in Healthy Volunteers, Epilepsy Res, 105(3):362–367. doi: 10.1016/j.eplepsyres.2013.02.018.

[40] Id. at 366.

higher peak consistent with gastrointestinal absorption (Petition at 11).[41] In general, the appearance of a second peak in plasma profiles could be due to enteral absorption, as well as several factors unrelated to swallowing, including enterohepatic recycling,[42] and therefore a second peak cannot be definitively attributed to swallowing and subsequent gastrointestinal absorption. In addition, sumatriptan nasal spray is manufactured by several companies, and the literature relied on by the Petitioner did not include relevant details regarding the specific sumatriptan formulation that was evaluated. As discussed above, formulation characteristics such as excipients, volume of spray administered, etc., could potentially lead to differences in nasal drippage and the amount of drug swallowed. The literature relied on by Petitioner cites an additional study that postulated that similar absorption and excretion of sumatriptan intranasal spray relative to the oral dosage form was "perhaps due to a proportion of the dose being swallowed," but the study did not offer further qualitative or quantitative characterization of absorption following intranasal administration.[43] Based on these limitations, it is not possible to definitively conclude that nasal drippage leads to swallowing of a substantial amount of sumatriptan.

Finally, we disagree with the Petitioner's characterization of statements made by FDA reviewers regarding Nayzilam (midazolam) nasal spray, a 505(b)(2) NDA (NDA 211321) (Petition at 11). Specifically, the Petition notes that FDA did not require a food-effect study for Nayzilam despite stating in the Agency's Clinical Pharmacology and Biopharmaceutics Review of the drug that "a significant amount of midazolam is more likely absorbed in the gut . . . following intranasal administration....." (Petition at 11).[44] The Petitioner takes this statement out of context. FDA made the statement specifically in the context of a mathematical, physiologically based pharmacokinetic (PBPK) modeling exercise to interpret the potential for drug-drug interactions; FDA was not noting any *clinical* significance regarding enteral absorption.

*3. Enteral Absorption of Low-Volume Nasal Spray Drug Products Is Negligible*

The Petitioner asserts that a low-volume nasal spray drug product typically requires a higher concentration of a drug and that any amount that is swallowed would be swallowed in a higher concentration than if administered orally (Petition at 8). According to the Petition, the higher concentration of the swallowed drug may affect absorption of the drug substance and the need for food (Petition at 8). Although we agree that low-volume nasal spray drug products may be relatively concentrated solutions, we do not believe that the amount or concentration of a low-

[41] Djupesland PG, 2013, Nasal Drug Delivery Devices: Characteristics and Performance in a Clinical Perspective -- A Review, Drug Deliv. and Transl. Res. 3:42-62 (citing Duquesnoy C, Mamet JP, Sumner D, Fuseau E, 1998, Comparative Clinical Pharmacokinetics of Single Doses of Sumatriptan Following Subcutaneous, Oral, Rectal and Intranasal Administration, Eur J Pharm Sci, 6(2):99-104, doi: 10.1016/s0928-0987(97)00073-0).

[42] Enterohepatic recycling occurs when a drug undergoes biliary excretion, followed by intestinal reabsorption, and can result in a second plasma concentration peak. Roberts MS, Magnusson BM, Burczynski FJ, Weiss M., 2002, Enterohepatic Circulation: Physiological, Pharmacokinetic and Clinical Implications, Clin Pharmacokinet, 41(10):751-90. doi: 10.2165/00003088-200241100-00005.

[43] Duquesnoy C, Mamet JP, Sumner D, Fuseau E, 1998, Comparative Clinical Pharmacokinetics of Single Doses of Sumatriptan Following Subcutaneous, Oral, Rectal and Intranasal Administration, Eur J Pharm Sci, 6(2):99-104, doi: 10.1016/s0928-0987(97)00073-0.

[44] FDA Clinical Pharmacology and Biopharmaceutics Review (NDA 211321) at 11, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211321Orig1s000TOC.cfm.

volume nasal spray drug product that might be swallowed or otherwise deposited off-target would result in significant drug loss and thereby compromise bioavailability and efficacy.

First, the amount of a low-volume nasal spray drug product that might be swallowed is negligible. Low-volume nasal spray drug products, which include Valtoco, generally are packaged in single-use, single-dose device formats containing very small quantities of the solution formulation: approximately one-tenth of a milliliter (0.1 mL). By design, the vast majority of a nasally administered drug product reaches systemic circulation through nasal absorption, circumventing presystemic clearance (e.g., hepatic first-pass metabolism) to enhance and speed bioavailability. Thus, notwithstanding the drug product's concentration, the volume of solution is so small that, after a spray inside the nostril, there is a negligible amount of drug solution left to pass down the back of the throat, enter the stomach, and interact with food.

The Agency's NDA review process confirms this. In the case of a 505(b)(2) NDA, the applicant typically demonstrates through comparative bioavailability data that reliance on FDA's finding of safety and efficacy of the listed drug is scientifically justified. For example, in an absolute bioavailability study comparing Valtoco (diazepam) nasal spray with intravenous diazepam, Valtoco demonstrated an absolute bioavailability of 97 percent.[45] An absolute bioavailability study assesses the amount of a drug product's active ingredient that reaches systemic circulation after administration of a particular formulation (e.g., nasal spray) and compares it with the amount that reaches systemic circulation after intravenous administration.[46] The 97 percent absolute bioavailability of Valtoco suggests that a vast majority of the intranasally administered diazepam dose reaches systemic circulation, circumventing pre-systemic clearance (e.g., hepatic first-pass metabolism). In addition, a secondary peak concentration was not observed in the Valtoco absolute bioavailability study.[47] Thus, very little of the drug product was lost to nasal drippage and first-pass hepatic metabolism, which can impact efficacy.

In contrast, the Petition relies on a study sponsored by Petitioner (Rogawski study) to challenge the view that only a negligible, clinically insignificant amount of Valtoco is absorbed in the gastrointestinal tract and to challenge the view that nasally administered diazepam lacks a clinically meaningful food effect (Petition at 13).[48] In the Rogawski study, PK concentrations were significantly different when dosed after a high-fat, high-calorie meal compared to dosing in

[45] Valtoco PI, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211635s008lbl.pdf; see also Agarwal SK, et al., 2013, A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration in Healthy Volunteers, Epilepsy Res, 105(3):362–367. doi: 10.1016/j.eplepsyres.2013.02.018.

[46] Atkinson AJ, 2012, Chapter 4 – Drug Absorption and Bioavailability, in: Atkinson AJ, Huang, S, Lertora JJ, Markey SP, editors, Principles of Clinical Pharmacology, 3d ed., at 45, doi: https://doi.org/10.1016/B978-0-12-385471-1.00004-0.

[47] Agarwal SK, et al., 2013, A Pilot Study Assessing the Bioavailability and Pharmacokinetics of Diazepam After Intranasal and Intravenous Administration in Healthy Volunteers, Epilepsy Res, 105(3):362–367. doi: 10.1016/j.eplepsyres.2013.02.018. . The diazepam solution formulation was the final Valtoco formulation, and the data from this study was submitted as part of Valtoco's NDA. Valtoco Clinical Pharmacology Review, NDA 211635, at 18 (Oct 3 2019), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/211635Orig1s000TOC.cfm.

[48] Rogawski MA and Slatko G, 2023, A Randomized, Open-Label, Two-Treatment Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of Diazepam Nasal Spray in Healthy Adults, Epilepsia, 64(2):364–373. doi: 10.1111/epi.17459.

a fasted state. In the Neurelis Comment, Neurelis states that this 20-subject study was not conducted in accordance with the study protocol, which provided for dosing in accordance with the FDA-approved Valtoco instructions for use (Neurelis Comment at 7). Instead, Neurelis claims that three steps were added through the Rogawski study's informed consent form: the subject would be asked to keep their head tilted back; sniff gently inward; and breathe in through the nose and out through the mouth for 5 to 10 seconds during dosing (Neurelis Comment at 7). These additional steps might have driven a significant portion of the Valtoco nasal spray droplets into the posterior portion of the nasal passages and the oropharynx, thereby increasing the likelihood of nasal drippage and swallowing of the drug (Neurelis Comment at 7). There is no verifiable data to support this assertion, but it is plausible (although not definitive) that the additional steps used in the Rogawski study contributed to the study findings.

Given the absence of evidence that low-volume nasal spray drug products are routinely swallowed in amounts and concentrations significant enough to affect efficacy, we decline to require food-effect studies for all such drug products. The impact of food on bioavailability depends on many factors, including factors that can be distinct to the particular drug substance. In the case of nasally administered drug products, we do not believe that the literature justifies requiring food-effect studies on a routine basis when the active moiety, in an oral dosage form, has a demonstrated food effect.

### B. FAERS Data Do Not Reveal a Signal Regarding Decreased Efficacy or Lack of Efficacy

FDA uses the term *signal* to mean information that arises from one or multiple sources (including observations and experiments) that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify.[49] Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the drug product caused the adverse event.[50] The determination of whether there is a causal association between a drug product and an adverse event should be based on the strength of the evidence from the totality of data from all relevant sources, including preclinical data, literature, other safety databases, clinical trials, epidemiological studies, product utilization data, and reporting ratios (or rates).[51] The quality of the adverse event data is critical for appropriate evaluation of the relationship between the drug product and adverse events.[52] For example, the most useful individual case safety reports contain detailed descriptive information in the narrative section to describe the course of the adverse event as it occurred in the patient (e.g., onset relative to start of the suspect drug product, presentation, evaluation conducted,

[49] FDA, *Best Practices for FDA Staff in the Postmarketing Safety Surveillance of Human Drug and Biological Products* (January 2024) at 3 (Safety Surveillance Best Practices), available at https://www.fda.gov/media/130216/download.

[50] Id.; see also guidance for industry, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) at 4.

[51] Safety Surveillance Best Practices at 29–30.

[52] FDA, guidance for industry, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) at 4.

diagnosis, treatment, and outcome).[53] The absence of adverse event data does not mean there is no signal.

Disproportionality analyses are used to identify statistical associations between drug products and events in adverse event databases, such as FAERS. The Petitioner conducted a disproportionality analysis of FAERS data for Diastat (diazepam) rectal gel and the following six nasally administered drug products:

- Diazepam nasal spray (Valtoco);
- Sumatriptan nasal spray (Tosymra);
- Ketorolac tromethamine nasal spray (Sprix);
- Midazolam nasal spray (Nayzilam); and
- Dihydroergotamine mesylate metered nasal spray (Migranal, Trudhesa).[54]

The Petitioner used specific reaction terms related to lack of efficacy to calculate proportional reporting ratios (PRRs) and reporting odds ratios (RORs) for the disproportionality analysis.[55] The Petitioner used Diastat (diazepam) rectal gel "as a representative comparator due to its active moiety (diazepam) with a known food effect and the rectal administration of the product allows for an independent assessment of a signal for both a non-nasal and non-oral administration control" (Petition at 14). The Petitioner concludes that Valtoco (diazepam), Tosymra (sumatriptan), and Migranal/Trudhesa (dihydroergotamine mesylate) "are noted to have an elevated PRR and ROR, which confirms a signal that warrants further exploration" (Petition at 15).

We disagree with the Petitioner's assertion that its FAERS disproportionality analysis "confirms a signal that warrants further exploration" (Petition at 15). Moreover, the Agency has conducted a thorough case-level review of FAERS data and did not confirm a signal for decreased efficacy or lack of efficacy for the selected nasal spray drug products discussed in this Petition.

*1. The Petitioner's FAERS Disproportionality Analysis Does Not Confirm a Signal Regarding Decreased Efficacy or Lack of Efficacy Due to a Food Effect*

The Petitioner's disproportionality analysis of FAERS data is insufficient to confirm a signal of decreased efficacy or lack of efficacy for the selected nasal spray drug products.

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[53] Safety Surveillance Best Practices at 21.

[54] The Petitioner's FAERS disproportionality analysis analyzed the two dihydroergotamine products, Migranal and Trudhesa, together.

[55] PRR and ROR are statistical measures of association that reflect the strength of an association between a drug product and an adverse event. See Report of Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII, 2010, Practical Aspects of Signal Detection in Pharmacovigilance (Rev. 2010), Geneva: CIOMS, at 53, available at https://cioms.ch/wp-content/uploads/2018/03/WG8-Signal-Detection.pdf (CIOMS Report).The PRR is the proportion of reports for an event that involve a particular drug product compared to the proportion of reports of this event for all drug products in an adverse event database. See CIOMS Report at 113. The ROR is the odds of finding an adverse event term among all case reports that mention a particular drug product divided by the odds of finding the same adverse event term among all other case reports in the adverse event database that do not mention the drug product. See CIOMS Report at 114.

Disproportionality analyses are considered hypothesis-generating and do not, by themselves, represent a signal.[56] In general, there is a high volume of "drug ineffective" reports across different products in FAERS.[57] There are many reasons why a drug product may be the subject of an adverse event report in FAERS regarding decreased efficacy or lack of efficacy. In addition to food-effect issues, such reports may be prompted by drug product quality issues, failure to follow labeling instructions regarding administration, drug-drug interactions, disease progression, and more. Thus, the existence of a signal cannot be confirmed without a case-level analysis of the adverse event reports in FAERS. Depending on the quality and content of the reports, one may be able to determine whether further evaluation is warranted. It is critical that reports be of high quality for optimal evaluation of the relationship between the drug product and adverse event.

The Petitioner did not conduct a case-level review to determine whether the efficacy-related adverse event reports for the selected nasal spray drug products are due to food effects or are caused by one of many other reasons that could trigger such reports. Accordingly, the Petitioner's disproportionality analysis does not confirm a signal regarding the efficacy of the selected nasal spray drug products that were evaluated.

*2. Comprehensive FAERS Case-Level Analysis Did Not Identify a Signal for Decreased Efficacy or Lack of Efficacy Due to a Food Effect*

The Petition requests that FDA investigate the lack of efficacy complaints documented in FAERS (Petition at 2). The Agency conducted a disproportionality analysis of FAERS data to identify patterns of associations or unexpected occurrences (i.e., *potential signals*) for the selected nasal spray drug products (i.e., drug products included in the Petition's analysis) with event terms related to lack of efficacy and drug-food interactions. Our analysis identified patterns of disproportionate reporting similar to the Petitioner's findings that indicated a potential signal. Because an analysis of individual case safety reports that underlie the disproportionality metrics is necessary to confirm a signal, we conducted a case-level analysis of the FAERS reports associated with disproportional reporting.

We found that most of the FAERS reports were missing information (e.g., temporality, past medical history, concomitant medications, reason for use) needed to assess causality. Additionally, in our review of the FAERS reports of lack of efficacy for the selected nasal spray drug products, no FAERS reports mentioned the presence or absence of a potential food effect. As the Petition acknowledges, FAERS data usually contain minimal case details regarding relevant medical history, disease severity, and whether the patient was fed or fasting at the time of the adverse event (Petition at 15). Without such information, it is not possible to make a reasonable inference about whether there is a causal relationship between a drug product and an adverse event.

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[56] See FDA white paper, Data Mining at FDA, revised Aug 20, 2018, at 2, available at https://www.fda.gov/media/91848/download; see also CIOMS Report, at 30; European Medicines Agency, Screening for Adverse Reactions in EudraVigilance, revised Dec 19, 2016, at 7, available at https://www.ema.europa.eu/en/documents/other/screening-adverse-reactions-eudravigilance_en.pdf.

[57] Misu T, Kortepeter CM, Muñoz MA, Wu E, Dal Pan GJ, 2018, An Evaluation of "Drug Ineffective" Postmarketing Reports in Drug Safety Surveillance, Drugs Real World Outcomes, 5(2):91-99.

In addition, it is often difficult to distinguish the reported *drug ineffective* event from disease progression. This challenge is especially relevant here because there is a high background rate of breakthrough or persistent seizures, migraines, and pain in the affected patient populations using the selected nasal spray drug products.[58] We note that disproportional reporting for terms related to lack of efficacy is also observed for other pain, migraine, and seizure drug products with other routes of administration (e.g., opioids), potentially suggesting disease-related factors may be responsible for the statistical findings.[59] Overall, however, our case-level analysis did not identify a pattern or unique characteristic that raises the concern for a signal regarding the selected nasal spray drug products.

The Petition urges FDA to explore other databases that do not have the limitations inherent in FAERS (Petition at 15). We note that the databases available to FDA for conducting epidemiologic studies are not conducive to determining whether decreased efficacy or lack of efficacy is due to food effects. These databases, which primarily consist of health care claims data, do not capture details relevant to food effects, including whether a medication was in fact taken with or without food and the precise time at which a patient was exposed to a drug product. In addition, disease severity is unlikely to be well ascertained in code-based claims data and is challenging to obtain even with electronic health record information. Given the conclusions in section II.A of this document and the Agency's comprehensive FAERS data case-level analysis, no further investigation is warranted.

## III. CONCLUSION

For the reasons stated above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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