Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 214697 S-002
Link to EDR	\\CDSESUB1\EVSPROD\nda214697\0236
Submission Date	4/30/2025
Submission Type	Efficacy Supplement
Brand Name	Neffy
Generic Name	Epinephrine
Dosage Form and Strength	1 mg/0.1 mL of epinephrine per spray in a single-dose nasal spray 2 mg/0.1 mL of epinephrine per spray in a single-dose nasal spray
Route of Administration	Nasal Spray
Proposed Indication	Emergency treatment of type I allergic reactions, including anaphylaxis in adults and pediatrics patients who weigh 15 kg or greater
Approved Dosing Regimen	30 kg or greater: one spray of neffy 2 mg 15 kg or greater: one spray of neffy 1 mg
Applicant	ARS Pharmaceuticals, Inc
OCP Division	DIIP
OND Division	DPACC
OCP Review Team	Qianni Wu, PharmD
OCP Final Signatory	Yunzhao Ren, MD; PhD

1. EXECUTIVE SUMMARY

The Applicant initially submitted a Prior Approval Supplement (PAS) dated April 30, 2025, and later amended on July 10, 2025. The Applicant proposed the following clinical pharmacology-related updates in Prescribing Information, Patient Information, and Instructions for Use:

- To remove the age restriction (4 years and older)
- (b) (4) "avoid sniffing during and after administration"

Upon further review, the Agency classified this supplement as an efficacy supplement per 21 CFR 314.3(b), because the proposal of removal of the 4 years of age limit, constitutes an addition or modification to the current indication and expansion of the intended patient population. Based on this, a General Advice Letter (GAL) was conveyed to the Applicant dated August 19, 2025, to request that the Applicant modify the supplement as an efficacy supplement. In a response dated September 4, 2025, the Applicant updated the class of the supplement (i.e., an efficacy supplement).

Because children 4 years of age were the youngest subjects enrolled in pediatric trial EPI 10 conducted in neffy program, the 4-year age limit was included in the current label, regardless of the body weight criteria (i.e., there is a possibility that children younger than 4 years of age can weigh 15 kg and above). From clinical pharmacology perspective, there is an uncertainty of epinephrine PK in pediatric subjects < 4 years of age with body weight 15 kg to < 30 kg following the approved 1 mg dose of neffy due to the anatomy differences between children < 4 years of age and > 4 years of age. Particularly, the different sizes of nostril by age groups that may affect the drug delivery via a nasal spray device (e.g., the tip of neffy nasal spray device may not be small enough to be inserted into nostrils in children < 4 years of age).

However, there is no dedicated studies conducted to investigate the growth of nostril size throughout the age range in young children. In a response to Information Request dated July 10, 2025, the Applicant submitted two publications indicating that the mean ± standard deviation of nostril size ranged from 10.64 ± 1.66 mm to 12.31 ± 1.24 mm in children 4-5 years of age[1], and 4.26 ± 0.60 mm to 4.31 ± 0.61 mm in newborns with gestational age > 37 weeks and birth weight ≥ 3 kg[2]. The Applicant did not find any literature that evaluated nostril size in children aged 2 to 3 years. Assuming a stable growth of nose, the Applicant estimated that the nostril size of children aged 2 to 3 years should be between that of newborns and that of children aged 4 to 5 years (4 to 12 mm). Of note, the size of the tip of neffy/Valtoco nasal spray device is 10.4 mm.

[1] Sforza C, Dolci C, Gibelli DM, et al. Age-related and sex-related changes in the normal soft tissue profile of native Northern Sudanese subjects: a cross-sectional study. Br J Oral Maxillofac Surg. 2016;54(2):192-197. doi:10.1016/j.bjoms.2015.11.015

[2] Ribeiro DFC, Nakato AM, Hembecker XPK, Fernandes BL, Nohama P. Correlation between nasal anatomical characteristics in newborns and short binasal prong dimensions. J Pediatr (Rio J). Published online October 28, 2023. doi:10.1016/j.jped.2023.09.007

The possibility that the nostril size is smaller than the size of tip of neffy/Valtoco for children aged < 4 years with body weight ≥ 15 kg cannot be ruled out based on available literature for nostril sizes in different ages. It is unclear how nostril size in this age group will affect the drug delivery using neffy spray device.

Given the knowledge gap of nostril size in children < 4 years of age, the review team considers that unless there is a dedicated PK study demonstrating that the different sizes of nostril between children < 4 years of age and > 4 years of age within the same body weight category (i.e., 15 kg to < 30 kg) do not impact the drug delivery by the same neffy device and with the same delivery volume (0.1 mL), a nostril size measurement study in children < 4 years is likely needed to support the removal of age restriction in the label.

In alignment with the Agency's thinking, in the same response letter dated July 10, 2025, the Applicant referred to a recently approved (on April 15, 2025) pediatric supplement (Supplement 10) of Valtoco (NDA 211635), a diazepam nasal spray product uses the same intranasal spray device and spray volume (i.e., 0.1 mL per spray) as neffy. NDA 211635 Supplement 10 supported approval of Valtoco nasal spray product in pediatric subjects with epilepsy down to 2 years of age.

Given the criticalness of Valtoco evidence, in the same GAL dated August 19, 2025, the Agency requested the Applicant to revise Form FDA 356h specifying reliance on NDA 211635 Valtoco as an additional relied-upon listed drug. On September 4, 2025, the Applicant submitted a right of reference letter from Valtoco sponsor Neurelis Inc. to provide FDA an access to NDA 211635 (Supplement 10) in reviewing NDA 214697 Supplement 2.

The approval of NDA 211635 Supplement 10 was supported by a pediatric PK trial DIAZ.001.08 conducted in pediatric subjects aged 2 years to 5 years. The study demonstrated that following the single dose of intranasal administration of Valtoco, diazepam systemic exposures in children 2 to 5 years of age following the proposed dose is comparable to or higher than diazepam exposures in adults 18 years and older following the approved dose. For details, refer to Clinical Pharmacology review by Dr. Adarsh Gandhi and Dr. Michael Bewernitz.[3] The bioanalytical method used in trial DIAZ.001.08 was reviewed by Dr. Jagan Mohan Parepally and Angela Men.[4]

The neffy clinical pharmacology review team re-visited trial DIAZ.001.08 and conducted a separate analysis comparing the diazepam systemic exposure between children 2 to < 4 years and children ≥ 4 years with body weight ≥ 15 kg following the same dose (i.e., 10 mg). The results demonstrated a similar systemic exposure of diazepam between two age groups. Therefore, based on the same nasal spray device and spray volume between Valtoco and neffy, PK

[3] Cross-Discipline Team Leader Review for NDA 211635/S-10 dated December 18, 2024 (Reference ID: 5498374)
[4] Clinical Pharmacology Review for Original NDA 211635 dated October 3, 2019 (Reference ID: 4501611)

comparison results from trial DIAZ.001.08 sufficiently provided the needed justification to relieve the concern of impact of nostril size on neffy drug delivery via neffy nasal spray device in children 2 years and above.

The reviewer acknowledges that the 95th percentile of body weight in children 23.5 months old is about 15 kg[5]. For evaluating the usage of neffy in children younger than 2 years of age with body weight ≥ 15 kg, defer to clinical review of this supplement.

1.1 Recommendations

The Office of Clinical Pharmacology reviewed the submission and recommend approval for the following labeling changes:

- Remove the age restriction (4 years and older) without changing of the body weight cutoff (i.e., 15 kg) in the drug label.
- Modify "Avoid sniffing during and after administration" to "refrain from sniffing during and after administration due to potential decrease in the absorption of neffy. Monitor clinically to assess if a second dose is needed" in the label

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Evaluation of systemic exposure of a drug between children 2-5 years of age when delivered by a nasal spray device that is the same as neffy

DIAZ.001.08 is a single-dose, open-label PK study in pediatric subjects with epilepsy aged 2 years to 5 years old. A single dose of 5 mg, 10 mg or 15 mg was administered during an interictal period based on body weight as shown below:

- 6 kg to 11 kg: 5 mg in 0.1 mL
- 12 kg to 22 mg: 10 mg in 0.1 mL
- 23 kg to 33 kg: 15 mg in 0.1 mL

PK samples were collected from each subject at specified time depending on the sequence allocation of this subject. Each subject was assigned to one of the three PK sampling sequences:

- Sequence 1: Pre-dose, 60-, 120-, 180-, 240-, and 360-min time points
- Sequence 2: Pre-dose, 15-, 75-, 195-, 300-, and 360-min time points
- Sequence 3: Pre-dose, 45-, 90-, 150-, 210-, and 360-min time points

[5] https://www.cdc.gov/growthcharts/data/zscore/wtageinf.csv

The baseline age and body weight for subjects who participated in this trial are shown in **Table 1**. As 10 mg was administered in both age groups (2 to 3 years and 4 to 5 years). This review focused on diazepam PK data following 10 mg.

Table 1. Median (Range) Baseline Age and Body Weight for Subjects in Trial DIAZ.001.08

Age Group	**2 to 3 years**		**4 to 5 years**	
Dose	**5 mg**	**10 mg**	**10 mg**	**15 mg**
N	3 (N=2 for age 2)	16 (N=5 for age 2)	13	4
Age (year)	2.4 (2-3.8)	3.55 (2-3.9)	4.6 (4-5.8)	5 (4.8- 5.3)
Body Weight (kg)	11 (11-11.2)	15.9 (12.8-19.8)	17 (13.8-20.4)	30.3 (23.6-32.2)

Source: adsl.xpt for trial DIAZ.001.08

Since neffy is currently approved for subjects ≥ 15 kg, this review will focus on the comparison of diazepam PK data from subjects who weighed ≥ 15 kg following a single dose of 10 mg between two age groups: 2 to 3 years (N=12) and 4 to 5 years (N=11). The selected body weight cutoff is the same as approved body weight range of neffy to ensure that the nostril sizes of these subjects reflect those who may be eligible to use neffy based on the currently approved weight-based dosing. The diazepam PK comparison between two age groups will help evaluate whether the drug device is adequate to deliver drug in younger subjects (age 2 to 3 years) who may have smaller nostril.

The Office of Study Integrity and Surveillance (OSIS) was consulted to conduct clinical and bioanalytical site inspections for Study DIAZ.001.08 and the results were discussed in the review for NDA 211635 S-10.[6] The OSIS reported that one subject ((b) (6) , age 3 years) from sample sequence 1 whose blood drawn for PK samples could not be determined.[7] This subject is thus excluded from this review.

The PK comparison results (**Table 2**) showed similar diazepam AUCs, Cmax, and Tmax values between children 2 to 3 years of age and children 4 to 5 years of age, indicating that different nostril size between these two age groups, if there are any, do not affect the mean systemic exposure/bioavailability of diazepam by Valtoco/neffy nasal spray device.

Table 2. Geometric Mean (CV%) Diazepam PK Parameters by Age Group in Pediatric Subjects Weighing 15 kg or Greater Following a Single Dose of 10 mg Valtoco, Trial DIAZ.001.08

PK Parameter	**2 to 3 years (N=9)**	**4 to 5 years (N=9)**
$AUC_{0\text{-}3h}$ (ng*h/mL)	221.8 (138.6)	277.6 (117.5)
AUC_{last} (ng*h/mL)	556.4 (132.8)	671.5 (113.4)
C_{max} (ng/mL)	133.3 (138.0)	157.5 (119.6)
T_{max} (h)[a]	3.3 (1.8, 6.1)	3.2 (1.2, 6.0)

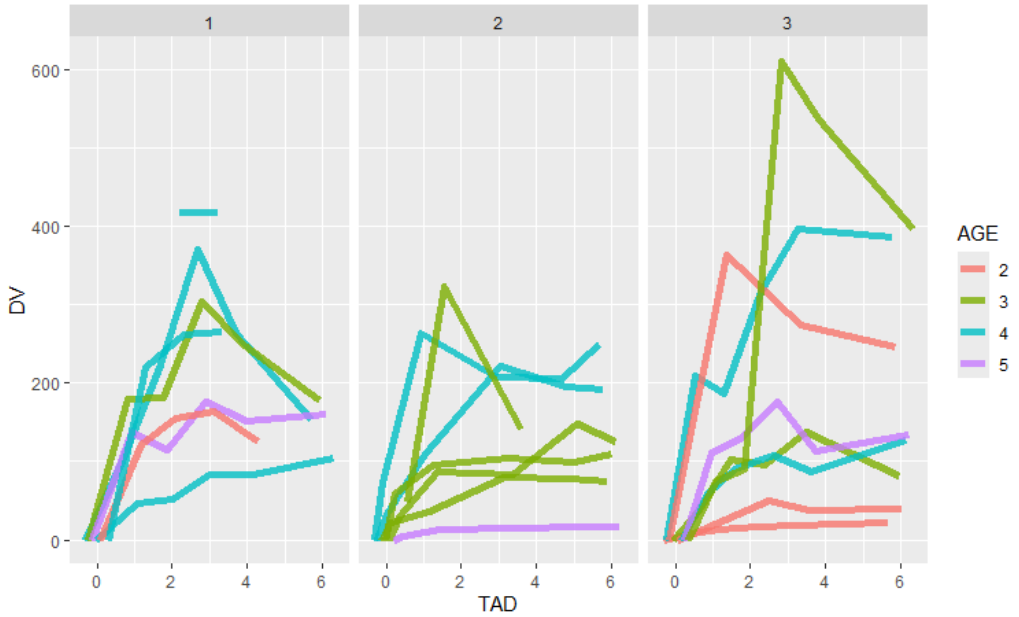
[6] NDA 211635/S-10 Cross Discipline Team Leader Review (Reference ID: 6598374)
[7] OSIS Review NDA 211635/S-10 (Reference ID: 5439001)

Source: NMPKFORM.xpt dataset NDA 211635 SDN372. Subjects (N=2 from 2-3 years group and N=2 from 4-5 years group) with missing sample at 6 h were excluded.
[a] Median (range)

To further ensure the PK comparison results, the reviewer examined and compared the diazepam PK profiles at individual level by different PK sampling scheme (i.e., three PK sampling schemes were investigated by three PK sampling sequences, respectively, in Study DIAZ.001.08).

When looking at the individual PK profile in each sample sequence, two subjects aged 2 years old in sample sequence 3 had lower diazepam PK (<60 pg/mL over 6 hours post-dose), as shown in **Figure 1**. It was also noted that one subject aged 5 years old from sample sequence 2 also had lower diazepam PK in around 10 to 20 pg/mL range over 6 hours post-dose. Given that low diazepam exposure was observed in the 5-year-old subject, which was unlikely explained by small nostril size, the results may reflect a high PK variability of diazepam when delivered by the Valtoco/neffy nasal device.

Figure 1. Individual Diazepam Concentration Time Profiles Following A Single Dose 10 mg Valtoco Grouped by Sample Sequences and Age, Trial DIAZ.001.08



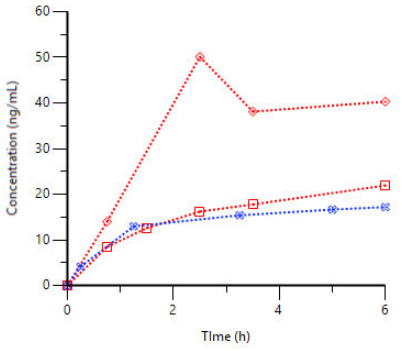
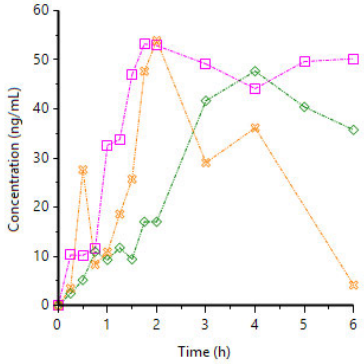
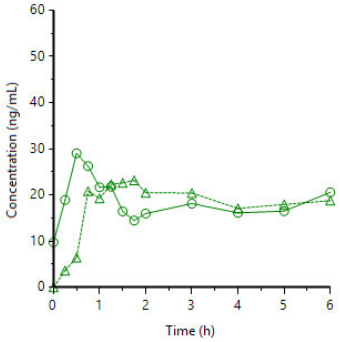
Source: reviewer's analysis based on NMPKFORM.xpt dataset NDA 211635 SDN372
TAD=time (h); DV=concentration (ng/mL)

Next, the reviewer compared the pediatric exposure from trial DIAZ.001.08 to PK results from another trial (DIAZ.001.04) in adult and pediatric subjects aged 6 years and older with epilepsy who received a single dose of Valtoco under both ictal or peri-ictal conditions and normal (i.e., non-seizure) condition. Trial DIAZ.001.04 was reviewed under Original NDA 211635 clinical

pharmacology review by Dr. Jagan Mohan Parepally and Angela Men.[8] Large inter-subject variability for diazepam PK following Valtoco has been noted in the previous review.

In trial DIAZ.001.04 under normal conditions, there were 3 out of 11 subjects (27%) and 2 out of 14 subjects (14%) in 10 mg and 15 mg groups, respectively, with low diazepam systemic exposure (< 60 ng/mL over 6 hours post-dose). The low systemic exposure of diazepam observed in the younger pediatric subjects (2 and 5 years old) from trial DIAZ.001.08 were within the range of subjects who were 6 years and older in DIAZ.001.04, as shown in **Figure 2**. Of note, the same bioanalytical method was used to assess diazepam in these studies.

Figure 2. Individuals With Low Diazepam PK, Trials DIAZ001.08 and DIAZ001.04

DIAZ.001.08 Individual with Low Diazepam PK (< 60 ng/mL) 10 mg During Interictal Period	DIAZ.001.04 Individual with Low Diazepam PK (< 60 ng/mL) 10 mg Under Non-Seizing Condition	DIAZ.001.04 Individual with Low Diazepam PK (<60 ng/mL) 15 mg Under Non-Seizing Condition
 Red: 2 years old Blue: 5 years old	 Yellow: 6 to 11 years Purple: 12 to 16 years Green: > 16 years	 Green: > 16 years old

Source: reviewer's analysis based on NMPKFORM.xpt from NDA 211635 SDN372 and adpc.xpt for DIAZ.001.04 from NDA 211635 SDN 113. Each line represents a PK profile from an individual participated in respective studies.

Therefore, examining and comparing the diazepam individual PK profiles between children and adults further confirmed high PK variability of diazepam when delivered by Valtoco/neffy nasal spray device.

In conclusion, PK results from DIAZ.001.08 supported that the nasal device used for Valtoco, which is identical to neffy, can deliver drug of the same volume (0.1 mL) in pediatric subjects aged 2 to < 4 years of age with the comparable bioavailability when compared to pediatric subjects 4 to 5 years of age with body weight ≥ 15 kg.

[8] Clinical Pharmacology Review for Original NDA 211635 dated October 3, 2019 (Reference ID: 4501611)

2.2. Impact of Sniffing on Epinephrine PK

In the original NDA review of neffy, the geometric mean epinephrine PK profile was noticeably lower in subjects who sniffed during or after neffy administration (N=29) compared to those who did not (N=13) in self-administration trial EPI 17[9]. Based on this sensitivity analysis, in the original review, in order to maximize the clinical benefit from neffy, the review team considered it is necessary to include a labeling language to instruct patients to avoid sniffing.

In this supplement, the Applicant revisited this topic without providing additional data and justified that the majority of subjects may instinctively sniff after administration of a nasal spray. This has been reflected in EPI 17, as 29 out of 42 subjects (70%) experienced sniffing when self-administered neffy. In addition, the Applicant also noted a theoretical concern that the current language may lead to a misinterpretation by the community that patients will need to take a second dose if they sniff during the first dose regardless of their symptom control status after the first dose.

While the review team agrees that sniffing does not necessarily translate into the need of the second dose, a proper dosing instruction should be included in the labeling based on available data to inform prescribers and patients, especially when there was a noticeable trend of lower epinephrine PK observed in subjects who sniffed in EPI 17 and there was no additional data provided by the Applicant to definitively rule out the potential adverse impact on efficacy. Therefore, the review team agrees to modify the current labeling language "avoid sniffing during and after administration" to "refrain from sniffing during and after administration due to potential decrease in the absorption of neffy. Monitor clinically to assess if a second dose is needed".

[9] Unireview for Original NDA 214697 (neffy) dated September 19, 2023 (Reference ID: 5246974)

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