Division of Pulmonology, Allergy, and Critical Care Memorandum

Date	January 13, 2026
NDA	214697
Drug Name(s)	neffy (epinephrine nasal spray)
Sponsor	ARS Pharmaceuticals
Indication	emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients 4 years of age and older who weigh 15 kg or greater
Clinical Review Team	Jennifer Lan, MD Miya Paterniti, MD

Executive Summary

This Division of Pulmonology, Allergy, and Critical Care (DPACC) clinical memorandum addresses NDA 214697 (neffy/epinephrine nasal spray) efficacy supplement S-002, wherein the Applicant proposed four key modifications to the product labeling:

- removal of the age restriction limiting use to patients 4 years and older
- (b) (4) instruction to "avoid sniffing during and after administration"
- modification of the excursion statement regarding freezing conditions
- revision of the excursion statement pertaining to high temperature exposures

The recommendation is **approval** of this efficacy supplement with acceptance of removal of the age from the indication and minor modifications to excursion statements and sniffing instructions. However, due to a delay in the Sponsor submitting certifications to patents, a tentative approval will be issued. A full approval will be issued once the 45- day waiting period ends on February 27, 2026 for any potential litigation on patent infringement and the 505(b)(2) committee is able to clear the application.

Background

Neffy is currently indicated for the emergency treatment of type I allergic reactions, including anaphylaxis, in adults and pediatric patients 4 years of age and older who weigh 15 kg or greater. The age limitation was originally established based on the Applicant's assessment in their Pediatric Study Plan that the device was only suitable for patients 4 years of age and older due to potential anatomical constraints related to nares size in younger pediatric subjects. Consequently, the pediatric pharmacokinetic (PK) trial (EPI 10) was conducted exclusively in subjects 4 years of age and older weighing ≥ 15 kg. Studies in pediatric subjects < 4 years of age were waived because necessary studies are impossible or highly impracticable (with the current device).

(b) (4)

The Division recognizes the clinical significance of removing the age limit from the current indication given the potential therapeutic gap that could result from maintaining the age restriction. (b) (4) ,without a regulatory pathway to remove the age limitation for subjects weighing more than 15 kg, a subset of pediatric patients (those weighing more than 15 kg but under 4 years of age, such as a 3-year-old weighing more than 15 kg) could potentially lack access to this therapeutic option.

Therefore, the Division collaborated with the Applicant to identify an appropriate regulatory pathway to remove the age restriction.

Removal of Age Restriction

The Applicant initially proposed removing the age as other epinephrine products do not include an age limitation, and the device used for neffy is approved down to 2 years of age for Valtoco based on clinical PK data in patients down to 2 years of age, but did not include any data; Valtoco was not included as a listed drug. In response to an Information Request sent June 16, 2025, the Applicant submitted on July 10, 2025, two publications providing nares size for children 4-5 years of age (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) and mean nostril size of newborns (4.26 ± 0.60 mm to 4.31 ± 0.61 mm). 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.

Given the knowledge gap of nostril size in children < 4 years of age, the Agency requested Valtoco be included as a listed drug so that the Valtoco PK study down to 2 years of age could be relied upon to remove the indicated age. In response, the Applicant submitted a right of reference letter to Valtoco (NDA 211635).

The supportive evidence from pediatric PK trial DIAZ.001.08, conducted in subjects 2 to 5 years of age for the Valtoco supplement, was leveraged to justify removing the age restriction for neffy. This trial demonstrated that following single-dose intranasal administration of Valtoco, diazepam systemic exposures in children 2 to 5 years of age were comparable to or exceeded diazepam exposures observed in adults 18 years and older following the approved dose. The neffy clinical pharmacology team conducted an additional 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. Given these findings for Valtoco and considering the identical nasal spray device and spray volume utilized by both Valtoco and neffy, the neffy clinical pharmacology team determined that the PK comparison results from DIAZ.001.08 provided sufficient justification to address concerns regarding the impact of nostril size on drug delivery via the neffy nasal spray device in children 2 years of age and above, as detailed in Dr. Qianni Wu's clinical pharmacology review (in DARRTs February 3, 2026).

Although the clinical pharmacology review indicated that the available data were sufficient to support use in children under 2 years of age, age was not included in the indication for the following reasons:

1. A weight-only indication aligns with class labeling for epinephrine products for anaphylaxis
2. Children under 2 years of age rarely weigh 15 kg or more. Analysis of CDC growth charts (used for 2 years of age and above) revealed that 2-year-olds at the 95th percentile would weigh 15 kg or above. Using the WHO growth curve (which is used from 0 to 24 months of age), a 17-month-old weighing 15 kg would be at the 99th percentile in weight. At 24 months (or newly 2 year of age) child, a child who weighs 15 kg would fall between the 85th or 90th percentile according to the WHO growth curve.

The Valtoco study was not included in labeling as the primary evidence to support approval for pediatric subjects ≥ 15 kg relies upon the trial conducted pediatric pharmacokinetic trial (EPI 10) was conducted in subjects 4 years of age and older weighing ≥ 15 kg.

Sniffing Instructions

The impact of sniffing on drug absorption was previously evaluated in the original review of neffy (dated September 19, 2023). The original review demonstrated that the geometric mean epinephrine PK profile was notably reduced in subjects who sniffed during or after neffy administration, leading to the inclusion of labeling language instructing patients to avoid sniffing. The Applicant requested (b) (4) due to concerns that patients might unnecessarily administer a second dose if they accidentally sniffed during or after administration. As no additional supporting data were provided, the Division did not agree with (b) (4) . Instead, the Division revised the language to "refrain from sniffing" and added the instruction to "monitor clinically to assess if a second dose is needed" to address the Applicant's concerns while maintaining appropriate safety guidance.

The Patient Information was also modified to “Avoid sniffing during or after receiving a dose of neffy. If you do sniff by accident, and your symptoms continue or get worse, give a second dose of neffy in the same nostril, starting 5 minutes after the first dose” to align with the prescribing information

Excursion Statements

The Applicant proposed two modifications to excursion statements. First, under Section 16, the Applicant proposed a minor linguistic modification from "if neffy freezes, it will not deliver epinephrine" to "if neffy is frozen, it will not deliver epinephrine." Additional specificity was incorporated into the Patient Information section, explicitly stating not to intentionally freeze the product below 5°F. The Division accepted this modification as appropriate and further added “neffy may be used if it has been thawed after being previously frozen.”

The Applicant further proposed modifying the Patient Information section to remove [(b) (4)] " regarding storage or exposure of neffy to high temperatures up to 122°F. The Division disagreed with removal of [(b) (4)], as this would leave patients without guidance regarding [(b) (4)], potentially resulting in increased overall product degradation and concomitant decreased efficacy.

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