CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214697Orig1s000

OTHER ACTION LETTERS

NDA 214697

COMPLETE RESPONSE

ARS Pharmaceuticals, Inc.
C/O Pacific Link Consulting
11682 El Camino Real
Suite 120
San Diego, CA 92130

Attention: Richard Lowenthal
CEO and President

Dear Richard Lowenthal:

Please refer to your new drug application (NDA) dated August 19, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Neffy (ARS-1, epinephrine nasal spray), 2 mg/0.1 mL.

We acknowledge receipt of your major amendments dated May 30, 2023, and June 5, 2023, which extended the goal date by three months, September 19, 2023.

We have completed our review of this NDA, as amended, and have determined that we cannot approve this NDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/CLINICAL PHARMACOLOGY

Deficiency

Anaphylaxis is a life-threatening emergency and approval for this indication, in the absence of clinical efficacy trials, requires a high level of confidence in the PK/PD results under conditions likely to be encountered by the target population. Since PK/PD data were not obtained from subjects with anaphylaxis, a nasal allergen challenge approach was agreed upon to reflect changes in the nasal mucosa that may be present in some patients with anaphylaxis; these changes may impact absorption of ARS-1. In addition, proposed labeling for ARS-1, in alignment with labeling for approved epinephrine injection products, recommends administration of a second dose for patients with severe persistent anaphylaxis. The submitted data do not provide substantial evidence of effectiveness for the use of ARS-1 (epinephrine nasal spray) for its proposed indication, the treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh ≥ 30 kg, under conditions likely to be encountered by the target population.

The single dose ARS-1 PK/PD comparison to single dose epinephrine injection products in subjects with allergen-induced acute rhinitis (EPI 16) raises concerns regarding the durability of the drug's effect under such conditions. Specifically, although systolic blood pressure remained comparable or higher than the Adrenalin comparator through 60 minutes, the ARS-1 epinephrine plasma concentration and pulse rate reduced to below that of Adrenalin 0.3 mg starting approximately 20 minutes after administration. In addition, a repeat dose trial has not been conducted in subjects with allergen-induced acute rhinitis to compare PK/PD findings for ARS-1 to single and repeat doses of a listed epinephrine injection product. A repeat dose trial is necessary to address concerns of durability of effect from a single dose, and to demonstrate sustainability and strength of PK/PD for patients with severe persistent anaphylaxis who may require a repeat dose, consistent with proposed conditions of use. Since the initial dose of ARS-1 administered under acute rhinitis conditions may impact the PK/PD profile of a subsequent dose administered in the same naris, and in the absence of clinical data to reliably predict the effects, a repeat dose study is also needed to provide PK/PD profiles with repeat dosing under acute rhinitis conditions when administered in the ipsilateral or contralateral naris, reflective of anticipated real-world use. Due to the complex interaction between allergen-induced acute rhinitis and local pharmacologic effects of epinephrine, adequate PK/PD data assessing durability of effect in patients with allergen-induced acute rhinitis are needed to have confidence in the results sufficient to support approval.

Information to Resolve Deficency

In order to resolve the above deficiency, provide PK/PD data assessing repeat doses of ARS-1 compared to repeat doses of epinephrine injection product(s) under allergen-induced allergic rhinitis conditions. Include an assessment of PK/PD findings when the second dose of ARS-1 is administered in the ipsilateral and contralateral naris.

PRODUCT QUALITY

Deficiency

FDA expects manufacturers and applicants to ascertain the presence of Nitrosamine Drug Substance-Related Impurities (NDSRIs) in their drug products. FDA has recommended, in guidance, a 3-step mitigation strategy.[1] The 3-steps are: 1) conduct risk assessments for nitrosamines in APIs and drug products; 2) conduct confirmatory testing if risks are identified; and 3) report changes implemented to prevent or reduce the presence of nitrosamine impurities in APIs and drug products in approved and

[1] On August 7, 2023, FDA published a guidance for industry, *Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)* (August 2023) (NDSRI Guidance), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-acceptable-intake-limits-nitrosamine-drug-substance-related-impurities. The NDSRI Guidance refers to a 3-step mitigation strategy described in FDA's guidance for industry, Control of Nitrosamine Impurities in Human Drugs (Feb. 2021) (Nitrosamine Guidance) (b) (4)

pending NDAs and ANDAs. With respect to applications pending before the Agency, the NDSRI Guidance states that "[a]pplicants with pending applications should conduct a risk assessment for NDSRIs expeditiously and inform FDA if confirmatory testing finds NDSRI levels above the [acceptable intake] [AI] limits recommended in this guidance. If an NDSRI is detected above the recommended AI limit, the applicant should amend the application as appropriate." [2]

(b) (4)

Your NDA does not include data or information, such as a risk assessment, and/or confirmatory testing data as needed, demonstrating that you have ascertained the presence of NDSRIs in your drug product, including specifically (b) (4)

Information to Resolve Deficency

Provide information to FDA regarding potential NDSRIs in your application, specifically with respect to (b) (4)

If the (b) (4) impurity is detected in your drug product, submit confirmatory testing data using sensitive and appropriately validated analytical method(s) from at least three primary batches to demonstrate that (b) (4) (b) (4) in your drug product is at or below the level corresponding to the recommended AI limit ((b) (4) ng/day) based on the approved maximum daily dose (MDD) at release and throughout the shelf-life. FDA recommends that applicants develop an appropriate control strategy to ensure that the nitrosamine level is reliably at or below the recommended AI limit in your submission (b) (4)

If the level of (b) (4) is above the corresponding recommended AI limit ((b) (4) ng/day) based on the approved MDD at release and throughout the shelf-life,

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(b) (4)

investigate the root cause and implement changes in the manufacturing process or product formulation to eliminate, mitigate, or reduce nitrosamine impurity consistent with the recommendations in the NDSRI Guidance referenced above if applicable (b) (4) (b) (4)

Alternatively, you may provide a scientifically justified rationale to pursue an AI limit different than the FDA recommended AI limit associated with N-nitroso-epinephrine. For FDA's current thinking on this topic, refer to the recommendations in the NDSRI Guidance referenced above, if applicable (b) (4) (b) (4)

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[6]

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, November 2, 2022 which addresses the proposed proprietary name, Neffy. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[5] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[6] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

DEVICE

In your submission, you included cytotoxicity, sensitization, and irritation testing for the Aptar device constituent part of the proposed combination product. Additionally, you provided cytotoxicity and sensitization testing for the (b) (4) device constituent part of the proposed combination product. However, you did not provide irritation testing for the (b) (4) device constituent part of the proposed combination product. An adequate irritation assessment is important because exposure to the device (if it includes even a small amount of an irritant) can result in a localized non-specific inflammatory response which can lead to redness, swelling, itching, dryness, cracking of the skin, blistering or pain. Therefore, provide methods and results from irritation testing of the (b) (4) device constituent part of the proposed combination product (e.g., according to a recognized standard such as ISO 10993-10). Refer to recommendations in Attachment A of FDA's Biocompatibility Guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" (https://www.fda.gov/media/85865/download) for devices with your nature and duration of tissue contact,

OTHER

We note that on June 12, 2023, Viatris Inc. submitted a citizen petition to FDA (Docket No. FDA-2023-P-2392) regarding Neffy (NDA 214697). The issues raised by this peititon are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. The comments included in this communication reflect the deficiencies that CDER has determined preclude approval of the NDA in its current form, and do not represent a final decision by the Agency on approval of the NDA or the issues raised in the pending citizen petition.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.110(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Ji Hyun LaRose, Regulatory Project Manager, at (301) 796-9017.

Sincerely,

{See appended electronic signature page}

Kelly Stone, MD, PhD
Associate Director for Therapeutic Review
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KELLY D STONE
09/19/2023 03:11:30 PM