NDA 219870

COMPLETE RESPONSE

Aquestive Therapeutics Inc.
Attention: Melina Cioffi, PharmD
Vice President, Regulatory Affairs
30 Technology Drive
Warren, NJ 07059

Dear Dr. Cioffi:

Please refer to your new drug application (NDA) dated and received (b) (4), and your amendments, submitted pursuant to (b) (4), for dibutepinephrine sublingual film.

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

HUMAN FACTORS AND CLINICAL

The results of the human factors (HF) validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. Specifically:

- Participants demonstrated difficulty opening the pouch, were unable to open the pouch, or tore the film while opening the pouch. Resulting delays in dose administration, inability to administer a dose, or underdosing raises significant safety concerns in the setting of anaphylaxis.

- Participants placed the film in incorrect locations or chewed the film. The impact on PK and clinical efficacy related to the chewing or incorrect placement of the film (i.e. placing it on the roof of the mouth or on the tongue) is uncertain.

- Some participants, mainly pediatric participants, identified “tingling” or “burning” and/or taste that led them, or would lead them, to remove the film prematurely. We note the HF study used a placebo with a different formulation compared to dibutepinephrine sublingual film that limits interpretation of these results. However, based on this finding in the HF study and the high rate of local adverse events reported in the pivotal PK trials, tolerability of dibutepinephrine sublingual film is a concern.

- We also note that there were several use issues with other critical tasks (besides the ones noted above) where several participants provided subjective feedback that they did not see instructions/were not aware of the instructions or pointed to label organization as the root cause.

We acknowledge the additional risk controls implemented post-validation; however, our review indicates that additional risk controls are necessary.

To resolve the deficiencies, you need to:

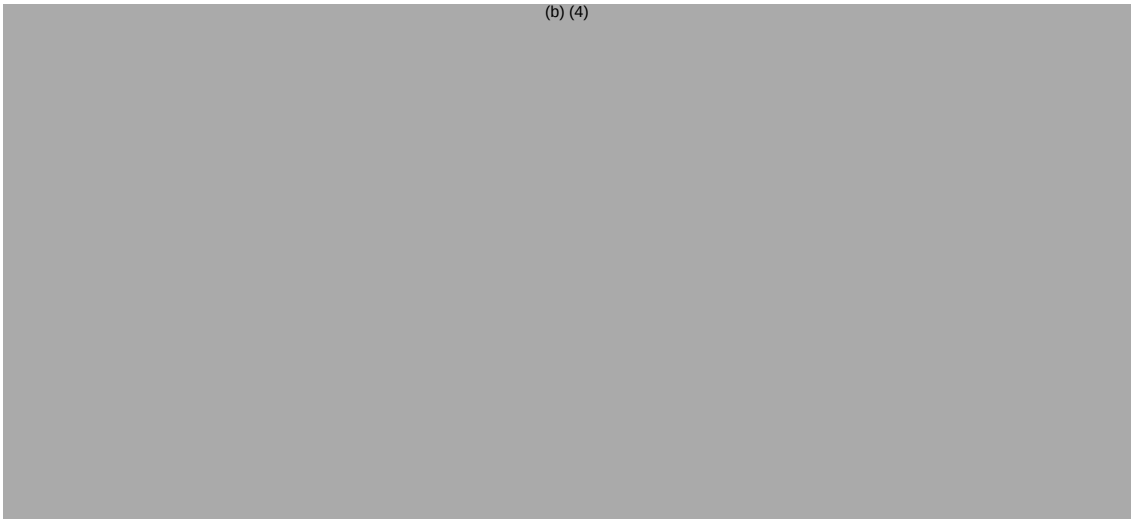
1. Review the HF study results and subjective feedback *for all tasks* to identify additional, potential areas of optimization. Additionally, we acknowledge you implemented post-validation risk controls to address some identified use issues (i.e., incorrect placement of the film); however, based on the criticality of the impacted tasks, the revised user interface and additional risk controls should be evaluated for effectiveness.

2. Implement additional design modifications and user interface revisions identified in item #1 above, along with the following recommendations:

    a. Container Closure Design

        i. Revise the opening mechanism of the proposed container closure or consider an alternative container closure design to address the observed use issues with opening the proposed container closure. When redesigning the opening mechanism, consider the risk of the film being torn during opening and a user not being aware of the tear, which may lead to underdosing.

    b. Instructions for Use



(b) (4)

c. Pouch Label

(b) (4)

d. Carton Labeling

(b) (4)

3. Conduct another HF validation study to demonstrate that the revised user interface supports the safe and effective use of the product. In your HF validation study, include a placebo with the same formulation as dibutepinephrine sublingual film (without the active ingredient).

4. Address potential tolerability use issues in your resubmission.

CLINICAL PHARMACOLOGY

Given findings from the HF validation study, there are uncertainties regarding how some use errors may impact the epinephrine pharmacokinetic (PK) concentration-time profile following the incorrect administration of dibutepinephrine sublingual film. To address these uncertainties, evaluate epinephrine PK under the following three conditions (you may choose to evaluate these three conditions in a parallel-group design):

1. Dibutepinephrine sublingual film administered with chewing the film both with and without swallowing.

2. Dibutepinephrine sublingual film administered at alternative sites consistent with observations in the HF validation study (e.g., top of tongue, roof of the mouth).

3. Dibutepinephrine sublingual film given via self-administration with final instructions that reflect the recommended design modifications and user interface revisions based on the new HF validation study.

To better interpret the PK/PD results under these conditions and to compare the results to the existing results obtained from the completed clinical pharmacology studies, it is pertinent that every subject in this study also receive two additional control treatments:

1. Dibutepinephrine sublingual film administered by trained staff with instructions consistent with those used in Trial AQ109301.

2. A listed epinephrine injection product.

Of note, future revisions of the design, user interface, and administration instructions, and results of the new HF validation study will not obviate the need to evaluate epinephrine PK following the administration of dibutepinephrine sublingual film under the aforementioned conditions.

ADDITIONAL COMMENTS

We have the following comment/recommendation that is not an approvability issue:

Refer to the Filing Communication dated (b) (4). The uncertainty of the impact of drinking liquid/water immediately before the administration of dibutepinephrine sublingual film on epinephrine PK remains, as Trial AQ109203 did not include a within-study comparison to epinephrine PK following administration of injection products and dibutepinephrine sublingual film given with the same instructions used in Trial AQ109301 (i.e., no fluid/water administration prior to dibutepinephrine sublingual film dosing). Therefore, we recommend you evaluate epinephrine PK following dibutepinephrine sublingual film administration with or without immediate prior water

intake and compare to epinephrine PK following administration of a listed injection product.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Please refer to our correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

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.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

OTHER

We note that on October 1, 2025, ARS Pharmaceuticals Inc., through Arnall Golden Gregory, LLP, submitted a citizen petition to FDA (FDA-2025-P-4612) regarding AQST-109 Epinephrine Sublingual Film (“Anaphylm”). The issues raised by that petition are currently under review by the Agency, and FDA has not made any final decisions with respect to the petition. 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. 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 314.65. 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 product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact (b) (4) .

Sincerely,

{See appended electronic signature page}

(b) (4)

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/

(b) (4)

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