U.S. FOOD & DRUG ADMINISTRATION

NDA 218995

COMPLETE RESPONSE

Achieve Life Sciences, Inc.
22722 29th Dr. SE, Suite 100
Bothell, WA 98021

Attention: Sarah Telzrow
Vice President, Regulatory Affairs

Dear Sarah Telzrow:

Please refer to your new drug application (NDA) dated and received June 20, 2025, and your amendments, submitted under [(b) (4)] for cytisinicline tablet, [(b) (4)].

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.

FACILITY INSPECTIONS

(1) Following a CGMP inspection of [(b) (4)], listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on FDA Form 483 prior to your Complete Response submission. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your application. Therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483. Please refer to Compliance Program CP 7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a prior approval inspection (PAI) of the facility.

PRESCRIBING INFORMATION

(2) Submit draft labeling that is responsive to our electronic communication dated June 4, 2026, as a part of your resubmission.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading
- Additional resources for the PI, patient labeling, and carton/container labeling.

MEDICATION GUIDE

(3) Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

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

PROPRIETARY NAME

Please refer to our correspondence dated September 17, 2025, 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 drug 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 drug. Include an updated estimate of use for drug marketed in other countries.

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

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

As described in our letter dated April 22, 2026, we have determined that, if this application is approved, you will be required to conduct postmarketing studies to assess signals of serious risks of adverse maternal, fetal, or infant outcomes due to exposure to cytisinicline during pregnancy; and to identify an unexpected serious risk of infant toxicity due to exposure to cytisinicline that may be present in human milk during lactation.

Any additional specific details of these required postmarketing studies, including timetables and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete these studies prior to re-submitting your application, you may include the final reports and relevant data sets in your Complete Response submission to facilitate review of the information.

ADDITIONAL COMMENTS

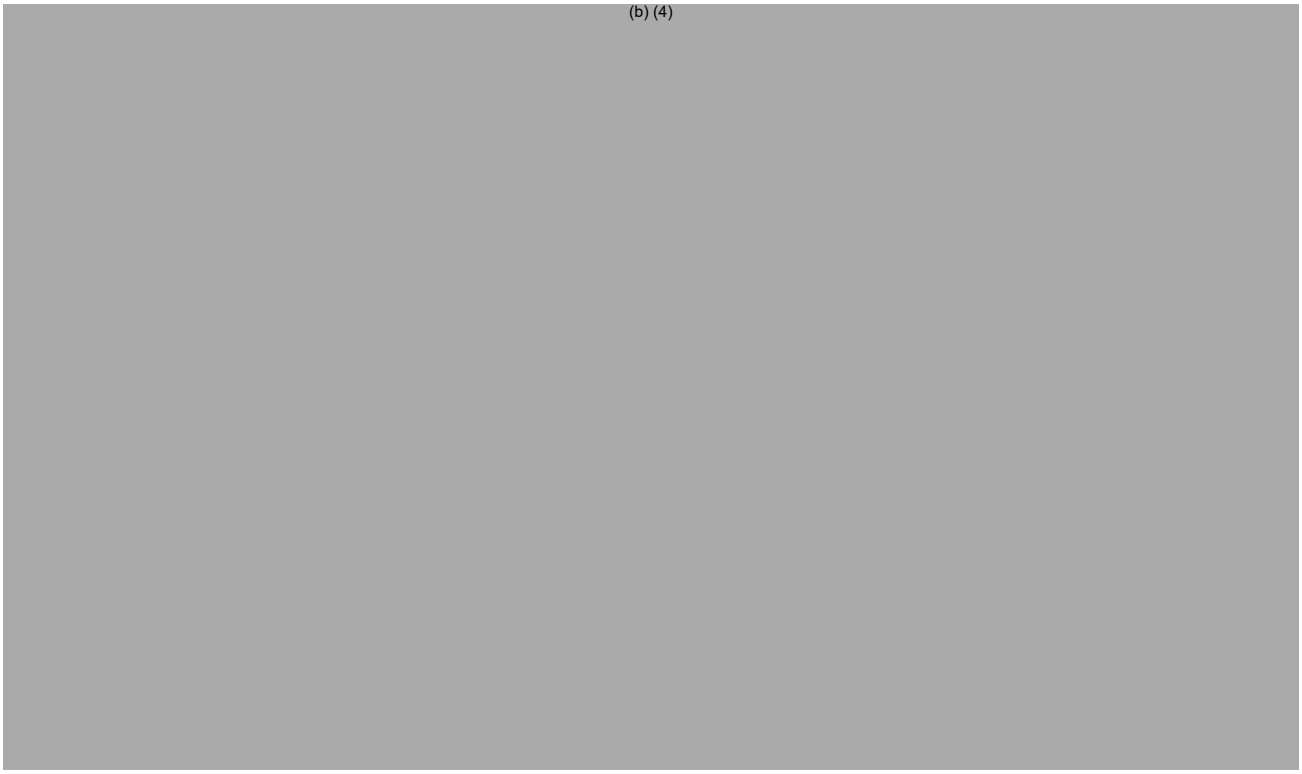
We have the following comments/recommendations that are not approvability issues:

Clinical Pharmacology:

The proposed dosing regimen of (b) (4) in End Stage Renal Disease (ESRD) patients is not adequately supported by the available pharmacokinetic data. Cytisinicline exposure in ESRD is critically dependent on dialysis-mediated drug removal, however, the available population pharmacokinetic simulations were conducted under a single fixed dialysis scenario. Thus, these simulations do not reflect the range of dialysis frequencies and session durations encountered in clinical practice. To support potential dosing recommendations for patients with ESRD, you should use modeling and simulation to characterize cytisinicline exposure across reasonably likely range of dialysis scenarios.

Nonclinical:

(b) (4)



OTHER

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*.

[4] See, e.g., FDA's draft guidance for industry titled, "Generally Accepted Scientific Knowledge in Applications for Drug and Biological Products: Nonclinical Information" (May 2023). When final, this guidance will reflect the Agency's current thinking.

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

If you have any questions, email (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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