

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214860Orig1s000

OTHER ACTION LETTERS



NDA 214860

COMPLETE RESPONSE

Acer Therapeutics Inc.
Attention: Renée M. Carroll, MS, RAC
Vice President, Head of Regulatory Affairs
One Gateway Center, Suite 351
300 Washington Street
Newton, MA 02458

Dear Ms. Carroll:

Please refer to your new drug application (NDA) dated and received on August 5, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for sodium phenylbutyrate.

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 INSPECTION

Our field investigator could not complete inspection of the Sharp Clinical Services, Inc., (FEI# 3003673570) manufacturing facility at 2400 Baglyos Circle, Bethlehem, PA, USA, 18020, because the facility was not ready for inspection. Satisfactory inspection is required before this application may be approved. Please notify us in writing when this facility is ready for inspection.

PRESCRIBING INFORMATION

Submit draft labeling that is responsive to our electronic communication dated June 15, 2022.

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

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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 Resources² and Pregnancy and Lactation Labeling Final Rule³ 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
- 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

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on our proposed revisions and communications dated May 24, 2022, and May 31, 2022.

PROPRIETARY NAME

Please refer to correspondence dated October 25, 2021, which addresses the proposed proprietary name, Olpruva. 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.

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>

SAFETY UPDATE

When you respond to the above deficiency 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.

ADDITIONAL COMMENTS

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

Nonclinical

In the chronic dog study of talc, absolute testis weights were statistically-significantly increased by 43-55% in all treated groups, and this abnormality persisted when absolute weights were normalized for terminal body weight or brain weight. There was no NOAEL established in this study for the testicular weight finding in males. The reason for this is unclear, as the pathology report has no microscopic correlative observations. No additional information or data have been submitted to help interpret this finding.

To facilitate further assessment of this finding, provide the following additional information in your resubmission:

- a. The exact ages of all dogs in the completed study, as well as the exact ages of the dogs in the testing facility's historical control database, and correlate these with testis weights, and
- b. A review of all published studies (in animals and/or humans) containing safety assessments with use of talc. Provide details including species, doses administered, and study durations for animal studies and relevant details for human studies. Summarize the relevance of this information to the dose of talc contained in 20 g of your proposed sodium phenylbutyrate product.

If the additional information and justification do not help elucidate the cause or mechanism for the testicular weight finding, you may need to conduct a new 9-month study of talc in male dogs using lower doses of talc than the ones used in the submitted study in order to identify a NOAEL. Longitudinal measurements of serum gonadotropins and testosterone, and accessory sex organ weights should be assessed. In the study report, include the exact ages (in weeks) of each dog at necropsy, as well as the exact ages of any dogs used by the testing facility in its historical control database.

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*.

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, contact Diego Diaz, Regulatory Project Manager, via email at Diego.Diaz@fda.hhs.gov or at (301) 796-7182.

Sincerely,

{See appended electronic signature page}

Patroula Smpokou, M.D.
Deputy Director
Division of Rare Diseases and Medical Genetics
(DRDMG)
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine (ORPURM)
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/

PATROULA I SMPOKOU
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