



NDA 218258

**COMPLETE RESPONSE**

Hikma Pharmaceuticals USA, Inc.  
Attention: Amy Schutte  
Senior Director, Regulatory Affairs  
2 Esterbrook Lane  
Cherry Hill, NJ 08003

Dear Amy Schutte:

Please refer to your new drug application (NDA) dated and received March 23, 2023, and your amendments, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for phenobarbital sodium injection.

We also acknowledge receipt of your amendment dated (b) (4), which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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.

**CLINICAL**

As stated in our (b) (4), Discipline Review Letter, your application does not provide analyzable efficacy and safety datasets which would allow for independent review by the FDA. The publication entitled, "Efficacy of Intravenous Levetiracetam in Neonatal Seizures (NEOLEV2)," which you identify as your "key supporting reference" for efficacy, does not provide a sufficiently detailed presentation of the efficacy and safety data to allow for independent analysis to verify the results which were reported in the publication. Therefore, no conclusions may be drawn regarding effectiveness and safety of phenobarbital sodium injection for the treatment of neonatal seizures.

Although your amendment to your NDA dated (b) (4), appears to contain a more detailed presentation of the NEOLEV2 study data, we are deferring review of that amendment's contents to the next review cycle. However, our preliminary assessment of this submission identified deficiencies. You should discuss with us the contents and formats of the efficacy and safety information derived from the NEOLEV2 study before any resubmission of an application reliant on these data. We further remind you that, if

you reference information for a product in another IND, you must obtain and submit a Letter of Authorization from the holder of that IND.

### **CONTROLLED SUBSTANCE STAFF**

The Application does not include an adequate assessment of the abuse potential of phenobarbital.

#### **Information needed to resolve the deficiency:**

Although your amendment to your NDA dated (b) (4), contains a revised abuse potential assessment for phenobarbital, we are deferring review of that amendment to the next review cycle. However, on cursory review, we note that the revised abuse potential assessment you submitted appears to remain deficient and limited in scope. We recommend that you conduct a comprehensive abuse potential assessment for our review in your response to this Complete Response letter. Consistent with our Information Request, dated (b) (4), and the potential review issues identified in the Filing Letter, dated (b) (4), we remind you of the following advice:

You appear to be relying on the Agency's prior findings for Sezaby (NDA 215910), as your proposed draft labeling language in Section 9 Drug Abuse and Dependence appears identical to that of the approved labeling for Sezaby. However, you did not specify Sezaby as a listed drug in your 505(b)(2) New Drug Application (NDA).

If you do not intend to specify Sezaby as a listed drug in your application, then you would need to independently address the abuse and physical dependence potential of phenobarbital. Your summary of abuse and physical dependence data for phenobarbital in your original NDA submission in Module 2, section 2.7.4.6 is not adequate to assess the abuse potential of your proposed phenobarbital product.

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling is required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of an NDA submission, see the guidance for industry, Assessment of Abuse Potential of Drugs, available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessment-abuse-potential-drugs>.

Your abuse potential assessment should provide, or reference, appropriate data related to abuse and dependence associated with phenobarbital such that your drug product, if approved, can be appropriately labeled in Section 9 and other

relevant sections of the prescribing information. Your abuse potential assessment should include a detailed summary of what is known about the abuse potential and dependence liability of phenobarbital to support your scheduling proposal for phenobarbital. Considering that there are examples of drugs in the barbiturate class in Schedules II, III, and IV, your discussion should include all abuse-related data for phenobarbital and other barbiturates, including available epidemiological data, as supportive of your proposed scheduling of phenobarbital. Your abuse potential assessment should provide cross-linkage to all other eCTD sections of your NDA that provide support for your conclusions. We acknowledge that phenobarbital has a long history of being marketed in the US as unapproved products. Therefore, the use of scientifically-valid, published investigations may be able to support your abuse assessment.

Alternatively, if you are intending, as it appears, to reference the Agency's prior findings for Sezaby by specifying Sezaby as a listed drug to support your abuse potential assessment and proposed labeling for Section 9, you must establish that such reliance is scientifically appropriate and provide the appropriate patent certification or statement for each listed drug upon which you intend to rely.

## **PRODUCT QUALITY**

(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<sup>1</sup> and Pregnancy and Lactation Labeling Final Rule<sup>2</sup> 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

---

<sup>1</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

<sup>2</sup> <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.<sup>3</sup>

## **CARTON AND CONTAINER LABELING**

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

## **FACILITY INSPECTIONS**

Following pre-approval inspection of the (b) (4) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this NDA may be approved.

## **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.

---

<sup>3</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- (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 comments/recommendations that are not approvability issues:

#### **Drug Product Quality**

(b) (4)



#### **Biopharmaceutics**

The FDA's recommendation on the approvability of your biowaiver request for the proposed Phenobarbital Sodium Injection 90 mg/mL is contingent to the submission of adequate and acceptable information/data showing evidence of acceptable safety and efficacy findings in the target patient population for the proposed indication.

## **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 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)

-----  
**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)

01/23/2024 10:51:37 AM