July 3, 2024

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUITABILITY PETITION
*******Priority Review Requested*******

Dear Sir or Madam:

The undersigned petitioner submits this petition, on behalf of a client, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), and in accordance with 21 C.F.R. § 10.20 and 21 C.F.R. § 10.30 requesting the Commissioner of the Food and Drug Administration ("FDA") to declare that the proposed drug product Levetiracetam in Sodium Chloride Injection, 1250 mg/100 mL (12.5 mg/mL) is suitable for consideration in an Abbreviated New Drug Application ("ANDA").

I. ACTION REQUESTED

The petitioner requests that the Commissioner of the FDA declare that the proposed drug product, Levetiracetam in Sodium Chloride Injection, 1250 mg/100 mL (12.5 mg/mL) is suitable for submission as an ANDA. The listed reference drug product (RLD), upon which this petition is based, is Levetiracetam in Sodium Chloride Injection, 250 mg/50 mL (5 mg/mL), 500 mg/100 mL (5 mg/mL), 1000 mg/100 mL (10 mg/mL) and 1500 mg/100 mL (15 mg/mL) by HQ Specialty Pharma Corp., NDA #202543. The petitioner notes that the 250 mg/50 mL (5 mg/mL) strength of HQ Specialty Pharma Corp is currently in the discontinued section of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" also known as the Orange Book. However, this fact should have no impact on the approvability of this

petition as the strength proposed by petitioner, 1250 mg/100 mL (12.5 mg/mL) is bracketed by two strengths of the RLD that remain in the market, 1000 mg/100 mL (10 mg/mL) and 1500 mg/100 mL (15 mg/mL) under NDA #202543. Priority review of this petition is requested pursuant to Section III.B.6 of the GDUFA Reauthorization Performance Goals and Program Enhancement Fiscal Years 2023-2027 Letter (GDUFA III Commitment Letter) as the proposed product represents a new strength of a parenteral product that could aid in eliminating pharmaceutical waste.

The petitioner hereby seeks approval of a change in strength in both, total drug content (1250 mg/100 mL) and concentration (12.5 mg/mL) compared to the approved 1000 mg/100 mL (10 mg/mL) and 1500 mg/100 mL (15 mg/mL) of the RLD.

II. *STATEMENT OF GROUNDS*

The FD&C Act § 505(j)(2)(C) provides for the submission of an ANDA for a drug product that differs in strength from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

For drug products administered parenterally, the change in strength can consist of a change in concentration, total drug content (by changing fill volume) or both a change in concentration and total drug content. The change proposed in the context of this petition is a change in both concentration and total drug content where the new proposed concentration of 12.5 mg/mL with a fill volume of 100 mLs results in a new total drug content of 1250 mg/100 mL. Petitioner notes that both the change in concentration and the change in total drug content will result in a finished product where the proposed concentration and total drug content are bracketed by strengths of the RLD- 1000 mg/100 mL (10 mg/mL) and 1500 mg/100 mL (15 mg/mL). The active ingredient, dosage form, route of administration, dosing recommendations, indications, warnings, and directions for use will remain the same as that of the RLD. Levetiracetam in Sodium Chloride Injection is indicated for:

> "….adjunct therapy in adults (≥ 16 years of age) with the following seizure types when oral administration is temporarily not feasible"
>
> - Partial-onset seizures
> - Myoclonic seizures in patients with juvenile myoclonic epilepsy
> - Primary generalized tonic-clonic seizures

The addition of the new strength of 1250 mg/100 mL (12.5 mg/mL) will permit health care practitioners administering this product to reduce medical waste by providing the proposed product in ready-to-use format that may be appropriate for certain patients, particularly those that may be switching from oral to intravenous therapy. Currently, for a patient to receive a 1250 mg dose, the practitioner will need to compound the product in a pharmacy or to first administer a 1000 mg/100 mL product over 15 minutes followed by a 250 mg/50 mL product over 15 minutes. Therefore, availability of the proposed 1250 mg/100 mL product would reduce medical waste associated with the administration of a second bag of Levetiracetam in Sodium Chloride for Injection.

Dosing recommendations in the RLD package insert are as follows (taken from Revision 3/2024 Package Insert listed on Drugs@FDA, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/202543s024lbl.pdf)

Dosage and Administration

Initial Exposure to Levetiracetam

- *Partial-Onset Seizures: Initial dose is 500 mg twice daily, Increase by 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily.*
- *Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy: Initial dose is 500 mg twice daily. Increase by 500 mg twice daily every two weeks to the recommended dose of 1500 mg twice daily.*
- *Primary Generalized Tonic-Clonic Seizures: Initial dose is 500 mg twice daily. Increase by 500 mg twice daily every 2 weeks to the recommended dose of 1500 mg twice daily.*

Switching from or to oral Levetiracetam: The total daily dosage/frequency of levetiracetam injection should be equivalent to those of oral levetiracetam.

Renal Impairment: Dose adjustment necessary based on creatinine clearance.

Dosing recommendations for different dosage forms of levetiracetam are generally consistent for adult patients, patients over the age of 16, which is the only patient population for which Levetiracetam in Sodium Chloride Injection is currently approved per the limitation of use found in section 1.4 of the approved labeling for NDA #202543. This limitation represents a potential disconnect for patients previously maintained on oral levetiracetam products who may have been maintained on a 1250 mg dose twice a day. When a patient has previously been adequately maintained on oral therapy at single doses of 1250 mg twice daily, a dose readily achieved by taking one 750 mg tablet and one 500 mg tablet, that patient should receive the same 1250 mg dose intravenously per the recommendation in labeling that "The total daily dosage/frequency of levetiracetam injection should be equivalent to those of oral levetiracetam" per Section 2.3 and 2.4 of the package insert for NDA #202543. Because a 1250 mg single dose is unachievable for intravenous therapy, outside of compounded preparations, a patient will either be given a dose of 1000 mg intravenously twice daily, an amount that may not provide adequate seizure control, or more likely would receive 1500 mg intravenously twice daily, an amount that is more than necessary for some patients. Alternatively, a practitioner may decide to achieve the 1250 mg dose by first administering a 1000 mg/100 mL product over 15 minutes followed by a 250 mg/50 mL product over 15 minutes. A process that prolongs infusion time for the patients and delivers additional unnecessary fluid and sodium chloride which may not be optimal for patient health not to mention the additional burdens on the health care practitioners tasked with administering the additional infusion.

While a 1250 mg single dose is not explicitly identified in the labeling of NDA #202543, it is undisputedly an intermediate dose falling between established single doses of 1000 mg and 1500 mg and is contemplated in Table 1 of the RLD label which recommends doses of between 500 mg to 1,500 mg every 12 hours for individuals with normal creatinine clearances of greater than 80 mL/min.

III. *Inapplicability of the Pediatric Research Equity Act ("PREA")*

PREA, which is codified at FD&C Act§ 505B, does not apply to a new strength such as the one proposed in this petition. As such, PREA should not serve as an impediment to the Agency's granting of this petition.

IV. *Environmental Impact*

The petitioner claims a categorical exclusion under 21 CFR 25.31.

V. *Economic Impact*

The petitioner will submit information on economic impact upon request by the agency if applicable.

VI. *Certification*

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,

Martin Shimer Digitally signed by Martin Shimer Date: 2024.07.03 17:25:04 -04'00'

Martin Shimer
Executive Director, Regulatory Services
Lachman Consulting Services, Inc.

Attachments accompanying this petition:

- Attachment 1: Copy of the relevant excerpt from the current electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) –
- Attachment 2: Current Package Insert for LEVETIRACETAM IN SODIUM CHLORIDE INJECTION, NDA #202543 Revision 3/2024; source: Drugs@FDA
- Attachment 3: Draft Package Insert Proposed for Levetiracetam in Sodium Chloride Injection, 1250 mg/100 mL