Newcastle
BIOSCIENCE

July 9th, 2024

VIA ELECTRONIC SUBMISSION 7/9/24

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

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR 10.30 requesting the Commissioner of the Food and Drug Administration to declare that the drug products, Lacosamide Orally Disintegrating Tablets, in strengths of 25 mg, 37.5 mg, 75 mg, 112.5 mg and 175 mg are suitable for consideration in an abbreviated new drug application (ANDA}.

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that, Lacosamide Orally Disintegrating Tablets, in strengths of 25 mg, 37.5 mg, 75 mg, 125 mg,and 175 mg mg are suitable for submission as an ANDA. The reference-listed drug product (RLD), upon which this petition is based, is Vimpat (lacosamide) Tablets 200 mg, subject of NDA 22253 held by UCB Inc., as designated in the Orange Book (see copy of the page from the current Electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (**Attachment 1**)}. Newcastle previously submitted a petition to FDA requesting permission to submit an ANDA for Lacosamide Orally Disintegrating Tablets, 50 mg, 100 mg, 150 mg and 200 mg, petition number 2023-P-4291 which was approved by FDA on 3/13/24 (see **Attachment 2** for submitted petition and **Attachment 3** for FDA's response letter).

B. Statement of Grounds

The Federal Food, Drug, and Cosmetic Act provides for the submission of an Abbreviated New Drug Application 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.

The RLD, Vimpat (lacosamide) Tablets by USB Inc. is a tablet product containing 200 mg of lacosamide in each tablet. As noted above, Vimpat is also approved in strengths of 50 mg, 100 mg, and 150 mg tablets. The proposed drug product will be an orally disintegrating tablet dosage form, containing 37.5 mg, 75 mg, 112.5 mg and 175 mg . This petition is thus seeking a change in both strength and dosage form compared to existing Vimpat Tablets.

The proposed 37.5 mg, 75 mg and 112.5 mg strengths represent differences in strength that are contemplated with the dosing recommendations of the RLD's approved labeling for patients with renal or hepatic impairment (sections 8.4 and 8.5) where dose is reduced by 25%.

1.1 Dosing Information

The recommended dosage for monotherapy and adjunctive therapy for partial-onset seizures in patients 1 month of age and older and for adjunctive therapy for primary generalized tonic-clonic seizures in patients 4 years of age and older is included in Table 1. In pediatric patients, the recommended dosing regimen is dependent upon body weight. Dosage should be increased based on clinical response and tolerability, no more frequently than once per week. Titration increments should not exceed those shown in Table 1.

Table 1: Recommended Dosages for Partial-Onset Seizures (Monotherapy or Adjunctive Therapy) in Patients 1 Month and Older, and for Primary Generalized Tonic-Clonic Seizures (Adjunctive Therapy) in Patients 4 Years of Age and Older*

Age and Body Weight	Initial Dosage	Titration Regimen	Maintenance Dosage
Adults (17 years and older)	**Monotherapy**:** 100 mg twice daily (200 mg per day) **Adjunctive Therapy:** 50 mg twice daily (100 mg per day)	Increase by 50 mg twice daily (100 mg per day) every week	**Monotherapy**:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
	Alternate Initial Dosage: 200 mg single loading dose, followed 12 hours later by 100 mg twice daily		
Pediatric patients weighing 50 kg or more	50 mg twice daily (100 mg per day)	Increase by 50 mg twice daily (100 mg per day) every week	**Monotherapy**:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)

Age and Body Weight	Initial Dosage	Titration Regimen	Maintenance Dosage
Pediatric patients weighing 30 kg to less than 50 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	2 mg/kg to 4 mg/kg twice daily (4 mg/kg/day to 8 mg/kg/day)
Pediatric patients weighing 11 kg to less than 30 kg	1 mg/kg twice daily (2 mg/kg/day)	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)
Pediatric patients weighing 6 kg to less than 11 kg ±			
Pediatric patients weighing less than 6 kg ±	**Intravenous:** 0.66 mg/kg three times daily (2 mg/kg/day)	**Intravenous:** Increase by 0.66 mg/kg three times daily (2 mg/kg/day) every week	**Intravenous:** 2.5 mg/kg to 5 mg/kg three times daily (7.5 mg/kg/day to 15 mg/kg/day)
	Oral: 1 mg/kg twice daily (2 mg/kg/day)	**Oral:** Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	**Oral:** 3.75 mg/kg to 7.5 mg/kg twice daily (7.5 mg/kg/day to 15 mg/kg/day)

when not specified, the dosage is the same for monotherapy for partial-onset seizures and adjunctive therapy for partial-onset seizures or primary generalized tonic-clonic seizures. Oral and intravenous dosages are the same unless specified.

Monotherapy for partial-onset seizures only

± indicated only for partial-onset seizures

8.6 Renal Impairment

Based on data in adults, no dose adjustment is necessary in adult and pediatric patients with mild to moderate renal impairment (CL_{CR} ≥30 mL/min). In adult and pediatric patients with severe renal impairment (CL_{CR} <30 mL/min) and in those with end-stage renal disease, a reduction of 25% of the maximum dosage is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment

Based on data in adults, for adult and pediatric patients with mild to moderate hepatic impairment, a reduction of 25% of the maximum dosage is recommended. Patients with mild to moderate hepatic impairment should be observed closely during dose titration [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].

The proposed 37.5 mg, 75 mg and 112.5 mg strengths represent a 25% reduction of the existing 50 mg, 100 mg and 150 mg strengths. Dosing recommendations for Adults and Pediatric patients for maintenance treatment of Partial-Onset Seizures using Vimpat for Monotherapy is 150 mg to 200 mg twice daily and for Adjunctive Therapy is 100 mg to 200 mg twice daily. The proposed 75 mg ODT product represent a 25% reduction in the 100 mg dose, the proposed 112.5 mg ODT product represents a 25% reduction in the 150 mg dose. The 37.5 mg ODT product represents a 25% reduction in the recommended 50 mg dose that is normally used to titrate patients. Therefore, the 37.5 mg ODT, 75 mg ODT, and 112.5 mg ODT all represent doses contemplated in the labeling for patients with either renal or hepatic impairment.

The proposed 25 mg ODT product would give the clinician the flexibility of titrating patients more gradually when warranted. As noted in the approved labeling section 1.1 and Table 1, titration based on body weight would necessitate maximum flexibility in dosing. Pediatric patients in particular could benefit from availability of the 25 mg ODT product as these patients would no longer be required to use the oral solution product when their therapy required a dose that is less than 50 mg which is the lowest available strength for Vimpat Tablets. In addition to being useful for treating patients with renal or hepatic impairment, the 37.5 mg ODT product will also be useful to treat certain pediatric patients based on their weight.

The proposed 125 mg ODT and 175 mg ODT products represent intermediate doses that should not cause any safety or efficacy concerns. These products are being proposed based on the statement in Vimpat's approved labeling located just prior to Table 1 which reads

> "Dosage should be increased based on clinical response and tolerability, no more frequently than once per week. Titration increments should not exceed those shown in Table 1."

This statement clearly reflects that patient dosing must be individualized based on patient response. As stated in the previous paragraph, the 25 mg ODT product will provide additional flexibility when titrating patients to the lowest effective dose. Clinicians that chose to titrate their patients more gradually using the 25 mg ODT product may find that a 125 mg or 175 mg dose is the lowest effective dose for their patients. Therefore, the 125 mg ODT and 175 mg ODT products are being proposed to offered for patients that require these doses on a twice daily basis.

Pediatric Waiver Request

In September of 2007, Congress reauthorized the Pediatric Research Equity Act of 2003 (PREA) that amended the Federal Food, Drug, and Cosmetic Act to provide the Agency authority to require drug firms to study drugs in pediatric patients, if the Agency concludes that such study would provide beneficial health data for that patient population. The Act specifically requires that a request for a new dosage form is subject to a pediatric evaluation. The act also provides for a waiver from such requirement if the drug:

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(II) is not likely to be used in a substantial number of pediatric patients.

The proposed product will contain labeling that permits dosing for all patients for whom the drug is indicated (down to 17 years of age). The RLD labeling discusses the potential for adverse effects on CNS development and thus this product would not likely be utilized in children under the age of 17 due to potential impact on such development. While the product labeling does not cite any contraindications, it does warn that:

Lacosamide has been shown in vitro to interfere with the activity of CRMP-2, a protein involved in neuronal differentiation and control of axonal outgrowth. Potential adverse effects on CNS development cannot be ruled out. Administration of lacosamide to rats during the neonatal and juvenile periods of postnatal development resulted in decreased brain weights and long-term neurobehavioral changes (altered open field performance, deficits in learning and memory). The no-effect dose for developmental neurotoxicity in rats was associated with a plasma lacosamide exposure (AUC) approximately 0.5 times the human plasma AUC at the maximum recommended human dose of 400 mg/day.

Because of the potential for adverse CNS development, and the fact that there are other available AED treatments approved for pediatric patients, it is unlikely that the proposed product will be prescribed for or used by pediatric patients and therefore the petitioner hereby requests that a full waiver from the conduct of pediatric studies be granted for the approval of this petition to permit subsequent ANDA filing.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

E. 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 1t includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

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Attachments:

1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book listing, accessed 7/9/24
2. Previous suitability petition letter 2023-P-4291
3. FDA response letter to petition 2023-P-4291
4. Draft insert labeling for proposed product
5. Approved labeling for reference-listed drug, Vimpat (lacosamide) Tablets