Newcastle
BIOSCIENCE

Attachment Two

Previous suitability petition letter 2023-P-4295

Newcastle
BIOSCIENCE

October 1, 2023

VIA ELECTRONIC SUBMISSION 10/1/23

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 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Topiramate Orally Disintegrating Tablets (ODT), in strengths of 25 mg, 50 mg, 100 mg, and 200 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 Topiramate Orally Disintegrating Tablets, in strengths of 25 mg, 50 mg, 100 mg and 200 mg are suitable for submission as an ANDA. The reference-listed drug product (RLD), upon which this petition is based, is Topamax (Topiramate) Tablets 100 mg approved under NDA 020-505 currently held by Janssen Pharmaceuticals, 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)). It should be noted that the RLD is also approved in strengths of 25 mg, 50 mg and 200 mg. Therefore, the petitioner seeks only a change in dosage form from that of the reference listed drug product, from conventional tablets to orally disintegrating tablets.

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 dosage form from that of the listed drug provided that FDA has approved a petition declaring that the proposed changed product does not raise any questions of safety or effectiveness.

The RLD, Topamax (Topiramate) Tablets by Janssen is a conventional tablet product containing 100 mg of Topiramate in each tablet. As noted above, the RLD is also approved in strengths of 25 mg, 50mg and 200 mg. The proposed drug product will be an orally disintegrating tablet dosage form, containing 25 mg, 50 mg, 100 mg, or 200 mg of Topiramate. This petition is thus

seeking a change in dosage form of the RLD to an orally disintegrating tablet from that of a conventional oral tablet in the exact same strengths as that of the RLD.

The proposed product will contain the same dosing schedule as that of the RLD and the only difference will be that the ODT product will be recommended to be dissolved in the mouth prior to swallowing. The current dosing instructions in the approved labeling of the RLD are as follows:

Dosage and Administration:

2.1 Dosing in Monotherapy Epilepsy

Adults and Pediatric Patients 10 Years of Age and Older

The recommended dose for TOPAMAX® monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in two divided doses. The dose should be achieved by titration according to the following schedule (Table 1):

Table 1: Monotherapy Titration Schedule for Adults and Pediatric Patients 10 years and older

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

Pediatric Patients 2 to 9 Years of Age

Dosing in patients 2 to 9 years of age is based on weight. During the titration period, the initial dose of TOPAMAX® is 25 mg/day nightly for the first week. Based upon tolerability, the dosage can be increased to 50 mg/day (25 mg twice daily) in the second week. Dosage can be increased by 25–50 mg/day each subsequent week as tolerated. Titration to the minimum maintenance dose should be attempted over 5–7 weeks of the total titration period. Based upon tolerability and clinical response, additional titration to a higher dose (up to the maximum maintenance dose) can be attempted at 25–50 mg/day weekly increments.

The total daily dose should not exceed the maximum maintenance dose for each range of body weight (Table 2).

Table 2: Monotherapy Target Total Daily Maintenance Dosing for Patients 2 to 9 Years of Age

Weight (kg)	Total Daily Dose (mg/day)* Minimum Maintenance Dose	Total Daily Dose (mg/day)* Maximum Maintenance Dose
Up to 11	150	250
12 – 22	200	300
23 – 31	200	350
32 – 38	250	350
Greater than 38	250	400

* Administered in two equally divided doses

2.2 Dosing in Adjunctive Therapy Epilepsy

Adults (17 Years of Age and Over)

The recommended total daily dose of TOPAMAX® as adjunctive therapy in adults with partial onset seizures or Lennox-Gastaut Syndrome is 200 to 400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. TOPAMAX® should be initiated at 25 to 50 mg/day, followed by titration to an effective dose in increments of 25 to 50 mg/day every week. Titrating in increments of 25 mg/day every week may delay the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial onset seizures.

Pediatric Patients 2 to 16 Years of Age

The recommended total daily dose of TOPAMAX® as adjunctive therapy for pediatric patients 2 to 16 years of age with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome. The total daily dose should not exceed 400 mg/day.

2.3 Dosing in Migraine Prophylaxis

The recommended total daily dose of TOPAMAX® as treatment for patients 12 years of age and older for prophylaxis of migraine headache is 100 mg/day administered in two divided doses (Table 3). The recommended titration rate for TOPAMAX® for migraine prophylaxis is as follows:

Table 3: Migraine Prophylaxis Titration Schedule for Patients 12 Years of Age and Older

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

2.4 Administration Information

TOPAMAX® can be taken without regard to meals.

2.5 Dosing in Patients with Renal Impairment

In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m2), one-half of the usual adult dose of TOPAMAX® is recommended [see Use in Specific Populations (8.5, 8.6), Clinical Pharmacology (12.3)].

2.6 Dosing in Patients Undergoing Hemodialysis

To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of TOPAMAX® may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

The proposed orally disintegrating tablets would provide for ease administration for those patients that have difficulty swallowing conventional tablets (including the pediatric patients for whom the product is labeled), are infirmed or may have dysphagia. The product could also be taken without water which may provide patients greater ease or convenience over traditional tablets.

There are no proposed changes in labeling with the exception of the obvious changes in dosage form sought in this petition which would encompass directions of use of the orally disintegrating tablet. Such a label change is permitted in accordance with the regulations based on an approval of an ANDA suitability petition for a permitted change. The uses, indications, warnings and directions for use will remain the same as that of the RLD. Draft labeling for the proposed products is included in Attachment 2, and the RLD's approved labeling is provided in Attachment 3.

Therefore, the petitioner's request for the Commissioner to find that a change in dosage form from an oral tablet to an orally disintegrating tablet should raise no questions of safety or effectiveness, and the Agency should approve the petition.

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 ages of pediatric patients for whom the drug is indicated (down to 2 years of age). While the proposed labeling does state that topriamate tablets are bitter and should therefore not be broken, the proposed product will be taste masked making it suitable for an orally disintegrating product for all labeled ages.

The RLD product was originally approved in 1996 and supplemental NDA were submitted for additional pediatric and adult indications and approved in 1999 and 2001 and it appears from available public data that all of the pediatric written requests were fulfilled by submission in 2009. The product thus appears to have been studied in pediatric patients to the satisfaction of the FDA and the products is not likely to be used in a substantial number of pediatric patients under the labeled age of 2 years. Based on this information, it is believed that it is not likely that this product would, nor should, be used in a younger age group than described in the labeling and that all of the pediatric requirements have been met.

The petitioner hereby requests that a full waiver from the conduct of pediatric studies be granted for this petition to permit a subsequent ANDA filing, as the product has been studied in pediatric patients for its labeled indications to the satisfaction of the Agency.

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.

Newcastle
BIOSCIENCE

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 it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Gene Nakagawa
President
Newcastle Bioscience LLC
gene@newcastlebio.com
Mobile: 310-936-0931

Attachments:
1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book Listing, accessed 9/12/23
2. Draft insert labeling for proposed product
3. Approved labeling for reference-listed drug, Topamax (Topiramate) Tablets by Janssen.