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November 25, 2019

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

CITIZEN PETITION

Dear Sir/Madam:

The undersigned, on behalf of a client, submits this Citizen Petition pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FDC Act") and in accordance with 21 C.F.R. § 314.93 and 21 C.F.R. § 10.30, to request that the Commissioner of the U.S. Food and Drug Administration ("FDA") declare that the drug product, Tramadol Hydrochloride Tablets, 25 mg, is suitable for consideration in an Abbreviated New Drug Application ("ANDA").

A. Action Requested

The petitioner requests that the FDA declare that Tramadol Hydrochloride Tablets, 25 mg, is suitable for submission as an ANDA. As designated in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), the Reference Listed Drug ("RLD") upon which this petition is based is ULTRAM® (tramadol hydrochloride) Tablets, 50 mg, which is approved under NDA 020281 and is currently held by Janssen Pharmaceuticals. The petitioner seeks to introduce a new 25 mg strength of tramadol hydrochloride tablets.

B. Statement of Grounds

FDC Act § 505(j)(2)(A)(iii) provides for the submission of an ANDA for a drug product that differs in strength from that of the listed drug provided FDA has first approved a petition permitting the submission of such an application.

ULTRAM® contains 50 mg of tramadol hydrochloride in a scored tablet. A copy of the current Orange Book entry for ULTRAM® (NDA 020281) is included in ***Attachment 1***. The proposed drug product also contains tramadol hydrochloride in tablet dosage form but contains only 25 mg of the active ingredient and does not include a score. The petition is thus seeking a change in strength to 25 mg of tramadol hydrochloride from that of the RLD.

The proposed change in strength is consistent with the dosing recommendations of the RLD's approved labeling. For example, the prescribing information for ULTRAM® provides the following dosing information:

> For patients not requiring rapid onset of analgesic effect, the tolerability of ULTRAM® can be improved by initiating therapy with the following titration regimen: Start ULTRAM® at 25 mg/day and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, ULTRAM® 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.

ULTRAM Prescribing Information § 2.2. The proposed strength of 25 mg is thus consistent with the dose approved in the RLD's labeling. A 25 mg strength is well within the 400 mg maximum daily dose of tramadol hydrochloride. See ULTRAM Prescribing Information § 2.1 ("Do not administer ULTRAM at a dose exceeding 400 mg per day."). And because 25 mg is the lowest possible dose, no score is necessary.

Further, the ULTRAM® labeling directs providers to "[u]se the lowest effective dosage for the shortest duration consistent with individual patient treatment goals." ULTRAM Prescribing Information § 2.1. Because the indication and dosing instructions will remain the same as the FDA-approved labeling of the RLD, use of such a strength is consistent with the dosing instructions for the RLD and could aid patient compliance with the lowest effective dosage form requirements, which is particularly important given that

this product is an opioid. As such, the proposed change in strength from that of the RLD not raise questions of safety or efficacy for the proposed product. Therefore, the Agency should conclude that clinical investigations are not necessary to demonstrate the proposed product's safety or effectiveness.

There are no proposed changes in labeling with the exception of the change in strength sought in this petition. The uses, indications, warnings, and directions for use will remain the same as that of the RLD. Approved labeling for ULTRAM®, updated on October 7, 2019, is included as ***Attachment 2***. Draft labeling for the proposed product is included as ***Attachment 3***. Therefore, the Petitioner requests that FDA find that a change in strength from 50 mg to 25 mg of Tramadol Hydrochloride Tablets raises no questions of safety or effectiveness.

The Pediatric Research Equity Act ("PREA"), enacted in December 2003, amended the FDC Act by requiring certain applications for a drug submitted under FDC Act § 505 to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is deferred or waived. See FDC Act § 505B(a)(I)(A)(i). Specifically, PREA applies to all applications for a new active ingredient, dosage form, indication, route of administration, or dosing regimen. See id. ANDAs submitted under an approved suitability petition for a change in strength are not subject to PREA requirements. See FDA, Draft Guidance for Industry, How to Comply with the Pediatric Research Equity Act, 4 (Sep. 2005). Petitioner asserts that PREA is not applicable to the proposed Tramadol Hydrochloride Tablets, 25 mg, drug product because the proposed change concerns only a new strength. As such, PREA should not serve as an impediment to the Agency granting this petition.

C. Environmental Impact

A claim for categorical exclusion of the requirements for an environmental assessment is made pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is submitted only when requested by the Commissioner. This information will be promptly provided, if so requested.

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.

Sincerely,

Kurt R. Karst

Attachments:

1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book listing accessed November 6, 2019.
2. ULTRAM® Prescribing Information, updated October 7, 2019.
3. Draft Prescribing Information, Tramadol Hydrochloride Tablets, 25 mg.