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CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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September 3, 2004

OVERNIGHT COURIER 9/3/04

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

CITIZEN PETITION

Dear Sir or Madam:

The undersigned, on behalf of a client, submits this petition in quadruplicate under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("the FDC Act") and 21 C.F.R. 10.20, 10.30, and 314.93 to request that the Commissioner of Food and Drugs make a determination that an Abbreviated New Drug Application (ANDA) may be submitted for Tramadol Hydrochloride Oral Solution, 50 mg per 5 mL.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs make a determination that Tramadol Hydrochloride Oral Solution, 50 mg per 5 mL drug product is suitable for submission as an ANDA. The reference-listed drug product upon which this petition is based is ULTRAM[®] (tramadol hydrochloride tablets, 50 mg) manufactured by Ortho-McNeil Pharmaceuticals NDA 20-281. Therefore, this petition requests a change in the dosage form, from tablets to oral solution.

B. Statement of Grounds

Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act provides for the submission of an ANDA for a new drug that differs in dosage form from a listed drug, provided that the FDA has approved a petition seeking permission to file such an application. This petition requests a change in the dosage form (i.e., from tablet to oral solution). The listing of ULTRAM[®] (tramadol hydrochloride) Tablets, 50 mg is on page 3-347 of the 24th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as "The Orange Book") Please see Attachment A.

Tramadol HCl is a centrally acting analgesic. The proposed change in dosage form, from a tablet to an oral solution, is designed to provide a more convenient dosage form for those adult patients that cannot or find it difficult to swallow tablets. In addition, for those who are elderly or infirm and may not be able to consume tablets or find it difficult to do, this alternate dosage form offers a unique flexible alternative to achieve proper dosing. The proposed product would offer the physician an option of utilizing a dosage form that may be more appropriate for certain adult

patients that, as mentioned above, may not be able to consume a tablet and will also permit appropriate dosage titration in accordance with the approved labeling of the RLD without the patient having to take multiple dosage units or split the tablet (to achieve an intermediate dose between 50 mg and 100 mg for appropriate patients) to meet the required dosing schedule.

The recommended maximum daily dosage for tramadol hydrochloride, according to the labeling of the reference-listed drug product is up to 400 mg per day. The approved labeling indicates that the usual dosage is "one tablet [50 mg] every four to six hours as needed for pain, not to exceed 400 mg per day." In addition, for a certain subset of the population, doses of 50 to 100 mg may be given every 4-6 hours (not to exceed 400 mg/day). The oral solution product will permit appropriate titration in accordance with the prescribing health care practitioner's individualized instructions without requiring the patient to take multiple tablets or break tablets to obtain the appropriate dose. The approved package insert for ULTRAM[®] (tramadol hydrochloride) tablets, 50 mg, is included in Attachment B. The usual dosage for the proposed product is "one teaspoon (50 mg) every four to six hours as needed for pain, not to exceed 400 mg per day." This dosage is consistent with the dosage listed in the approved ULTRAM[®] (tramadol hydrochloride) Tablets, 50 mg, package insert and will include the appropriate titration dosing schedule as permitted by the RLD labeling and any controlling patent.

In summary, the proposed change in dosage form from that of the RLD, will not affect the product's safety or efficacy. The indication remains unchanged and the proposed dosing is the same as the dosing recommendations in the approved labeling for the RLD. Therefore, the Agency should conclude that clinical investigations are not necessary to demonstrate the proposed product's safety or effectiveness. The proposed labeling for Tramadol Hydrochloride Oral Solution, 50 mg per 5 mL is included as Attachment C. Labeling for the proposed product will be consistent with the approved labeling for ULTRAM[®] (tramadol hydrochloride) Tablet, 50 mg, product with the exceptions being because the product is made by a different manufacturer and because of the change in dosage form and period of patent protection.

For the aforementioned reasons, the undersigned requests that the Commissioner grant this petition and authorize submission of an ANDA for Tramadol Hydrochloride Oral Solution, 50 mg per 5 mL.

Pediatric Waiver Request

In December of 2003, Congress passed the Pediatric Research Equity Act of 2003 that amended the Federal Food, Drug and Cosmetic Act to provide the Agency authority to require drug firms to study certain drugs in pediatric patients, if the Agency felt that such study would provide beneficial health data for that patient population. The act also provides a provision for a waiver from such requirement if:

- (iii) the drug or biological product;
- (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 petitioner hereby requests that a waiver from the conduct of pediatric studies be granted for the approval of this petition to permit a subsequent ANDA filing.

The RLD product is an immediate-release tablet. This product is used for "management of moderate to moderately severe pain **in adults.**" (Emphasis added.) The product is not indicated for the treatment of patients below the age of 17. The proposed product will contain the same warnings and recommendations against use in patients below the age of 17 years.

Based on the use and nature of the RLD, the proposed change in dosage form to an oral solution from an immediate-release tablet will not likely make the product any more likely to be used in pediatric patients. In addition, with the limitations of use (adults only) described in the labeling of the RLD, it makes it unlikely that the proposed product would be used in a substantial number of pediatric patients. Also, it is noted that Tramadol did appear on the historical listing of approved drug products for which additional pediatric information may provide health benefits in the pediatric population. The innovator did receive a written request for such studies and conducted and submitted those studies in accordance with the written request and was awarded 6 months of pediatric exclusivity. To date, according to the FDA's list on its web page,¹ the submitted studies have not resulted in a change in labeling to include additional information on the pediatric use of the product. It can be inferred that the studies that were requested and conducted, either confirmed that the product should not be used in children, or that the Agency has not yet approved a supplement permitting any such labeling change. However, since pediatric studies were conducted to determine if Tramadol is appropriate for use in the pediatric population and exclusivity was granted, there should be no reason to request that those studies be repeated.

In addition, there are clearly other alternative drug products approved to treat moderate to moderately severe pain in the pediatric population. Thus, the proposed product would not represent a meaningful therapeutic benefit over existing therapies. Based on the restricted labeling of the RLD, which will be carried over to the proposed labeling, the oral solution product will not likely be used in a substantial number of pediatric patients.

C. Environmental Impact

According to 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic Impact Statement

According to 21 C.F.R. § 10.30(b), petitioner will, upon request by the Commissioner, submit economic impact information.

¹ Pediatric Exclusivity Labeling Changes as of May 7, 2004, Accessed July 19, 2004

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,


Robert W. Pollock *pk*

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RWP/pk

Attachments:

- Attachment A: Page 3-347 of the 24th Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations
- Attachment B: Package Insert for ULTRAM[®] (tramadol hydrochloride) tablets, 50 mg
- Attachment C: Proposed Labeling for Tramadol Hydrochloride Oral Solution, 50 mg per 5 mL

cc: Emily Thakur (Office of Generic Drugs)

M24P4247