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August 2, 2013

OVERNIGHT COURIER 08/02/13

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, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act, and in accordance with 21 C.F.R. § 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/300 mg is 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 Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/300 mg is suitable for submission as an ANDA. The reference listed drug product (RLD) upon which this petition is based is Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/300 mg, ANDA No. 040658, currently held by Mikart, as designated in the Orange Book. Therefore, the petitioner seeks a change in strength of the hydrocodone bitartrate component from that of the listed drug product from 5 mg to 2.5 mg.

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an ANDA for a drug product that differs in dosage strength from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

The RLD, Hydrocodone Bitartrate and Acetaminophen USP, by Mikart is a tablet product containing 300 mg of acetaminophen in combination with 5 mg of hydrocodone bitartrate. See product listing for ANDA 040658 from the electronic Orange Book also known as the *Approved Drug Products with Therapeutic Equivalence Evaluations*, accessed August 2, 2013, which reflects the approval of this RLD (Attachment 1). The proposed drug product also represents a tablet dosage form containing 300 mg of acetaminophen, but in combination with 2.5 mg of hydrocodone bitartrate. This petition is thus seeking a change in strength of only the hydrocodone bitartrate component from that of the RLD.

This proposed strength of hydrocodone bitartrate in combination with acetaminophen will provide healthcare practitioners with an additional dosing option to more precisely meet individual patients' pain-relief needs. At the same time, this new strength offers healthcare practitioners the ability to titrate the patient to the lowest dose necessary to achieve the desired response and thereby reduce the patient's exposure to the narcotic component in this combination drug product.

In addition, please note that the proposed dosage strength is consistent with the dosing recommendations of the RLD's approved labeling. The current dosing instructions in the approved labeling of the RLD are as follows:

> Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.
>
> **Xodol®[1] 5/300** (Hydrocodone Bitartrate and Acetaminophen Tablets, USP 5 mg/300 mg): The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

Thus, the hydrocodone bitartrate dosage ranges from a minimum of 20 mg per day (one tablet every six hours) to a maximum of 40 mg per day (maximum daily dosage of eight tablets). Mikart's package insert for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/300 mg is included in Attachment 2.

Similarly, the dosage for the proposed product, as illustrated in the enclosed draft labeling (Attachment 3) would be as follows:

> Hydrocodone Bitartrate and Acetaminophen Tablets, USP 2.5 mg/300 mg: The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 12 tablets.

The proposed product will, therefore, offer hydrocodone bitartrate dosages in a range from 10 mg per day (one tablet every six hours) to a maximum of 30 mg per day (maximum daily dosage of twelve tablets). The maximum daily dosage of acetaminophen, which corresponds to the above dosing instructions, is 3,600 mg. These dosages are consistent with the dosing recommendations and allowances approved in the reference listed drug product's labeling and offer additional options for titrating patients to the lowest effective dose of hydrocodone bitartate and acetaminophen combination drug product to achieve pain relief.

In summary, the proposed change in strength of the hydrocodone bitartrate component from that of the reference listed drug will not raise questions of safety or efficacy for the proposed product. The indication remains unchanged and the proposed dosing is consistent with that recommended in the labeling of the approved reference listed drug 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 obvious changes that are associated with 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. As previously noted, draft labeling for the proposed product is included in Attachment 3.

Therefore, the petitioner's request for the Commissioner to find that the change in strength of hydrocodone bitartrate in the proposed Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/300 mg, should raise no questions of safety or effectiveness, and the Agency should approve the petition.

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[1] The FDA's Orange Book does not list the proprietary name, "Xodol", in connection with Mikart's hydrocodone bitartrate and acetaminophen drug products. However, the products are drug listed in FDA's NDC Directory under the Xodol proprietary name and reference Mikart's ANDA No. 040658 (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/300 mg).

Inapplicability of the Pediatric Research Equity Act ("PREA"). PREA, which is codified at FDC Act § 505B, does not apply to a new strength, such as the one proposed in this Petition. (See FDC Act § 505B(a)(1)(A).) As such, PREA should not serve as an impediment to the Agency's granting of this Petition.

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

Respectfully submitted,

Joan Janulis
Vice President

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Attachments:

1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book listing accessed August 2, 2013
2. Labeling for reference listed drug products (RLD), Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/300 mg, updated June 2011
3. Draft Insert Labeling Proposed for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 2.5 mg/300 mg

cc: Martin Shimer (OGD)

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