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May 10, 2007

OVERNIGHT COURIER 5/10/07

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 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Acetaminophen, Butalbital, Caffeine and Hydrocodone Bitartrate Capsules, 650 mg / 50 mg / 40 mg / 5 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 Acetaminophen, Butalbital, Caffeine and Hydrocodone Bitartrate Capsules, 650 mg / 50 mg / 40 mg / 5 mg is suitable for submission as an ANDA. The listed reference drug product (RLD), upon which this petition is based, is Fioricet® with Codeine (Acetaminophen, Butalbital, Caffeine and Codeine Phosphate) Capsules, 325 mg / 50 mg / 40 mg / 30 mg, NDA 20-232 currently held by Watson Pharmaceuticals 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]). Reference is also made to the approval of Citizen Petition 99P-1657 which provided for a change in strength of acetaminophen from 325 mg to 650 mg in a similar combination product (Attachment 2), Citizen Petition 99P-2150, which provided for a change in strength of Acetaminophen from 500 mg to 750 mg (Attachment 3), and Citizen Petition 93P-0346 which provided for a change in active ingredient from Codeine Phosphate to Hydrocodone Bitartrate (Attachment 4).

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 strength and/or active ingredient in a combination product from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

The RLD, Fioricet® with Codeine Capsules by Watson Pharmaceuticals is a capsule product containing 325 mg of Acetaminophen, 50 mg of Butalbital, 40 mg of Caffeine, and 30 mg of Codeine Phosphate. The proposed drug product is also a capsule dosage form, but containing 650 mg of Acetaminophen, 50 mg of Butalbital, 40 mg of Caffeine, and 5 mg of Hydrocodone Bitartrate. This petition is thus seeking a change in strength of the Acetaminophen component (from 325 mg to 650 mg) and a change in active ingredient (from Codeine Phosphate to Hydrocodone Bitartrate) from that of the RLD.

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The proposed change in strength (325 mg of Acetaminophen to 650 mg of Acetaminophen) represents a dosage strength that is consistent with the dosing recommendations of the RLD's approved labeling.

The current dosing instructions in the approved labeling of the RLD states: "One or 2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules." The RLD, therefore, has a total maximum Acetaminophen Exposure = 1.95 g/day well below the maximum 4 g permissible daily exposure level. The approved package insert labeling for Fioricet® with Codeine Capsules (Acetaminophen 325 mg, Butalbital 50 mg, Caffeine 40 mg and Codeine Phosphate 30 mg) is provided in Attachment 5.

The dosage for the proposed product (provided in Attachment 6) is: "One capsule every 4 hours. Total daily dosage should not exceed 6 capsules." The proposed product, therefore, has a total maximum Acetaminophen exposure = 3.9 g/day also below the 4 g permissible daily exposure level. This dosage is consistent with the single maximum dosage approved in the reference-listed drug product's labeling and other FDA approved products and is consistent with safe and effective doses in the Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use.

The proposed change in active ingredient from Codeine Phosphate to Hydrocodone Bitartrate is a change that has been previously granted under Citizen Petition 93P-0346. In the approval letter (see Attachment 4), the Agency acknowledged the potency ratio of Codeine Phosphate to Hydrocodone Bitartrate to be 6:1 (i.e., 30 mg of Codeine Phosphate is equivalent to 5 mg of hydrocodone bitartrate). Hydrocodone Bitartrate and Codeine Phosphate are both centrally acting narcotic analgesics and are expected to provide the same therapeutic effect in equipotent doses. Thus, the proposed 5 mg of Hydrocodone Phosphate in one (1) capsule of the proposed product is equivalent to 30 mg of Codeine Phosphate provided by one (1) capsule of the reference-listed drug. We acknowledge that the approval for Citizen Petition 93P-0346 was recently withdrawn. However, this withdrawal was due to the need for pediatric studies for a new combination product, not due to the inappropriate substitution of Hydrocodone Bitartrate for Codeine Phosphate. As discussed later in this petition, the 650 mg dose of Acetaminophen in the proposed product is not a dose that can be safely administered in the pediatric population and thus a waiver from conducting such studies is being sought.

The proposed change in strength of Acetaminophen (from 325 mg to 650 mg) and the proposed change in active ingredient (Codeine Phosphate to Hydrocodone Bitartrate) will provide greater flexibility to the healthcare practitioner in achieving the best-tolerated dose to relieve symptoms of the complex of tension (or muscle contraction) headache.

There are no proposed changes in labeling with the exception of the obvious changes in dosage strength, the resultant revision in dosing instructions required by the new strength and change in active ingredient sought in this petition. The uses, indications, warnings and directions for use will remain the same as that of the RLD. Draft labeling for the proposed product is included in Attachment 6, and the RLD's approved labeling is provided in Attachment 5.

Therefore, the petitioner's request for the Commissioner to find that a change in strength of the Acetaminophen component from 325 mg to 650 mg and a change in active ingredient from Codeine Phosphate to Hydrocodone Bitartrate should raise no questions of safety or effectiveness, and the Agency should approve the petition.

Pediatric Waiver Request

In December 2003, Congress passed 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 active ingredient (in this case a new combination product) be 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 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.

The reference listed drug product that is the subject of this petition, Fioricet with Codeine Capsules was first approved for use in 1992, and was not on the list of drug products for which additional pediatric information may produce health benefits in the pediatric population (May 2001) nor are Acetaminophen, butalbital, caffeine, or hydrocodone bitartrate (components of the proposed product) on the current list of drugs for which pediatric studies are needed (April 2006). Additionally, we note that the proposed product will be available in a dosage strength not suitable for the pediatric population (i.e., each capsule will contain 650 mg of Acetaminophen). The Tentative Final Monograph (TFM) for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use states the total daily maximum Acetaminophen exposure in children should not exceed 2.4375 g/day and the total maximum single dose exposure in children should not exceed 487.5 mg. Thus, the proposed product is not suitable for the pediatric population since it provides a total single dose exposure of 650 mg of Acetaminophen and a total daily maximum exposure of 3.9 g/day.

Furthermore, we note the Agency's approval of Citizen Petition 99P-1657 (see Attachment 2), which provided for a new dosage form as well as a change in strength of Acetaminophen from 325 mg to 650 mg. In this case, the Agency could have requested additional pediatric studies, but acknowledged that the proposed product in that case did not provide a meaningful therapeutic benefit to the pediatric population. Additionally, we note the Agency's approval of Citizen Petition 99P-2150 (see Attachment 3) which provided for a change in strength of Acetaminophen from 500 mg to 750 mg. In this case, the Agency acknowledged that once again, the product that is the subject of the petition did not provide a meaningful benefit to the pediatric population and would not likely be used in a substantial number of pediatric patients since the higher dose of 750 mg of Acetaminophen is not appropriate for use in children. Similarly, the proposed fixed-dose combination product of Acetaminophen 650 mg, Butalbital 50 mg, Caffeine 40 mg, and Hydrocodone Bitartrate 5 mg does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and will not likely be used in pediatric patients due to the high dose of Acetaminophen. Based on the nature of the medication, it is not likely that the product will be used in a substantial number of pediatric patients.

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,

Robert W. Pollock
Senior Vice President

RWP/pk

Attachments:
1. Approved Drug Products with Therapeutic Equivalence Evaluations, Electronic Orange Book listing, accessed 4/24/2007
2. Approval Letter for Citizen Petition 99P-1657, dated April 14, 2000
3. Approval Letter for Citizen Petition 99P-2150, dated April 14, 2000
4. Approval Letter for Citizen Petition 93P-0346, dated November 15, 1994
5. Approved labeling for reference-listed drug, Fioricet® with Codeine Capsules
6. Draft insert labeling for proposed product

cc: Craig Kiester (OGD)

Fioricet® is a registered trademark of Watson Pharmaceuticals.

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