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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

CITIZEN PETITION

This petition is submitted under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. § 355(j)(2)(C), which authority has been delegated to the Commissioner of Food and Drugs under 21 C.F.R. § 5.10. The petitioner requests that the Commissioner of Food and Drugs declare that abbreviated new drug applications ("ANDAs") may be submitted for a drug product containing a combination of 12.5 mg ketoprofen and 7.5 mg hydrocodone bitartrate.

A. Action Requested

King & Spalding LLP requests that the Commissioner declare that ANDAs may be submitted for a drug product containing 12.5 mg ketoprofen in combination with 7.5 mg hydrocodone bitartrate in a tablet for oral administration.

B. Statement of Grounds

The FDC Act allows an ANDA applicant to petition FDA for permission to file an ANDA for a combination drug product for which one active ingredient differs from the corresponding ingredient in the listed drug. See 21 U.S.C. § 355(j)(2)(C); 57 Fed.Reg. 17950, 17952 (1992). This petition requests acknowledgement of the appropriateness of substituting an equipotent dose of one of the active ingredients in a fixed combination drug product with another of the same pharmacologic class.

The reference listed drug upon which this petition is based is Abbott Laboratories' Vicoprofen® (hydrocodone bitartrate and ibuprofen) Tablets, 7.5 mg/200 mg, approved under NDA 20-716. A copy of the results of an Electronic Orange Book query by proprietary name (ketoprofen) is attached. Approved Drug Products with Therapeutic Equivalence Evaluations 23rd Edition ("Electronic Orange Book" at www.fda.gov/cder/ob/default.htm) (**Attachment A.**) The proposed product is similar to the reference product in that the proposed product contains the opioid analgesic agent, hydrocodone bitartrate ("hydrocodone"), in combination with a currently marketed and very well-characterized nonsteroidal anti-inflammatory drug ("NSAID"). The proposed product differs from the reference product in that, instead of the 7.5 mg hydrocodone and 200 mg ibuprofen combination, the proposed product contains 7.5 mg hydrocodone in combination with 12.5 mg ketoprofen, another approved and commonly used NSAID.

Hydrocodone is a narcotic with antitussive and analgesic properties. A ratio of 6 (*vis a vis* codeine phosphate) has been adopted for the FDA hydrocodone substitution policy for

suitability petitions. For analgesia, the recommended dosing regimen for hydrocodone (from MEDEX drug evaluation) is 5 to 10 mg every six hours, with a recommended daily maximum dose of 40 mg. However, hydrocodone usually is not used alone. All marketed products in the United States containing hydrocodone are combinations of varying strengths of hydrocodone and an analgesic/antipyretic/NSAID agent, such as ibuprofen, acetaminophen, and aspirin. These products are approved for a range of pain indications.

Ibuprofen is an NSAID with well-characterized analgesic, anti-inflammatory, and antipyretic activity. As an over-the-counter ("OTC") analgesic, the recommended dosing regimen for ibuprofen is 200 mg every four to six hours. If pain or fever does not respond to one tablet, two tablets may be used. The maximum daily OTC dose for ibuprofen is six tablets (1200 mg). Like ibuprofen, ketoprofen is an approved NSAID with well-characterized analgesic, anti-inflammatory, and antipyretic effects. As an OTC analgesic, the recommended adult dosing regimen is one 12.5 mg tablet every four to six hours as needed for pain; if pain or fever does not improve in one hour, a second 12.5 mg tablet may be taken. The maximum daily OTC dose of ketoprofen is six tablets (75 mg). Dosing for ketoprofen 12.5 mg tablets is essentially the same as dosing for ibuprofen 200 mg tablets for the same general OTC pain indications.

The approved package insert for the reference listed drug, Vicoprofen®, is attached. (**Attachment B.**) According to the approved labeling, the recommended adult dosage for short-term (generally less than ten days) management of acute pain is one Vicoprofen® tablet containing 7.5 mg hydrocodone and 200 mg ibuprofen, every four to six hours, as necessary. Dosage should not exceed five tablets in a 24-hour period. The lowest effective dose or the

longest dosing interval should be sought for each patient, especially the elderly. After observing the initial response to therapy with Vicoprofen®, the dose and frequency of dosing should be adjusted to suit the individual patient's need, without exceeding the total daily recommended dose. Thus, the recommended dosing (one tablet every four to six hours) for the reference listed drug is essentially the same as for OTC ibuprofen and OTC ketoprofen, except that the maximum daily dose for the reference listed drug is five tablets daily, compared to six tablets daily for OTC ibuprofen and OTC ketoprofen. However, this difference may be accounted for by the need to keep the maximum daily dose for hydrocodone in the reference listed drug at 40 mg.

Recommendations for adult dosing of the proposed drug are attached. (**Attachment C.**) Labeling for the proposed product will be consistent with approved labeling for the reference listed drug, with minor differences required by substitution of the OTC dosage of ketoprofen for the OTC dosage of ibuprofen. The proposed drug product will have the same dosage and frequency of administration (one tablet every four to six hours, not to exceed five tablets daily) as the reference listed drug. A side by side comparison of dosing recommendations for the reference and proposed products is attached. (**Attachment D.**)

The proposed substitution of an equipotent dose of one OTC NSAID active ingredient for another of the same pharmacologic class from that of the reference listed drug does not pose questions of safety or effectiveness because the uses, dosage, and route of administration of proposed product are the same as that of the listed drug product. Ketoprofen and hydrocodone will be present in the proposed drug product in amounts known to provide safe and effective

analgesia for the target population. The safety and effectiveness of 7.5 mg of hydrocodone as a constituent of opioid analgesics is established by FDA's approval of the reference listed drug, Vicoprofen® (hydrocodone bitartrate and ibuprofen) Tablets, 7.5/200, (NDA No. 20-716). Additionally, FDA has approved several products combining hydrocodone with acetaminophen and aspirin for moderate to moderately severe pain, including Zydone (acetaminophen and hydrocodone bitartrate) Tablets, 7.5/400 (NDA No. 40-288), Lortab (acetaminophen and hydrocodone bitartrate) Tablets, 7.5/500, Lortab ASA (hydrocodone bitartrate and aspirin) Tablets 5/500, and Norco (acetaminophen and hydrocodone bitartrate) Tablets, 7.5/325. The proposed ketoprofen dose of 12.5 mg is recognized by FDA as safe and effective, as established in approval of NDA 20-429, Whitehall Laboratories' NDA for OTC ketoprofen. In addition, when FDA re-examined safety issues associated with OTC NSAIDs (*e.g.*, gastrointestinal bleeding, renal toxicity) at the September 2002 meeting of the Nonprescription Drug Advisory Committee, ibuprofen and ketoprofen were considered the same for purposes of assessing risks and proposed warnings for product labeling. Accordingly, FDA should conclude that investigations are not necessary to demonstrate the safety or effectiveness of the proposed product, and should grant this petition.

This petition does not raise consideration of clinical studies pursuant to FDA's pediatric use regulation, as the proposed ANDA does not contemplate a new active ingredient, indication, dosage form, dosing regimen, or route of administration. 21 C.F.R. § 314.55(a).

C. Environmental Impact

As provided in 21 C.F.R. § 25.31, neither an environmental assessment nor an environmental impact statement is required.

D. Economic Impact

As provided in 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition.

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 includes representative data and information known to us which are unfavorable to the petition.

Sincerely,

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Attachments