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BEFORE FEDERAL COURTS AND AGENCIES.

December 9, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FDC Act) and 21 C.F.R. § 314.93, § 10.20, and § 10.30 to request permission from the Commissioner of Food and Drugs to submit an abbreviated new drug application (ANDA) for a proposed drug product that differs from the reference listed drug in strength.

A. Action Requested

We request that the Food and Drug Administration (FDA) permit an ANDA to be filed for ondansetron hydrochloride injection, 8mg/4mL prefilled syringes.

B. Statement of Grounds

1. Rationale For Proposed Product

The reference listed drug is ZOFRAN® (ondansetron hydrochloride injection). Among other forms, ZOFRAN is available in a 4mg/2mL single-dose vial, listed in the 2004 Orange Book as "EQ

2004P-05421

CP1

Citizen Petition
December 9, 2004
Page 2

2MG BASE/ML," NDA 20-007, sponsored by GlaxoSmithKline. This petition requests permission to submit an ANDA for a generic version of ZOFTRAN injection in an 8mg/4mL prefilled syringe. The proposed drug product is a different strength of the reference listed drug at the same concentration (different volume of drug in single dose container). Under section 505(j)(2)(C) of the FDC Act and 21 C.F.R. § 314.93(b), an ANDA suitability petition may be submitted for a change in strength.

ZOFTRAN is approved for use for, in relevant part, the following indications and conditions of use:

- Prevention of chemotherapy-induced nausea and vomiting: recommended I.V. dosage is a single 32mg dose or three 0.15mg/kg doses to be infused before the start of emetogenic chemotherapy.
- Dosage adjustment for patients with impaired hepatic function: in patients with severe hepatic impairment, a single maximal daily dose of 8mg to be infused before the start of emetogenic chemotherapy.

The proposed 4mg/8mL prefilled syringe strength provides the appropriate, premeasured dose of ondansetron hydrochloride for preparing admixtures of ondansetron hydrochloride for patients with severe hepatic impairment (8mg of ondansetron hydrochloride). More generally, it also provides the correct dose for preparing admixtures for 53kg (117 pound) individuals, at the approved dosage of three 0.15mg/kg doses.

Prefilled syringes eliminate the need to withdraw doses from a larger container. This minimizes preparation time, which is important when treating a condition that causes patient discomfort, such as nausea and vomiting. Moreover, by using prefilled syringes, the syringes are

Citizen Petition
December 9, 2004
Page 3

labeled throughout dose preparation and administration. This reduces the risk of error from drawing an incorrect amount of ondansetron hydrochloride from a larger container dose into a syringe.

The FDA-approved labeling for ZOFTRAN (obtained from www.zofran.com on December 8, 2004) is Enclosure A. A copy of the proposed labeling for the proposed drug product, with appropriate changes from the labeling of the reference listed drug, is Enclosure B.

The active ingredient of the proposed drug product is of the same pharmacological or therapeutic class as that of the reference listed drug, in that it is the same active ingredient.

The proposed drug product is expected to have the same therapeutic effect as the reference listed drug when administered to patients for each conditions of use in the reference listed drug's labeling for which an ANDA will be submitted, in that the proposed drug product will contain the same active ingredient at the same concentration, administered under the same conditions of use as the reference listed drug. The proposed product will be shown to be bioequivalent to the reference product in accordance with FDA's usual criteria.

2. Prior Related Submissions

We are aware that Abbott Laboratories previously filed an ANDA suitability petition seeking the same relief sought by this petition, namely, permission to file an ANDA for 8mg/4mL prefilled syringes of ondansetron hydrochloride injection (Docket No. 2004P-0048, January 30, 2004, Item CP1). Abbott withdrew its petition before FDA made a decision (March 22, 2004, Item WDL1).

Citizen Petition
December 9, 2004
Page 4

One comment was submitted in opposition to Abbott's petition (March 5, 2004, Item C1). Below we address some of these arguments raised in that comment, based on our belief that the same arguments may be raised again in opposition to this petition.

The comment objected to the Abbott petition on the basis that Abbott had sought permission to file an ANDA for a new dosage form or a new single-unit dose, which the comment asserted are not proper bases for an ANDA suitability petition. In our view, the proposed change is properly viewed, not as a change in dosage form or dose, but as a new strength of the drug product. The dosage form remains the same, "injectable" (using the Uniform Terms, Dosage Forms in Appendix C of the 2004 Orange Book). The product that is the subject of this petition would be capable of use at the dosing regimen set forth in the currently approved labeling of the reference listed drug. Thus, this petition is not seeking a new dose.

The only example cited by the comment, FDA's July 9, 2002 decision denying an ANDA suitability petition submitted by Pharmaceutical Associates, Inc. (Docket No. 01P-0130), is readily distinguishable. Among other changes, that petition sought a change in dosing regimen (characterized by FDA as "a change in the volume of drug product administered per dose (dosing regimen) from that of the reference listed drug. FDA denied the petition because a change in dosing regimen is not a change that can be addressed in an ANDA suitability petition. Here, the only change addressed by this petition is a change in the strength of the drug product (different volume at same concentration). The proposed product can be administered in accordance with the labeling of the reference listed drug.

Citizen Petition
December 9, 2004
Page 5

The comment also asserted that Abbott's petition should be denied because the change sought raised questions of safety and effectiveness that would require clinical studies and significant labeling changes to ensure safe use. Again, both examples cited by the comment are readily distinguishable.

In the comment's first example, on July 3, 2002 FDA denied an ANDA suitability petition submitted by Shotwell & Carr, Inc. that sought permission to file an ANDA for a 200mg carisoprodol tablet, where the reference listed drug is a 350mg tablet (Docket No. 01P-0526). In that matter, the approved labeling for the reference product (MedPointe Pharmaceuticals' (formerly Wallace Laboratories') Soma®) provides for a "usual adult dosage" of one 350mg tablet; the approved labeling does not include any information to support the safe and effective use of a 200mg tablet. Here, as noted, the proposed product sought by this petition could be used in full compliance with the FDA-approved labeling for the reference listed drug.

The comment's second example was FDA's April 12, 2002 denial of a citizen petition submitted by TestoCreme, LLC seeking permission to change the strength of testosterone topical gel from 1% to 5% (Docket No. 01P-0302). In that matter, the agency determined that clinical trials would be required to assess the safety and effectiveness of the proposed drug product. In comparison, the proposed product sought by this petition is at the same concentration as the reference listed drug and would, upon administration, be equivalent in all respects to the currently approved innovator product. We do not believe there is a basis for concluding that clinical studies are needed to assess the safety and effectiveness of the proposed product.

Citizen Petition
December 9, 2004
Page 6

The comment asserted that Abbott's petition should be denied because the proposed "new dosage form" requires pediatric study. This content is easily dismissed. As discussed above, the proposed drug product is properly viewed as a different strength of the reference listed drug, not a new "dosage form." Thus, by its express terms, section 505B of the FDC Act, regarding pediatric studies, is not applicable. Even if the agency were to view the proposed product as a "new dosage form," a waiver from the requirement for a pediatric study would be appropriate because, among other factors, the proposed product is not likely to be used in a substantial number of pediatric patients. See section 505B(a)(4) of the FDC Act. The proposed product is likely to be used in patients with severe hepatic failure; such patients are generally geriatric patients.

Finally, the comment asked that, in the event the agency decided to grant Abbott's petition, "it should remind Abbott that the product it proposes does not differ from the reference listed drug and will therefore be subject to the 180-day exclusivity, if any, of a generic version of the 2mg/ml product. The proposed product will contain 4 milliliters of ondansetron hydrochloride in the already approved strength, i.e., 2mg/ml." Any such request should be summarily denied. As a threshold matter, it has nothing to do with the subject of an ANDA suitability petition. More importantly, it is incorrect as a matter of substance. Recent FDA drug approvals have been listed in the Orange Book with separate listings for different volumes of the same concentration of an injectable drug product. For example, the 2004 Orange Book includes separate listings for ANDA 75-874, for Gensia Sicor Pharmaceuticals, Inc.'s approval for intravenous ifosfamide-mesna kit in two different volumes: (i) "EQ 1GM/20 ML (50 MG/ML) [ifosfamide]; EQ 1GM/10ML (100MG/ML) [mesna]"; and

Citizen Petition
December 9, 2004
Page 7

(ii) "EQ 3GM/60ML (50 MG/ML) [ifosfamide]; EQ 1G/10ML (100 MG/ML) [mesna]".¹ Thus, the two different volumes (strengths) of drug product (1gm ifosfamide per 20 mL and 3gm ifosfamide per 60mL are listed as separate drug products, even though they are at the same concentration (50mg/mL ifosfamide). Similarly, here, the proposed product (8mg/4mL syringe) and ZOFTRAN (4 mg/2mL single dose vial) are different strengths, even though they are at the same concentration.

As the comment recognized, and as has been upheld by a court (Apotex, Inc. v. Shalala, 53 F. Supp.2d 454 (D.D.C.), affirmed 1999 WL956686 (D.C. Cir. 1999)), each strength of a drug product is treated separately for 180-day exclusivity purposes.

Assuming for discussion purposes that the comment's argument is tenable for injectable drug products in multiple use containers, it makes no sense for single use dosage forms of the type under discussion. FDA regards different container sizes of the same "strength" of drug product as the same drug product (e.g., bottles of 100s and 1000s of a 100mg tablet). But a single use dosage form intended for injection is comparable to a single tablet or capsule. Thus, the innovator's 2mg/4mL product and the 4mg/8mL product proposed by this petition are different products because they are different "strengths," just as a 100mg tablet and a 200mg tablet are different drug products because they are different "strengths."

¹ We understand that resource limitations prevent FDA from revising the Orange Book so that all older approvals for injectable drug products are listed in this manner.

Citizen Petition
December 9, 2004
Page 8

C. Environmental Impact

This petition is eligible for a categorical exclusion under 21 C.F.R. § 25.31(a) because approval of this petition will not increase the use of the active moiety. The proposed drug product will not be administered at higher dosage levels, for longer duration, or for different indications than the reference listed drug.

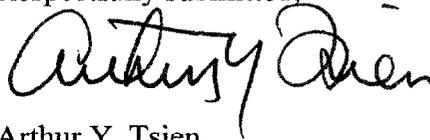
D. Economic Impact

Information on economic impact will be submitted upon request.

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,



Arthur Y. Tsien

AYT:jdc
Enclosures

- A – ZOFRAN labeling
- B – Labeling for proposed product