sanofi aventis

Because health matters

April 28, 2009 0259 9 APR 28 P2:20

BY HAND DELIVERY

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

Citizen Petition Supplement No. 2

(2006P-0523)

Sanofi-aventis U.S., LLC ("sanofi-aventis"), submits this Supplement No. 2 (the "Supplement No. 2") to its Citizen Petition dated December 19, 2006 (2006P-0523/CP1) (the "Citizen Petition") and supplement dated April 23, 2007 (the "Supplement No. 1"). Sanofi-aventis is the manufacturer of Eloxatin® (oxaliplatin injection) ("oxaliplatin"). The Citizen Petition and Supplement No. 1 requests the agency to give special consideration to any application for a generic version of oxaliplatin solution containing an acid other than oxalic acid or a conjugate base thereof, or a sugar.

I. BACKGROUND: THE CITIZEN PETITION

The Citizen Petition notes that sanofi-aventis' marketed Eloxatin solution product contains only oxaliplatin and water for injection. It does not contain an acid added, for example, to aid stability or to buffer the solution. Solutions containing oxaliplatin and the conjugate base of inorganic or carboxylic acids are likely to undergo chemical exchange reactions in which the conjugate base displaces the oxalate ligand. This reaction would lead to the formation of free oxalate and new Pt(diaminocyclohexane) complexes ("Pt(DACH) complexes"), which are likely to have biological activity and toxicity.[1]

Tartaroplatin, discussed at length in the Citizen Petition, is one example of a new Pt(DACH) complex formed in such solutions. Tartaroplatin is the result of ligand exchange of the oxalic acid in oxaliplatin with tartaric acid. The literature demonstrates that tartaroplatin is likely biologically active.[2] Moreover, the pharmacokinetics, tumor specificity and the toxicity of

---

[1] *See* Citizen Petition at 6-11 (citing Declarations of Professor Stephen G. Chaney and Professor Nicholas P. Farrell).

[2] *See id.* at 2, note 3 (citing supporting literature).

FDA-2006-P-0025 SUP

tartaroplatin and similar Pt(DACH) complexes formed in this manner are not predictable. Therefore, the safety and effectiveness profile of a product containing tartaroplatin cannot be assumed to be the same as Eloxatin.[3]

The literature and sanofi-aventis' oxaliplatin development experience with tartaric acid suggests that similar results may be obtained through the addition of other acids to oxaliplatin solutions, for example, either inorganic acids (*e.g.*, phosphoric acid, carbonic acid) or organic acids (e.g., carboxylic acids, amino acids), or by the addition of sugars.[4] The Citizen Petition and Supplement No. 1 therefore argue that if a company were to propose formulating oxaliplatin in a buffer system containing tartrate, the conjugate base of any other acid, or an added sugar, it should be incumbent on that company to demonstrate that no significant formation of new Pt(DACH) complexes occurs under anticipated storage and use conditions.[5] If new Pt(DACH) complexes did form upon storage or use, as a result of added acids or sugars, then preclinical and/or clinical tests should be performed to determine that these by-products do not have any unexpected toxicity or efficacy difference compared to the innovator's oxaliplatin.[6]

II. THE CURRENT SUPPLEMENT NO. 2

In an effort to further explore the effect of the addition of an acid or sugar to oxaliplatin solution formulations, sanofi-aventis analyzed samples of generic oxaliplatin products that are currently commercially available outside of the United States. The results of this testing are discussed below.

A. Tartaric Acid

To explore the effect of adding tartaric acid to oxaliplatin solution formulations, sanofi-aventis analyzed Hospira UK Limited's generic oxaliplatin solution product. The analyzed product was obtained commercially in the Netherlands and entailed a clear glass vial containing 5 mg/mL oxaliplatin solution to which tartaric acid and sodium hydroxide were added. Using an HPLC procedure and an ion chromatology (IC) procedure, the tartaric acid content in solution was assessed as 0.38% w/w.[7]

As predicted in the Citizen Petition, the addition of tartaric acid to Hospira's product resulted in the formation of a new Pt(DACH) complex (tartaroplatin) in Hospira's

---

[3] *See id.*

[4] *See* Declaration of Professor Stephen Chaney in Appendix A of Citizen Petition

[5] *See* Citizen Petition at 5-11; Supplement No. 1 at 4-9.

[6] *See id.*

[7] *See* Analytical Evaluation of Generic Oxaliplatin Solution Drug Product Mayne (Hospira) from UK (March 6, 2009) (attached hereto as Appendix A).

product that is not present in Eloxatin and at a level that exceeds ICH guidelines.[8] As demonstrated in the attached sanofi-aventis study report (attached hereto as Appendix A) the presence of tartaroplatin was computed based on area percent of oxaliplatin and reported as 0.34%. Tartaroplatin was not found in the control sample (Eloxatin).[9]

In addition to the formation of tartaroplatin, the addition of tartaric acid to Hospira's oxaliplatin formulation may have affected the generic product's overall impurity profile. The Hospira product also demonstrated a different impurity profile than Eloxatin, including the presence of two additional unknowns (0.14% each) that are not typically present in Eloxatin.[10]

B. Lactose Monohydrate

To explore the effect of adding lactose monohydrate to oxaliplatin solution formulations, sanofi-aventis analyzed Teva Pharmaceuticals' generic oxaliplatin solution product. The analyzed product was obtained commercially in Portugal and entailed a clear glass vial containing 5 mg/mL oxaliplatin solution to which lactose monohydrate was added at a concentration of 45 mg/mL.[11]

The addition of this particular sugar appeared to give rise to the formation of a new unspecified impurity.[12] Initial analysis showed the impurity profile of the Teva sample was different than the impurity profile of the tested Eloxatin control, including the presence of one unspecified impurity in the Teva product that is atypical of Eloxatin.

In addition to the initial analysis, the Teva and sanofi-aventis products were subjected to heat stress followed by comparative testing. A total of eight (8) unspecified impurities were detected in the Teva sample. One of the unspecified impurities was measured at 1.21%, while the corresponding level in Eloxatin control were well below specification (NMT 0.2%). Total unspecified impurities in the Teva product were measured at 1.58%, compared to the Eloxatin control product showing only 0.12%. Specification for total impurities is NMT 1.00%.

---

[8] *See* ICH Harmonized Tripartite Guideline: Impurities in New Drug Products (Q3B)R2 (June 2, 2006).

[9] Analytical Evaluation of Generic Oxaliplatin Solution Drug Product Mayne (Hospira), *supra* note 6.

[10] *See id.*

[11] *See* Analytical Evaluation of Generic Oxaliplatin Solution Drug Product Teva (Oxaliplatina) from Portugal (March 30, 2009) (attached hereto as Appendix B).

[12] *See id.*

One cannot exclude the possibility that these differences may have been caused by the addition of lactose monohydrate.

III. CONCLUSION

Sanofi-aventis' Citizen Petition and Supplement #1 predicted that when oxaliplatin is combined with an acid other than oxalic acid or a conjugate base thereof or a sugar, one could expect that new Pt(DACH) complexes would be formed. This prediction is now supported by the above-described analytical testing of commercially-available oxaliplatin products to which tartaric acid or lactose monohydrate has been added.

As originally stated in the Citizen Petition, these new Pt(DACH) complexes likely have biological activity and toxicity. Because Eloxatin does not contain an acid, other than oxalic acid, or a sugar, the safety and effectiveness of oxaliplatin products containing these new complexes has not been tested. The presence of complexes for which there is little to no supporting chemical and/or biological data (such as tartaroplatin or other complexes resulting from the addition of other acids or sugars to oxaliplatin) makes it extremely difficult to characterize such an oxaliplatin product as a therapeutically equivalent generic version of Eloxatin.

The safety and effectiveness of Eloxatin has been demonstrated through extensive chemical, pharmacological, toxicological and clinical studies conducted by the sponsor and submitted to the FDA. Based on these studies, FDA approval has been obtained for both metastatic colorectal cancer and adjuvant stage III colon cancer. It is essential that a generic version of oxaliplatin solution containing an acid other than oxalic acid or a conjugate base thereof, or a sugar, demonstrates that the formation of new impurities or of known impurities at higher than FDA approved or ICH levels does not impact safety or effectiveness as the formation and biological activity of these impurities can not be predicted due to complex chemical and biological reactions that occur with platinum agents. This Citizen Petition request is further re-enforced by the fact that active oxaliplatin species represented by ultrafilterable platinum have an extremely short alpha $T_{1/2}$ of 0.43 hours and that one of the FDA approved indications is in the adjuvant stage III colon cancer setting, in which Eloxatin treatment is with curative intent and in which long-term safety is critical.[13]

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Supplement No. 2 includes all information and views on which the Supplement

---

[13] ELOXATIN® (oxaliplatin) Prescribing Information March 2009.

No. 2 relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Mark W. Moyer

Mark Moyer
Vice President, U.S. Deputy Head,
Regulatory Development
sanofi-aventis U.S. LLC

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