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September 27, 2004

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

Re: Docket No. 2004P-0074
Comments to Citizen Petition Filed on Behalf of Savient Pharmaceuticals, Inc.

Dear Sir or Madam:

These comments to the February 16, 2004 Citizen Petition (the Savient Petition) filed by Savient Pharmaceuticals, Inc. (Savient) are respectfully submitted under 21 C.F.R. § 10.30(d). The Savient Petition requests that the Food and Drug Administration (FDA) establish specific bioequivalence requirements for oral products containing oxandrolone. As demonstrated below, there is no scientific or legal basis for the FDA to take such action.

The Savient Petition asserts that specific bioequivalence requirements are necessary for oral products containing oxandrolone because a recent drug-drug interaction study conducted by Savient (the Savient Study) demonstrated that oxandrolone's interaction with warfarin raises serious patient safety concerns. In reality, the Savient Study merely provided additional data regarding a well-known interaction, and did not result in any change in dosing recommendations for either warfarin or oxandrolone. Any safety issue raised by interaction between oxandrolone and warfarin is appropriately handled by routine

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warfarin dose-titration already in place due to warfarin's interaction with a myriad of drugs and foods.

Specific Bioequivalence Requirements for Oxandrolone Would Not Alter Warfarin Dosing or Improve Patient Safety

Warfarin, a narrow therapeutic index drug, is an anticoagulant indicated for prevention and treatment of various thrombotic events. While potentially lifesaving at the proper therapeutic dose, excessive or inadequate warfarin dosing can lead to uncontrolled or uncontrollable bleeding or thromboembolism, respectively. As a result the warfarin labeling carries a warning that states: "It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter Dosage should be controlled by periodic determination of prothrombin time (PT)/International Normalized Ratio (INR) or other suitable coagulation tests."¹ This point is reemphasized in the precautions section of the labeling: "Periodic determination of PT/INR or other suitable coagulation test is essential."² The Savient Petition notes that "precise titration of warfarin in subjects who are also on [oxandrolone] is of utmost importance for safety."³ In fact, as noted above, precise titration of warfarin in all patients is of utmost importance. Such tight control is necessary because PT/INR response to warfarin is affected by factors such as travel, age, race, hepatic function, and vitamin K consumption.

Over 150 drug classes and products are known to interact with warfarin.⁴ The class of anabolic steroids, of which oxandrolone is a member, is among these. The warfarin labeling recommends increased PT/INR monitoring whenever starting or stopping or changing doses of one of these drugs.⁵ Neither the warfarin labeling nor the labeling for any of these drugs contains actual dose adjustment guidance for warfarin. Such guidance cannot be written because of the need to individualize dose adjustment for each patient.

¹ Physicians' Desk Reference (PDR). 58th ed. Montvale, New Jersey: Thomson PDR, 2004: 1049.

² Id. at 1050.

³ Savient Petition at 8.

⁴ PDR at 1049.

⁵ Id. at 1050.

Neither the existence of specific bioequivalence requirements for oxandrolone, nor anything else in the Savient Petition, would alter this. Physicians will continue to periodically monitor warfarin patients and adjust dose as needed.

Standard Bioequivalence Criteria Do Not Permit Clinically Meaningful Variability in Drug Exposure

Determination of average bioequivalence involves the calculation of a 90% confidence interval for the ratio of the averages of the pharmacokinetic measures for the generic and reference listed drugs. The calculated confidence interval must fall entirely within 80-125% for the ratio of product averages in order to establish bioequivalence.

The Savient Petition characterizes FDA's routine use of the 80-125% criteria as permitting "considerable variability" and claims that these criteria permit generic drug products to vary in bioavailability from one another by as much as 50%.⁶ Such arguments and the request for a narrowed confidence interval are based on a fundamental misunderstanding of the bioequivalence criteria and of confidence intervals. That is, they are based on the false assumption that a generic drug product that consistently reaches only 80% of the average C_{max} and AUC of the reference listed drug would be deemed bioequivalent. In fact, test results for such a product would necessarily fall below the 80% lower limit with normal variation and would thus fail to meet the 80-125% bioequivalence criteria. The 80-125% range does not permit the approval of generic drugs that have clinically significant bioavailability differences, either greater or less than the innovator product. Instead the statistical test governing bioequivalence permits normal variations in the comparison of two drugs with no significant differences in rate or extent of absorption. Similar variations can be expected to occur in comparisons of two lots of the same drug product.⁷

⁶ Savient Petition at 3.

⁷ Letter from Roger L. Williams, M.D., Deputy Center Director for Pharmaceutical Science, Center for Drug Evaluation and Research (CDER) to Carmen A. Catizon, Executive Director, National Association of Boards of Pharmacy, 4 quoting conclusions of a 1986 FDA task force on bioequivalence (Apr. 16, 1997) available at <http://www.fda.gov/cder/news/ntiletter.htm>.

FDA has announced that it is prepared to use more stringent bioequivalence criteria if differences of 80-125% in the ratio of averages in the 90% confidence interval are shown to be clinically significant.⁸ In the 18 years since that announcement, no clinical data have compelled FDA to narrow the requirements for any drug, not even narrow therapeutic index drugs such as warfarin. In fact, FDA has approved generic equivalents of many narrow therapeutic index drugs on the basis of the 80-125% criteria and affirmed its view as late as 2003 that “the traditional BE limit of 80 to 125 percent . . . [should] remain unchanged for the bioavailability measures (AUC and Cmax) of narrow therapeutic range drugs.”⁹ Not surprisingly, generic versions of numerous drugs with warfarin interactions have been approved without narrowed confidence interval requirements. The Savient Petition contains no data that would alter this outcome for oxandrolone.

FDA generally grants requests for waivers of in vivo bioequivalence testing requirements for a maximum of three drug products of lower strengths than the reference listed drug. The Savient Petition, however, alleges that there is an increased potential for lack of dose proportionality across oxandrolone dosage strengths, and that abbreviated new drug applications (ANDAs) for oxandrolone drug products should contain data from bioequivalence testing at each proposed dosage strength. The Savient Petition contains no data to support such a deviation from FDA’s typical practice. The request appears to stem entirely from Savient’s misunderstanding of the 80-125% bioequivalence criteria, and, as such, must be rejected.

Drug Product-Specific Interaction Data Would Not Alter Warfarin Dosing or Improve Patient Safety

Prior to submission of the results from the oxandrolone–warfarin interaction study discussed in the Savient Petition, both the oxandrolone and warfarin labeling contained precautionary language regarding the potential interaction. The oxandrolone labeling precaution stated: “Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired

⁸ See *id.* at 1.

⁹ FDA, CDER, Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations 20 (Mar. 2003).

prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially where anabolic steroids are started or stopped.”¹⁰

Similarly, the warfarin labeling lists anabolic steroids (17-alkyl testosterone derivatives) among drugs that may be responsible for increased PT/INR response and notes that more frequent PT/INR monitoring is advisable when such drugs are started or stopped.¹¹

The Savient Study merely confirms this information. Savient requested, and was granted, a labeling change to include actual results of the Savient Study in its labeling. The results of the Savient Study are not so novel or remarkable as to warrant any change in the warfarin labeling. Oxandrolone is not even specifically mentioned there other than as part of the anabolic steroid class. Even the revised oxandrolone labeling does not direct physicians to decrease the warfarin dose when starting oxandrolone therapy. Rather, the labeling continues to call for monitoring and titration of the warfarin dose on the basis of PT/INR testing.

The Savient Petition claims that use of the Savient Study data in the labeling of generic oxandrolone drug products would present a “significant risk to patients”¹² and that drug product specific information regarding the warfarin interaction is “required to provide physicians the necessary tools for safe and effective patient care.”¹³ These statements are based on the assumption, unsupported by data, that generic oxandrolone and Savient’s oxandrolone would behave differently in relation to warfarin. They also fail to recognize that physicians must monitor an individual subject’s PT/INR in order to adjust the warfarin dose. Detailed data from studies with a particular oxandrolone drug product will not alter the monitoring nor dose titration of warfarin. Physicians will continue to take the same action: monitor individual PT/INR and adjust the warfarin dose. In light of this need for individualized titration, the Savient Petition’s claim that precautionary labeling for oxandrolone drug products must reflect clinical study data that is specific to the particular

¹⁰ PDR at 3043.

¹¹ Id. at 1049.

¹² Savient Petition at 10.

¹³ Id.

oxandrolone drug product is nonsensical. Indeed, FDA routinely approves generic versions of drugs whose labeling includes data from drug-drug interaction studies between the innovator product and warfarin.¹⁴ We are not aware of a single case in which FDA has required drug product specific data as requested in the Savient Petition.

Conclusion

The Savient Petition correctly notes that “it is widely accepted that warfarin dosing must be carefully titrated to assure proper anticoagulation control.”¹⁵ As a result of warfarin’s narrow therapeutic index and the impact of numerous drugs and foods on its dosing, careful PT/INR monitoring of warfarin patients and attention to any changes in their concomitant therapies is a matter of routine. The Savient Study does little more than confirm the long-standing knowledge that oxandrolone is one of the drugs that interacts with warfarin and that patients taking both drugs may require a decrease in warfarin dose if PT/INR testing so indicates. The study provides no information that would alter prescribing patterns or patient monitoring. It also provides no data to support the conclusion that generic oxandrolone products may interact differently with warfarin than Savient’s oxandrolone does. This assertion is apparently based entirely on the faulty assumption that generic oxandrolone products approved in accordance with the standard 80-125% bioequivalence confidence interval limits would, in fact, have different rates and extents of absorption than Savient’s oxandrolone.

In addition, as part of the normal course of ANDA review and approval, bioequivalence is demonstrated, identical labeling (except for minor variations) is adopted, and appropriate CMC controls are established to ensure the identity, strength, quality, purity and potency of the generic drug product. We trust that FDA will recognize the Savient Petition for what is – a weak attempt to extend the monopoly on a drug that was first approved over 40 years ago – and deny the actions requested therein.

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¹⁴ See Propafenone Hydrochloride labeling at http://www.watsonpharm.com/package_insert/data_stream.asp?Product_groups=68&p=pi.

¹⁵ Savient Petition at 2.

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HYMAN, PHELPS & MCNAMARA, P.C.

We appreciate the opportunity to submit these comments and look forward to FDA action on this issue.

Sincerely,



Robert A. Dormer



Josephine M. Torrente

RAD/JMT/tee