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February 21, 2006

Division of Dockets Management
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5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. 2004P-0074
Docket No. 2005P-0383
Comments to Citizen Petitions Filed on Behalf of
Savient Pharmaceuticals, Inc.

Dear Sir or Madam:

This comment responds to the February 2, 2006 submissions by Savient Pharmaceuticals, Inc. (Savient) to the above-referenced dockets. The Savient submissions provide a copy of a non peer-reviewed correspondence to the *Archives of Internal Medicine* which describes two anecdotal reports of increased prothrombin time, one with bleeding, on coadministration of warfarin with oxandrolone in one case, and a topical testosterone product in the other. Contrary to the implication in Savient's cover letters, these two anecdotes provide no new information relevant to the risks associated with approval of generic oxandrolone products.

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That coadministration of androgens, including oxandrolone, and warfarin decrease coagulation and increase prothrombin time due to inhibition of CP450 2C9 is well established. Information regarding this drug-drug interaction (and over one hundred others) is noted in the warfarin labeling along with general warnings regarding the need for increased monitoring of coagulation whenever stopping, starting or changing dose of various compounds in patients taking warfarin because of the latter's narrow therapeutic index. This information is also noted in the Oxandrin (oxandrolone) package insert: "Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require dose monitoring, especially where anabolic steroids are started or stopped." Physicians' Desk Reference. 58th Ed. Montvale, New Jersey: Thomson PDR, 2004; 1049.

Thus, FDA approved labeling for warfarin and oxandrolone instruct treating physicians to monitor prothrombin time after administration of oxandrolone (or other androgens) to a patient receiving warfarin. In the second anecdote cited in the published correspondence, such monitoring was conducted appropriately and led to titration of the warfarin dose, as it is intended to do. The published correspondence fails to address whether appropriate coagulation tests were conducted upon initiation of oxandrolone therapy in the patient who experienced bleeding. Because the effect of oxandrolone on warfarin metabolism would be detectable within a day of coadministration, the discovery of "frank bleeding" two weeks after initiation of oxandrolone therapy suggests that they were not. No specific bioequivalence requirements or geriatric labeling would have altered the result for this patient especially in light of the fact that existing labeling requiring monitoring was apparently ignored.

The Savient correspondence submitted to Docket No. 2005P-0383 implies that these events were somehow unique because of the involvement of geriatric patients and that the exclusivity-protected Oxandrin geriatric labeling is necessary to safe use of any oxandrolone product. In reality, there is no reason to expect the concomitant administration of the same two drugs in non-geriatric patients would have yielded a different clinical result. Further, the patient was dosed at 2.5 mg twice daily in accordance with the dosing recommendations in the Oxandrin label's geriatric use section (which fall within the dosing recommendations for adults generally). Thus, there is no reason the Oxandrin geriatric labeling would not have prevented or ameliorated this outcome.

That the use of oxandrolone with warfarin increases the risk of bleeding and requires monitoring is not new information. The latest Savient submissions merely serve to confirm this well-established fact. Nothing in this information supports a view that increased bioequivalence requirements or geriatric labeling would lessen this risk.

We trust that this latest baseless attempt by Savient to derail any ongoing FDA reviews of oxandrolone Abbreviated New Drug Applications (ANDAs) will be ineffective and that FDA will quickly complete these reviews.

Sincerely,

/Robert A Dormer

Robert A. Dormer

Josephine M. Torrente

RAD/JMT/tee