

October 22, 2004

Division of Dockets Management  
U.S. Food and Drug Administration  
5630 Fishers Lane -- Room 1061  
Rockville, MD 20852

James N. Czaban  
Shareholder  
(202) 912-2720  
(202) 912-2020 (fax)  
jczaban@hewm.com

**Docket No. 2004P-0074**  
**Response to Supplemental Statements Filed By Savient Pharmaceuticals**  
**In Support of Its February 17, 2004 Citizen Petition Regarding Oxandralone ANDAs**

These comments are respectfully submitted in response to statements filed on behalf of Savient Pharmaceuticals Inc. ("Savient") on September 17, 2004 in support of Savient's Citizen Petition. Savient's latest filing consists of unsworn statements by Robert H. Demling, M.D. and James A. Longstreth, Ph.D, relating to the concomitant use of oxandralone and warfarin.

On February 17, 2004, Savient filed a Citizen Petition requesting that FDA require oxandralone ANDA applicants to conduct new oxandralone/warfarin drug interaction studies to establish a product-specific dose reduction recommendation for generic products when co-administered with warfarin. In comments filed by the undersigned on August 4, 2004 ("August 4th Comments"), it was demonstrated that Savient's Petition is legally and scientifically unfounded. On September 17, 2004 Savient filed two statements purportedly in further support of its Petition, but as shown herein, those statements fail to address, much less rebut, our August 4 comments, and do not provide any new basis for FDA to require product-specific interaction studies for generic oxandralone products. Thus, for the reasons set forth below, in our August 4 comments, and in the September 27, 2004 comments filed by Hyman, Phelps and McNamara, the Savient petition remains wholly without merit and should promptly be denied.

**I. THE DEMLING STATEMENT**

The statement by Dr. Demling offers little more than general background information on the clinical uses of oxandralone, but fails to show how this is relevant to the issue raised in Savient's Petition – *i.e.*, whether generic oxandralone would be expected to have a different drug interaction with warfarin than does Oxandrin<sup>®</sup>. Specifically, Dr. Demling recounts the following remarkably unenlightening facts:

2004P-0074

C3

Heller Ehrman White & McAuliffe LLP 1666 K Street, NW, Suite 300 Washington, D.C. 20006-1228 www.hewm.com

New York Washington, D.C. Madison, WI San Francisco Silicon Valley Los Angeles San Diego Seattle Portland Anchorage  
Hong Kong Beijing Singapore Affiliated Offices: Milan Paris Rome

- Oxandralone is useful in treating patients with weight loss, Demling Statement at 1-3;
- Some patients receive both warfarin and oxandralone, *Id* at 3-4;
- Oxandralone interacts with warfarin, *Id* at 4-5; and
- An oxandralone dose reduction is necessary in patients receiving warfarin in order to avoid excessive bleeding, *Id* at 5-6.

The only place Dr. Demling even attempts to address the issue of whether generic oxandralone products may safely include the same dose reduction instructions as Oxandrin<sup>®</sup> is in three short paragraphs at pages 5-6 of his statement, in which he states:

The generic drug would most certainly not have the same potency and pharmacological activity as Oxandrin. Therefore, the Savient guidelines for warfarin and oxandralone use should not be applied to a generic drug, and should not be relied upon by a physician in this prescribing [sic]. The generic manufacturer would need to develop it's [sic] own guidelines.

Demling Statement at 5.

However, Dr. Demling offers no analytical basis for this conclusory statement, and in fact acknowledges that a brand-generic difference in drug interaction is speculative and unsupported. *See Id.* at 5 ("if the interaction of warfarin with a generic are different....") (emphasis added). Specifically, the Demling statement:

- does not address any of the arguments presented in our August 4, 2004 response rebutting Savient's Citizen Petition;
- does not provide any pharmacologic, pharmacodynamic, or pharmacokinetic rationale (or even hypothesis) for believing there may be a brand-generic difference in the warfarin interaction effect that would require separate drug interaction studies for generic oxandralone products; and
- does not address the fact that the mandatory conformity with FDA's established bioequivalence standards is a fully adequate basis for the approval of generic oxandralone products.

Moreover, the Demling statement fails to address the fact that Savient's own study reflects that the drug interaction between oxandralone and warfarin is consistent across a wide range of therapeutic doses, and that therefore, the currently approved Oxandrin<sup>®</sup> and warfarin labeling fully

and adequately advise physicians on how to individually address the oxandralone/warfarin drug interaction for patients who will receive generic oxandralone.<sup>1</sup> See August 4th Comments at 6-8.

Thus, although the Demling statement recognizes the well known need for oxandralone/warfarin dosing adjustments, it does not provide any basis to conclude that the interaction of generic oxandralone with warfarin would deviate at all from the interaction of Oxandrin<sup>®</sup> with warfarin so as to be potentially inimical to patient safety. Accordingly, the Demling statement does nothing whatsoever to support, or assist FDA in responding to, the Savient petition.

## II. THE LONGSTRETH STATEMENT

Like the Demling statement, the statement by Dr. Longstreth provides nothing useful or persuasive for FDA's consideration of the specific issues raised by Savient's petition. Rather, Dr. Longstreth simply:

- "summarizes [his] review and evaluation of the reported results of the clinical study sponsored by Savient in order to describe the extent of the interaction between oxandralone and warfarin;"<sup>2</sup>
- discusses generally the "mechanisms and pharmacologic activities" of oxandralone and warfarin; and
- provides an overview of several common mechanisms that cause drug-drug interactions.

Dr. Longstreth then discounts these common drug action and interaction mechanisms as possible bases for the observed oxandralone-warfarin interaction and concludes that "[i]t is not clear at this time *how* the rate and extent of oxandralone and warfarin availability interact, which parameters can be used to assess the extent of the interactions, or whether the effects are fundamentally pharmacokinetic or pharmacodynamic in nature." Longstreth Statement at 8 (emphasis added). However, Dr. Longstreth's inability to explain the cause of the oxandralone-warfarin interaction has

---

<sup>1</sup> Dr. Demling does, however, state that he has "reviewed the Savient research document which explains this [drug interaction] effect and which is the basis of the [dose reduction] recommendations. The clinical study is very well done and the recommendations are very valuable...." Demling Statement at 5. Because FDA's Citizen Petition regulations require a Petitioner to certify that the "petition includes all information and views upon which the petition relies," 21 C.F.R. § 10.30(b), and because Savient's counsel in fact signed such a declaration, Savient is now obligated to make public its clinical study "research document" upon which Dr. Demling relies in support of his statement filed by Savient in support of its petition. In the alternative, FDA could deem Savient's recent submission as providing implied consent for FDA to publicly disclose the study results and reports upon which Savient and its paid supporters rely.

<sup>2</sup> For the reasons explained in footnote 1 above, Dr. Longstreth's reliance on the Savient clinical study further requires Savient and/or FDA to make the study results and all related documents reviewed by Drs. Demling and Longstreth available in the public docket. Otherwise, FDA is obligated to refuse to accept or consider the supplemental statements of these purported experts.

no bearing on the issue of whether a bioequivalent generic oxandralone product would produce a qualitatively or quantitatively different drug interaction than that observed between Oxandrin® and warfarin.

Dr. Longstreth's assertion that none of the traditional or hypothesized mechanistic explanations can adequately explain the oxandralone-warfarin interaction does not bear on or support Savient's request that FDA require new clinical studies to examine interactions between warfarin and generic oxandralone products. *See* Longstreth Statement at 7. It is telling that the Longstreth Statement does not claim, or provide any reason to even hypothesize, that the drug interaction observed in Savient's study is unique to Oxandrin® and would be different for generic oxandralone products. Rather, his statement refers more generally to the interaction between oxandralone and warfarin as drug molecules, and, at most, suggests that this molecule-based interaction cannot be explained by known interaction mechanisms between warfarin and other drug molecules.

More particularly, the Longstreth statement does not relate a lack of understanding of the specific mechanistic interactions of warfarin with oxandralone to the most important issue concerning generic drug approval, *i.e.*, bioequivalence of the generic drug product to the innovator drug. Indeed, Dr. Longstreth nowhere states or suggests that (i) the drug interaction would be any different for generic oxandralone than for Oxandrin® or (ii) that clinical studies for generic oxandralone products would in any way provide greater insight into the oxandralone/warfarin drug-drug interactions so as to either overcome his lack of understanding of the interaction, or show that generic oxandralone interacts differently with warfarin than does Oxandrin®. Moreover, Dr. Longstreth does not indicate how such studies would impact on, or undermine, a showing of bioequivalence between a generic oxandralone product and Oxandrin®.

In addition, like the Demling Statement, the Longstreth Statement fails to rebut the key points of our August 4 comments to the Petition. For example, it was demonstrated that Savient's own study reflects that the drug-drug interaction between oxandralone and warfarin is consistent across a wide range of therapeutic oxandralone doses. This disposed of Savient's expressed concern that significant differences in bioavailability could exist in bioequivalent oxandralone products, thereby altering the scope of the drug interaction and requiring different dose reduction instructions. *See* August 4th Comments at 6-8. In this regard it is significant that Savient has now abandoned its original flawed premise, and now simply argues that generic oxandralone products should not be approved until absolute certainty is achieved with respect to the nature and cause of the molecular in-vivo interaction between oxandralone and warfarin. Raising an unanswered but wholly tangential question, such as Savient does here, is not a basis to impose additional drug approval requirements, either in general or with respect to oxandralone.

Moreover, it was shown that the dose reduction instructions for Oxandrin® require an individualized approach with frequent monitoring and dose adjustments, and that no physician would rely exclusively on the 80-85% average dose reduction requirement observed in Savient's study. August 4th Comments at 8-10. Dr. Longstreth's conclusion that the lack of understanding of the mechanism of the interaction "may lead to inappropriate dosing in some settings," Longstreth at 7, is based on his presumption that doctors would presume that the mechanism of the oxandralone-

warfarin interaction is fully known. This is a non-sequitur however, because even if the mechanism of the interaction was known, the Oxandrin and generic oxandralone labeling would still require physicians to dose individually with frequent monitoring and appropriate further dose adjustment.

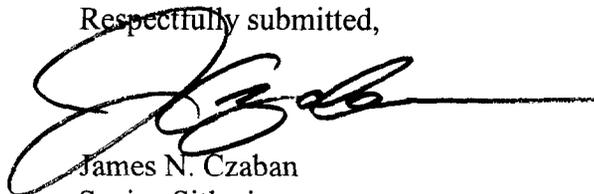
Finally, the absurdity of Savient's position (as reflected in the Longstreth statement) is that if the alleged mystery of this drug interaction requires drug product-specific clinical studies, then Savient should have been required to study Oxandrin's interaction with every available version of warfarin to ensure that changes in *warfarin* products do not alter the observed effect. FDA properly did not impose such a requirement on Savient, and should not impose such an oxandralone-product-specific requirement on generic applicants.

### III. CONCLUSION

As demonstrated herein, the supplemental statements submitted by Savient do not support the action requested in its Citizen Petition. Rather, Savient seeks to divert attention from the fact that its original bioequivalence- and safety-based arguments in support of the Petition were shown to be groundless. FDA should, and must, continue to apply its longstanding and well supported bioequivalence standards and procedures in evaluating and approving generic oxandralone applications, and not allow frivolous Petitions such as Savient's to detract from the Agency's important mission to review and approve bioequivalent generic drugs in the most timely manner possible.

Savient's petition should and must be denied.

Respectfully submitted,



James N. Czaban  
Sanjay Sitlani  
HELLER EHRMAN  
WHITE & MCAULIFFE LLP  
1666 K Street N.W.  
Washington, D.C. 20006  
(202) 912-2720