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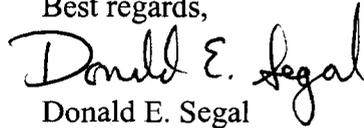
Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

**Subject: Docket No. 2004P-0074 - Statement in Support of the Citizen
Petition filed by Savient Pharmaceuticals**

Dear Sir or Madam:

Enclosed are an original and three duplicate copies of an expert statement in support of Savient Pharmaceuticals Inc.'s Citizen Petition regarding interactions between oxandrolone and warfarin.

Best regards,



Donald E. Segal
Edward John Allera
Theodore M. Sullivan

Enclosure

2004P-0074

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Oxandrolone-Warfarin Interactions

David Flockhart, M.D., Ph.D.
Indiana University School of Medicine

November 15, 2004

I. Introduction

My name is David Flockhart. I hold an M.D. from the University of Miami (1987) in Miami, FL and a Ph.D. from the Welsh National School of Medicine(1976). I am Chairman of the Division of Clinical Pharmacology at the Indiana University School of Medicine, where I am Professor of Medicine, Genetics and Pharmacology, and have practiced and conducted clinical research since 2001, after 14 years on the faculty at Georgetown University Medical Center, where I did my residency, was Chief Resident in Medicine, and where I did a fellowship in Clinical Pharmacology. I am a board-certified internist and I sit on the American Board of Clinical Pharmacology. I sit on the National Institutes of Health study section for General Clinical Research Centers, and on the FDA Advisory Committee on Clinical Pharmacology. My research and practice are focused on the understanding of inter-individual variability in drug response, and the improvement in rational drug prescribing. My internet website, www.drug-interactions.com has provided an overview of the human cytochrome P450 system as a teaching and reference tool for physicians and researchers for the last 10 years.

Based upon my clinical and scientific knowledge, a review of Savient Pharmaceuticals Inc's petition, and a review of scientific literature regarding the issues contained therein, it is my expert opinion that bioavailability of androgenic steroids, and in particular that of oxandrolone, represent a challenging and atypical situation. Thus, any review of the bioavailability and bioequivalence of a generic oxandrolone drug product requires additional scrutiny beyond the Food and Drug Administration's usual standards. Failure to consider the unusual nature of the oxandrolone bioavailability problem creates potentially serious safety risks for future generic oxandrolone patients.

The unusual nature of oxandrolone's bioavailability problem is based upon at least five different elements. Each of the elements may be present in other drug bioavailability scenarios, and separately do not necessarily present serious safety concerns, but taken as a whole, the oxandrolone bioavailability issue is unique. The number and magnitude of the elements present a "perfect storm" where the various elements come together and create a complex and potentially serious safety situation, and where it is particularly dangerous to assume that simple bioavailability guidelines will suffice. As a result, the safety of oxandrolone drug products should rely on empirical safety data from a controlled clinical environment, such as was provided by Savient's Oxandrin®-warfarin interaction study.

The five elements are:

1. Substantial inter-individual variability in oxandrolone pharmacokinetics after oral administration
2. Substantial degree of interaction between oxandrolone and warfarin
3. The complexity of the interaction between oxandrolone and warfarin: the interaction is unpredictable because the mechanisms underlying are complex and include pharmacogenetic variability in the enzymes and receptors involved.
4. The relationship between oxandrolone concentration and effect is not well described
5. Oxandrolone is prescribed to particularly vulnerable groups of patients

II. Inter-Individual Variation

Since there is substantial inter-individual variability in oxandrolone pharmacokinetics after oral administration(1), the variance on any individual pharmacokinetics parameter is greater, and so a larger number of subjects need to be studied to assure a reasonable scientist with confidence that bioavailability falls within between 80 and 125% of the progenitor.

III. Substantial Oxandrolone-Warfarin Interaction

There is a well documented interaction between anabolic steroids and warfarin(2-4), a drug of notably narrow therapeutic range, underdosing of which can result in death via thrombo-embolism and overdoing of which may result in over anti-coagulation, cerebral bleeds and death also.

While many drugs are reported to interact with warfarin to varying degrees, almost all are at a level far less than that demonstrated for oxandrolone, and the degree of the oxandrolone-warfarin interaction alone warrants additional concern. Further, many of the drugs reported to interact with warfarin most likely do not interact with it in a clinically meaningful way. The labeling for warfarin contains an extensive list of drugs with "known warfarin interactions." However, many of the drugs on that list interact through competitive protein binding, or "protein bumping," and this type of reaction is very short lived, and probably not clinically important. Clinically important interactions with warfarin are seen with drugs that fall into two categories: 1) competition, inhibition, or stimulation of metabolic pathways; or 2) Vitamin K interactions because warfarin acts by inhibiting Vitamin K carboxylase and the effects of the drug can be washed out by ingestion of sufficient Vitamin K. Oxandrolone interactions with warfarin are of these latter, clinically significant types.

Therefore, this drug-drug interaction between oxandrolone and warfarin is unusual, and represents a serious potential safety issue which should be closely examined for any generic oxandrolone drug product.

IV. Complexity of the Oxandrolone-Warfarin Interaction

The biochemical mechanism underlying the oxandrolone-warfarin interaction is likely complex and may be influenced by a number of factors. These include a) the ability of the steroid to alter hepatic synthesis of proteins involved in the coagulation cascade, b) its ability to inhibit the activity of hepatic and intestinal cytochrome enzymes, including particularly the enzymes designated CYP3A4 and CYP2C9, that are the principal enzymes involved in the metabolism of the active enantiomer of warfarin, S-warfarin {448}(5;6){155} and c) its ability to induce these enzymes via alterations in hepatic protein synthesis.

A. Effect on coagulation cascade

Oxandrolone, like other androgens, alters hepatic synthesis of proteins involved in the coagulation cascade. The effect of these changes, when combined with the anti-coagulation effects of warfarin, is largely unknown. The potentially serious nature of the combined effect of oxandrolone on hepatic synthesis with the anti-coagulation brought about by warfarin, necessitates additional scrutiny. Savient's clinical study of Oxandrin® represents the type of additional study necessary, where empirical clinical results are directly correlated to warfarin and oxandrolone dose. Similar clinical data should be generated for other oxandrolone drug products. Simple bioequivalence determinations may not be sufficient to ensure safety given the narrow range between therapeutic anti-coagulation and excessive bleeding with warfarin treatment.

B. Inhibition of cytochrome enzymes

Oxandrolone is believed to have an inhibitory effect on hepatic and intestinal cytochrome enzymes, including particularly the enzymes designated CYP3A4 and CYP2C9. These enzymes are involved in the metabolism of the more active enantiomer of warfarin, S-warfarin. The S-enantiomer of warfarin is believed to be approximately five times as active an anticoagulant as the R-enantiomer. This inhibition of S-warfarin metabolism by oxandrolone has the potential to dramatically change the blood concentrations and clearance rates of warfarin in patients taking both warfarin and oxandrolone. Additionally, oxandrolone also has an effect on the metabolism of the less active R-enantiomer of warfarin, which is metabolized through the Cytochrome P450 3A pathway. While the S-enantiomer is clinically more important than the R-enantiomer, the activity

levels of the R-enantiomer are still significant enough to be a concern for a narrow therapeutic range drug such as warfarin.

C. Alteration of hepatic protein synthesis

In addition to its inhibitory effect on cytochrome P450 isoforms, oxandrolone also indirectly impacts the warfarin metabolic pathways by altering the synthesis of the CYP3A4 and CYP2C9 enzymes in the liver, and may change the effect of a given concentration of S-warfarin by altering the synthesis of multiple key proteins within the coagulation cascade itself. This greatly complicates the drug metabolism analysis, introducing another order of complexity.

D. Genetic variation

A number of genetic variants in the androgen receptor that mediates the effects of androgenic steroids in the liver and other tissues, and in cytochrome P450 2C9 (7;8) and in the propeptide of factor IX(9) mean that there may be rare patients who have markedly unusual sensitivity to drug interactions between with warfarin.

V. Pharmacokinetics vs. Pharmacodynamics

In a situation where there are consistent pharmacokinetics and therefore consistently predictable drug interactions, the relationship between drug concentration and effect may not be linear and predictable. The relationship between oxandrolone concentration and effect is not well described and this leads to further uncertainty. As a result, pharmacodynamic analysis may be necessary to adequately describe the dose/response relationship.

VI. Vulnerable Patient Populations

Both oxandrolone and warfarin are prescribed to a very vulnerable group of patients who have significant other medical disabilities, and this simple reality contributes greatly to any regulatory requirement to ensure the safety of generic equivalents.

Typical patient populations include the elderly, burn and trauma patients, and patients with AIDS. Drug interactions with warfarin are most important to the elderly population, which is the population most likely to be taking warfarin as well as oxandrolone. This population presents several unique challenges:

1. Elderly patients are more likely than patients in other groups to be on multiple medications, and this complicates both interactions, and dosing compliance.
2. The elderly present a unique problem in that the patients are often more sensitive to relatively minor variations in drug dosing.
3. Some elderly patients, such as those with cognitive impairments, present compliance and self-monitoring challenges.

VII. Recommendations

Due to the complexity of the relationship between oxandrolone and warfarin, it is possible that other oxandrolone drug products may exhibit significantly different warfarin interactions when compared to Oxandrin®, even when the two drugs are bioequivalent according to the FDA's bioequivalence standard. The bioequivalence standard examines only the relative bioavailability of different versions of a drug, and does not consider the potential for differences in interactions between those versions and other drug products. Additionally, the bioequivalence standard is ill-suited to take into account confounding factors such as lack of a

linear dose/response curve, and vulnerable likely patient populations. In situations where complex drug-drug interactions exist along side other complicating factors, the bioequivalence standard cannot be a substitute for empirical clinical data. As a result, the review of any generic drug application for an oxandrolone drug product should take into account the following:

- 1) Reliance on the Savient Oxandrin® study as support for another oxandrolone drug product's interaction with warfarin is not appropriate scientifically. New clinical interaction studies conducted by the sponsor should be necessary for any generic oxandrolone drug product.
- 2) Multi-dose oxandrolone-warfarin interaction studies may also be necessary to determine the range of possible effects of oxandrolone on warfarin's action.
- 3) There is no indication that drug concentration is linear with effect for oxandrolone-warfarin interactions. Therefore, absent FDA issued guidance, specific dose adjustment information for each dosage strength of oxandrolone should be required.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "David Flockhart" with a stylized flourish at the end.

David Flockhart, M.D., Ph.D.

References:

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