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HAND DELIVERY - RETURN RECEIPT REQUESTED

February 17, 2004

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

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Subject: Savient Pharmaceuticals, Inc.'s Citizen Petition

Dear Sir or Madam:

Enclosed is an original and three duplicates of Savient Pharmaceuticals, Inc.'s Citizen Petition regarding safety and bioequivalence issues for the anabolic steroid oxandrolone.

Any correspondence regarding this petition should be directed to Buchanan Ingersoll, P.C., attention to the undersigned.

Respectfully yours,



Edward John Allera
Donald E. Segal
Theodore M. Sullivan

Enclosure

2004P-0074

CP1



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CITIZEN PETITION

The undersigned, Savient Pharmaceuticals, Inc., submits this petition in accordance with § 505(j) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), as well as 21 C.F.R. §§10.20, 10.30, 320.32, and 320.33, requesting that the Commissioner of Food and Drugs establish specific bioequivalence requirements for oral products containing oxandrolone because of several unique aspects of these drug products, including, (1) serious safety issues regarding interactions between oxandrolone and widely used anti-coagulant drugs containing the active drug ingredient warfarin; and (2) certain aspects of oxandrolone containing drug products that present "evidence of actual or potential bioequivalence problems" per 21 C.F.R. § 320.33.

The critical issue and public policy concern of this petition is patient safety. A significant number of patients treated with oxandrolone are concurrently treated with warfarin. A clinical study conducted by Savient demonstrated that a significant decrease (80-85%) in the warfarin dose was required to achieve the required therapeutic effect when the subject was also treated

with Oxandrin® (Savient's oxandrolone). The study results were dramatic, and FDA approved a clinically significant safety change to Oxandrin®'s label as a result. In part, the revised "drug interactions" section of the labeling states:

A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng*hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5.

Warfarin is a narrow therapeutic index ("NTI") drug (also referred to as "narrow therapeutic range" drug), and it is widely accepted that warfarin dosing must be carefully titrated to assure proper anticoagulation control. Failure to adjust and maintain appropriate warfarin levels can lead to excessive anti-coagulation with the risk of uncontrolled and/or uncontrollable bleeding, or inadequate anti-coagulation and the risk of failing to prevent the thrombosis and thrombo-embolic events for which the warfarin would have been prescribed. In either case, death or serious injury can result.

The dramatic decrease in the dose of warfarin necessary to achieve therapeutic effect when co-administered with oxandrolone (as shown in the Savient study), combined with the careful dose titration required for warfarin, presents a clinically significant safety concern that is only adequately addressed through specific precautionary labeling. Such precautionary labeling must reflect clinical study data that is specific to the particular oxandrolone drug product that is administered. Only evidence from such studies can ensure the bioequivalence of oxandrolone drug products.

Should an abbreviated new drug application (“ANDA”) approved version of oxandrolone be used, the considerable variability in bioavailability permitted by FDA’s usual criteria for bioequivalence could result in an oxandrolone drug product that has as much as a 20% difference in bioavailability of oxandrolone, with a corresponding difference in warfarin anti-coagulation effect. The difference between two ANDA versions of oxandrolone in their respective effect on warfarin dose could be even greater (as much as 50%). Thus, empirical evidence derived from a clinical trial for each oxandrolone drug product is necessary. Therapeutic equivalence AB rating can only be permitted for oxandrolone drug products where the dosing effect on warfarin is identical or nearly so for the two drug products, and where substitution would not alter the potential effectiveness of warfarin anti-coagulation therapy.

A. ACTION REQUESTED

The Drug Price Competition and Patent Term Restoration Act of 1994 (the “Hatch-Waxman Amendments”) created § 505(j) of the FFDCA, which provides a sponsor with the opportunity to receive FDA approval to market a new drug that is the same¹ as a previously approved drug without submitting substantial evidence of the drug product’s safety and effectiveness. Instead, the ANDA mechanism relies upon the FDA’s prior finding that the reference listed drug (“RLD”) is safe and effective and upon evidence to show that the ANDA is bioequivalent to the RLD. In addition to providing an approval mechanism, the statute also provides that ANDA drugs that are found to be bioequivalent, and that are the same in all other relevant respects (e.g., active ingredient, route of administration, strength, labeling, dosage form, etc.) are therapeutically equivalent and therefore generally substitutable under state law.

¹ Statutory requirements for determining whether a drug is the “same” as a previously approved drug are found in FFDCA § 505(j)(2)(A).

As we explain below, unique properties of oxandrolone create a situation in which the conventional methods for demonstration of bioequivalence do not provide sufficient assurance of safety to support approval of an ANDA for oxandrolone. The physiochemical properties of the active pharmaceutical ingredient ("API"), use of certain non-standard solid dosage manufacturing processes, and significant interactions of the drug with the often concurrently prescribed anti-coagulant drug, warfarin, mandate that all ANDA sponsors of oxandrolone drug products present evidence from additional studies to establish that their drug is the same as the reference listed oxandrolone drug product in all relevant respects, particularly with respect to *in vivo* bioequivalence, *in vitro* dissolution, and supportable labeling. These factors, and in particular the serious nature of potential drug interactions between oxandrolone and warfarin, compel FDA to create product specific guidance or regulations for determining bioequivalence of oxandrolone drug products.

Therefore, we respectfully request that FDA take steps to ensure the bioequivalence and thus the safety of any application for an oxandrolone drug products by preparing and 1) issuing guidance or regulations specifying how bioequivalence of oxandrolone drug products may be established, and 2) requiring applications for drug products containing oxandrolone to address the issues associated with the unique properties of the drug, especially the significant safety issue of oxandrolone-warfarin interaction. Specifically, such oxandrolone applications should:

- a) Include evidence from appropriately designed clinical studies to address the bioavailability issues associated with this drug product, including its use in conjunction with warfarin. Required studies must include drug-drug interactions studies with pharmacokinetic and pharmacodynamic ("PK/PD") endpoints based on the safety and effectiveness of warfarin.

- b) Include labeling identical to the approved labeling for the reference listed oxandrolone drug product in all aspects required under the FDCA and FDA regulations, and include the specific safety labeling regarding the interactions between oxandrolone and warfarin drug products. Because of the significant safety issues involved, evidence to support such labeling must come from appropriately designed clinical studies establishing the PK/PD of drug interactions between the proposed oxandrolone drug product and warfarin.
- c) Require that the results of such PK/PD studies produce results identical or nearly so to those in the reference listed oxandrolone labeling before approval of the any application for any other oxandrolone drug product. If an application is approved despite a lack of statutorily mandated conformity with the RLD's oxandrolone study and labeling, the ANDA oxandrolone cannot be approved, and cannot be deemed AB therapeutically equivalent with the reference listed oxandrolone drug product.
- d) Require that applications for oxandrolone drug products have additional Chemistry, Manufacturing and Controls as have been established for the RLD for this potentially problematic drug product, such as a well-controlled API particle size requirement and test procedure superior to that generally in place for an API in a solid dosage form, to assure acceptable product quality.
- e) Require that each oxandrolone submitted under an ANDA that contains more than one dosage strength of the drug demonstrate dose proportionality through pharmacokinetic studies in human subjects, or provide specific warfarin dose adjustment guidance for each dosage strength.

B. STATEMENT OF GROUNDS

I. Introduction

Oxandrin® is an oral tablet, which contains oxandrolone, USP as the API, indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiologic reasons fail to gain weight or to maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis. Oxandrolone, like other anabolic steroids, is also regulated as Schedule III controlled substances under the Controlled Substances Act, 21 U.S.C. §801 et seq. As such oxandrolone is strictly regulated by the Drug Enforcement Administration.

The product was developed by G.D. Searle (now Pfizer) in the 1960s and was first marketed by Savient in 1995. Since then, Savient has undertaken an intensive development effort to ensure complete compliance with current regulatory and quality requirements including establishment of a specification and methodology for particle size and dissolution in addition to development of a 10 mg. strength for patient compliance.

II. Unique Properties Associated with Oxandrolone containing Drug Products

a. Applications for oxandrolone drug products must include appropriately designed studies to address the safety question involving oxandrolone - warfarin interactions

Oxandrin® is used as a first line therapy for treatment of involuntary weight loss secondary to other disease and injury states. It is therefore regularly administered concomitantly with other medications. Approximately 40% of the Oxandrin® using population are patients in

long term healthcare facilities.² Most of this population consists of elderly patients, and a significant number of these patients are treated concomitantly with warfarin

Warfarin is a narrow therapeutic index³ drug indicated for prevention of thrombosis and thromboembolic events. The pharmacologic effect results from inhibition of clotting factors and coagulation. The therapeutic effect of warfarin is usually measured in terms of its "international normalized ratio" ("INR"), a standardized term used to represent an anti-coagulant effect. The INR range required for therapeutic effect is, in normal drug safety terms, very close to the level that poses a significant risk of hemorrhage. Thus, the drug is considered to be a NTI drug, and careful monitoring of patient coagulation times is required. Warfarin is also known to interact with a wide variety of other drugs, including (among a large number of others) 17- α testosterone derivative anabolic steroids, a class that includes oxandrolone.⁴ The NTI nature of warfarin makes potential drug interactions, already a serious concern, more of an issue. In recent years FDA has become more cognizant of the serious nature of potential warfarin interactions, and has imposed labeling requirements, including results from *in-vivo* interaction studies, and instructions to carefully monitor warfarin dose, for a number of approved drugs, e.g. Norvir, Celebrex,⁵ Xeloda,⁶ Cubicin.⁷ Scientific and legal consistency require such studies and labeling for each oxandrolone drug product.

² 4th quarter 2003 IMS data.

³ Also referred to as "narrow therapeutic range."

⁴ See attached Coumadin (warfarin sodium) labeling.

⁵ See attached Celebrex labeling (Celebrex (celecoxib) labeling was amended to include specific drug interaction information for interactions with warfarin despite a clinical trial finding that Celebrex treatment on the anti-coagulant effect of warfarin).

⁶ See attached Xeloda labeling (Xeloda (capecitabine) labeling was amended to include specific drug interaction information for warfarin as a result of reported deaths and serious injuries due to Xeloda-warfarin interactions, and clinical trial results that show a significant (91%) increase in warfarin effect in subjects taking Xeloda. This represents an approximate 50% reduction in warfarin dose compared to the 80-85% reduction in warfarin dose in patients treated with Oxandrin®).

⁷ See attached Cubicin label (daptomycin) labeling includes specific clinical study results for Cubicin-warfarin interactions despite a finding of no clinically significant effect on INR).

While the potential for interactions between anabolic steroids, such as oxandrolone, and warfarin may be known by physicians in general, the magnitude of the drug specific interactions is not. As a result of post-marketing surveillance, Savient proactively initiated a specially designed drug-drug interaction clinical study on the particular effect of Oxandrin® on warfarin activity. The results from this study indicated that precise titration of warfarin in subjects who are also on Oxandrin® is of utmost importance for safety. Concomitant administration of Oxandrin® with warfarin increased the anticoagulation effect of warfarin to a very significant degree, and the subjects in the clinical study obtained therapeutic levels of effect from warfarin with an 80-85% decrease in warfarin dose. The results were so crucial to safety that the labeling was revised to include the specific results from the study. FDA approved the revised labeling, and the Oxandrin® package inserts now contain the following precaution:

Concurrent dosing of oxandrolone and warfarin may result in unexpectedly large increases in the INR or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain desirable INR level and diminish the risk of potentially serious bleeding. (see PRECAUTIONS: Drug Interactions).

and:

Drug interactions ... Warfarin: A multidose study of oxandrolone, given as 5 or 10 mg BID in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng*hr/mL: similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dose if indicated are recommended when the oxandrolone dose is

changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.⁸

FDA is aware of the significant safety issues raised by warfarin - oxandrolone interactions, and it approved the labeling change to include the study specific drug interaction information in the PRECAUTIONS section of the package insert. Further, FDA requested that Savient issue a "Dear Healthcare Professional" letter to inform the healthcare community of the significance of the interaction and discuss the **specific data** from Savient's Oxandrin® study.⁹ This drug interaction issue is the single most serious potential safety issue with oxandrolone drug products.

1. The FDCA and FDA regulations require that ANDA oxandrolone drugs have labeling that is the same as Oxandrin®

Under the FDCA, an ANDA submitted under § 505(j) must contain labeling that is the same as that of the RLD, with certain specified minor exceptions (e.g. identity of the manufacturer). Therefore, each ANDA for oxandrolone must have labeling regarding interactions between that oxandrolone drug product and warfarin. Failure to include a precaution for the oxandrolone-warfarin drug interaction that includes the specific reduction in warfarin INR is a major safety and bioequivalence issue and renders that ANDA not approvable.¹⁰ For reasons discussed below, it is not sufficient for an ANDA to include the exact language and data provided in the Oxandrin® labeling, and each ANDA for oxandrolone must include data from a clinical study on the interactions of that particular oxandrolone drug product and warfarin.

⁸ See attached Oxandrin® label.

⁹ See attached "Dear Healthcare Professional" letter.

¹⁰ In a draft guidance, FDA has articulated its position that "labeling removed from an innovator drug product for reasons of safety or effectiveness cannot be referenced in an ANDA." Thus the old Oxandrin® label (the one without the specific warfarin interaction study results), withdrawn for safety reasons, cannot be referenced by ANDA applicants. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Draft Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications.

2. Patient safety requires drug interactions studies for each oxandrolone drug product

The data in the clinical study, and thus in the labeling precaution containing the results are specific to Oxandrin®. Such labeling does not apply to other oxandrolone drugs. The reduction of the warfarin dose of 80-85% in patients also taking Oxandrin® represents a very significant reduction in warfarin dose.¹¹ The dramatic increase in potency of warfarin in such patients represents a significant potential safety issue, and accurate, drug product specific, information is required to provide physicians the necessary tools for safe and effective patient care. Use of the data in the Oxandrin®-warfarin study to support labeling of an ANDA for an oxandrolone product represents a significant risk to patients.

FDA standards for bioequivalence provide that a proposed generic drug product demonstrate bioequivalence of between 80% and 125% (AUC¹² and C_{max}¹³ using 90% confidence interval) when compared to the RLD to be considered therapeutically equivalent, and substitutable under most state pharmacy laws. For most drug products this approach represents a reasonable compromise between availability of generic drugs and patient safety. However, the facts specific to the oxandrolone-warfarin interaction create a situation where such an approach has significant safety risks.

Warfarin is an NTI drug, and as such, FDA takes the special concerns regarding bioavailability into account when approving generic versions of the drug.¹⁴ With FDA's standard

¹¹ Other drugs with specific warfarin labeling show less significant increases in warfarin effect.

¹² AUC - area under concentration time curve.

¹³ C_{max} - maximum plasma concentration.

¹⁴ "This guidance recommends that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs." U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Draft Guidance for Industry: BA and BE Studies for Orally Administered Drug Products – General Considerations.

bioequivalence criteria, ANDA-approved oxandrolone products could potentially vary in bioavailability by as much as 25% from the RLD, and by over 50% from each other. A hypothetical ANDA oxandrolone with a bioavailability of 125% compared to the RLD will have a bioavailability that is more than 50% greater than a ANDA oxandrolone with a bioavailability of 80% compared to the RLD. This represents a serious potential safety risk for patients taking oxandrolone and warfarin. If such a patient switched from an oxandrolone drug product that was on the low end of the bioavailability limit to one on the upper end, the level of increased bioavailable oxandrolone would increase significantly (up to 50%), and, more importantly, there would be a corresponding potentially dangerous increase in the anticoagulation activity of the warfarin.

Alternatively, the switch could go from a high potency oxandrolone to one on the low end of the bioavailability range, and the patient could receive a subtherapeutic effect from the concomitant warfarin treatment. In essence, in situations where oxandrolone is used concurrently with warfarin, variations in the levels oxandrolone can cause potentially dangerous variations in the anti-coagulation effects of the warfarin, without any actual change in warfarin dose. Thus, changes in oxandrolone source requires careful titration of warfarin and subsequent patient monitoring as defined under 21 CFR § 320.33 thus rendering the bioequivalence issue of oxandrolone bioavailability problematic and requiring additional studies to assess the effects of concomitant use of warfarin with each individual drug product containing oxandrolone.

The potential serious safety risk is exacerbated by the fact that the patient and his physicians would be unlikely to be aware of the change in the manufacturer of the generic oxandrolone products. As discussed previously, a significant number of patients on oxandrolone and warfarin are in long term healthcare facilities. These facilities often change suppliers of

generic drugs. Unlike most switches from RLD to generic, such generic to generic changes may go unnoticed by the long-term patient and the physician. In addition, individual patients may purchase oxandrolone from a variety of different sources. In both instances, patients may face a significant health safety risk due to the relatively wide bioavailability range permitted for the generic oxandrolone, when combined with its effects on the narrow therapeutic range of the warfarin.

3. Without identical or nearly identical effect on warfarin induced INR levels, an ANDA for oxandrolone is not approvable

Clearly, there is a real potential for significant changes in warfarin anticoagulation effect when concomitant oxandrolone treatment is to be changed from one version of the drug to another. This scenario requires that FDA go beyond traditional bioequivalence requirements in the review of any application for oxandrolone. FDA should require studies to include PK/PD based on the effectiveness of warfarin, and these results must be related to the PK/PD results for oxandrolone. Should those studies not support a identical or nearly identical effect of oxandrolone on the warfarin INR, the application must be deemed not approvable due to lack of safety and bioequivalence. In the event that FDA does deem the drug approvable, despite the lack of a comparable effect on the warfarin INR, the drug should not be determined to be AB rated for drug substitution purposes.

This approach is mandated not only by principles of science, medical practice and protection of the public health, but is legally necessary. The supplement, which led to the labeling change regarding oxandrolone-warfarin interactivity, was reviewed as bioavailability data. It would be an abridgement of Savient's trade secrets and proprietary rights, and an abuse of due process, for FDA to permit ANDA applicants to rely upon Savient's data. Furthermore,

the FDCA requires that bioequivalence be demonstrated, and for oxandrolone drug products a key component of that bioequivalence showing is equivalent effect on warfarin INR levels.

b. Oxandrolone represents a drug with actual or potential bioequivalence problems

Under § 505(j)(2)(A)(iv), ANDA drugs must show bioequivalence to the RLD. For immediate release oral dosage forms, FDA generally accepts an adequately designed *in vivo* bioequivalence study; however, FDA has recognized that certain drug formulations present situations where bioavailability of the drug is problematic, and two pharmaceutical alternatives may not be bioequivalent. The provisions of 21 CFR §320.33 detail such situations, and in particular, 21 CFR § 320.33(e) specifies situations where the chemical and physical properties of a drug substance may pose bioequivalence problems. This section of the regulation lists six specific properties that may present difficulties, and oxandrolone drug products have five of those properties.

1. 21 CFR § 320.33(e)(1) "the active ingredient has a low solubility in water, e.g. less than 5 milligrams in 1 milliliter" (5mg/ml). Per United States Pharmacopoeia XXVII (2004), oxandrolone is "practically insoluble in water"(Page 2774) with an aqueous solubility given as 5200:1 parts water to oxandrolone (0.19mg/ml) (Page 2792).
2. 21 CFR § 320.33(e)(2) "the dissolution rate of one or more such products is slow, e.g., less than 50 percent in 30 minutes when tested using either a general method specified in an official compendium" During the dissolution method development process, dissolution was examined via a USP paddle dissolution apparatus. Oxandrolone tablets were tested at a paddle speed of 100 rpm (standard speed is 50 rpm) and various sampling times in water, simulated gastric fluid (SGF), and

simulated intestinal fluid (SIF). At 30 minutes, average percent dissolution for 12 tablets were 27% (water), 26% (SGF), and 23% (SIF). Clearly, dissolution rates of less than 50% in 30 minutes in these media have been demonstrated, indicating that the product dissolution is "problematic" when the standard methods are used.¹⁵

3. 21 CFR § 320.33(e)(3) "the particle size and /or surface area of the active drug ingredient is critical in determining its bioavailability." Early tablet batch production of Oxandrin® showed varying tablet content uniformity results over a wide range, as did early tablet dissolution results during methodology development. Analysis of API batches revealed particle size over a wide range of values. It was shown, through manufacture of tablet batches with API of known particle size, that content uniformity and dissolution were enhanced when the particle size was kept in a range not typical of solid oral dosage forms. Traditional methods, such as sieve analysis, were found to be inadequate for determination of particle size, and more sophisticated methods were employed. Other development efforts revealed that some standard tablet manufacturing processes, e.g., direct compression, fluid bed granulation, etc. have not been able to produce a tablet demonstrating acceptable *in-vivo* bioavailability and/or *in-vitro* dissolution.
4. 21 CFR § 320.33(e)(4) "certain physical structural characteristics of the active drug ingredient, e.g., polymorphic forms, conforms, solvates, complexes and crystal modifications, dissolve poorly and this poor dissolution may affect absorption." Morphology studies with oxandrolone have indicated that the molecule can occur as five different polymorphic forms. The effect of each of these five polymorphs on

¹⁵ June 2003 Development Report submitted to the NDA on July 24, 2003.

bioavailability/dissolution are unknown. It is therefore important to determine which polymorphs may or may not be present in a biobatch. Additionally, several batches from the validated API process need to be tested to demonstrate that the same morphology exists in commercial batches as were present in the batch that demonstrated bioequivalence.

5. 21 CFR § 320.33(e)(5) "such products have a high ratio of excipients to active ingredients, e.g., greater than 5 to 1." Oxandrin® is formulated with an API to excipient ratio of greater than 50 to 1, far in excess of the example given in FDA regulations for drugs that present bioequivalence problems.

For the above reasons, ANDA oxandrolone drug products present bioequivalence problems, and cannot be presumed to be substitutable AB therapeutically equivalent drugs.

- c. Each dosage strength of oxandrolone submitted under an ANDA must demonstrate dose proportionality through pharmacokinetic studies in human subjects*

Ordinarily dose proportionality of different dosage strengths for each sponsor of immediate release oral dosage forms is considered demonstrated on the basis of a showing of bioequivalence to one dosage strength of the RLD. Such tests are not sufficient for approval of different dosage strengths of oxandrolone. For reasons discussed above, oxandrolone represents a drug that presents bioequivalence problems; therefore dose proportionality among dosage strengths must be proven, not assumed. This increased potential for lack of dose proportionality across dosage strengths in a particular sponsor's oxandrolone raises additional safety concerns for oxandrolone drug products due to the warfarin interaction issue.

If two dosage strengths of an ANDA version of oxandrolone are not dose proportional, then there is the potential that each dose's effect on warfarin potency could be significantly different. For example, if the 2.5 mg strength of a hypothetical oxandrolone drug product has 85% of the bioavailability of the RLD, while the 10 mg strength of the same ANDA oxandrolone drug product has 115% of the bioavailability of the RLD, then the dose adjustment for concomitant warfarin will potentially vary significantly. As a result, patient safety requires that different dosage strengths of the same oxandrolone product be dose proportional, and that their effect on warfarin dose adjustment be identical, or nearly identical. Alternatively, if different dosages of the same ANDA oxandrolone are not dose proportional to each other, specific warfarin dose adjustment guidance for each dosage strength must be included in labeling, and this labeling must be supported by drug and dosage strength specific clinical data.

III. Conclusion

The primary purpose for this petition is patient safety. The key concern is the significant effect that oxandrolone has on warfarin dose (80-85% reduction in warfarin dose with Savient's Oxandrin®) combined with the particular safety issues with warfarin therapy, including the potential for death and serious injury should proper therapeutic levels of warfarin not be maintained. This concern led to the drug product specific labeling approved by FDA for Oxandrin®, and it demands that all other oxandrolone drug products also have specific warfarin interaction data listed in their labeling. Potential significant variability in bioequivalence of oxandrolone drug products raises serious questions about differing effects on warfarin dose reduction. Unless actions requested in this petition are taken, variability in bioequivalence could lead to variability in warfarin dose reductions of over 50% between different ANDA versions of oxandrolone.

The bioequivalence variability is exacerbated by oxandrolone's physico-chemical characteristics that cause it to be a bioequivalence problem drug under 21 CFR § 320.33(e). That regulation lists six characteristics of drugs with a potential to present bioequivalence problems. Oxandrolone has five of those six characteristics: low solubility, low dissolution rate, critical particle size, complex morphology, and a high excipient to API ratio. These characteristics will likely render oxandrolone drug products not bioequivalent, and therefore not AB therapeutically equivalent. This further illustrates the need for drug specific warfarin interaction data in each oxandrolone drug product labeling.

In addition to the variation between oxandrolone drug products, there is a potential for variable bioavailability between dose strengths of the same manufacturer's oxandrolone. Different dosage forms of the same oxandrolone product must demonstrate dose proportionality in human studies, and that their effect on warfarin dose adjustment is identical, or nearly identical. If this is not demonstrated, each dosage strength of the drug product must have specific warfarin dose adjustment guidance in its label.

For the above listed reasons, public safety and demands that the actions requested in this petition, summarized below, be taken.

- FDA issue guidance or regulations specifying how bioequivalence of oxandrolone drug products shall be established.
- All oxandrolone applications include warfarin interaction labeling identical to the RLD. Support for such labeling must come from appropriately designed clinical studies specific to that drug product.

- All oxandrolone applications include evidence from appropriately designed clinical studies to address the bioavailability issues associated with this drug product, including drug-drug interactions studies with pharmacokinetic and PK/PD endpoints based on the safety and effectiveness of warfarin.
- Require of warfarin interaction studies must produce results identical or nearly so to those in the RLD labeling before approval any other oxandrolone drug product. If an application is approved despite a lack of conformity, that drug product cannot be deemed AB therapeutically equivalent with the RLD.
- All oxandrolone applications must have additional Chemistry, Manufacturing and Controls as this potentially problematic drug product.
- All oxandrolone applications with more than one dose strength of the drug must demonstrate dose proportionality through pharmacokinetic studies.

D. Environmental Impact

In accordance with 21 C.F.R. § 25.31(c), an environmental impact analysis is not required.

E. Certification

The undersigned certified, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

signature Ernest L. Kelly

Ernest L. Kelly
Senior Vice President
Quality Assurance
Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, NJ 08816

Phone number: 703-565-4665

List of Attachments

1. Labeling - Prescribing information, Coumadin (warfarin sodium).
2. Labeling - Prescribing information, Celebrex (celecoxib).
3. Labeling - Prescribing information, Xeloda (capecitabine).
4. Labeling - Prescribing information, Cubicin (daptomycin).
5. Labeling - Prescribing information, Oxandrin® (oxandrolone)
6. October 28, 2003 "Dear Healthcare Professional" letter for Oxandrin®.