

MYLAN PHARMACEUTICALS INC

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September 8, 2004

VIA FEDERAL EXPRESS

Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

**RE: Comments of Mylan Pharmaceuticals Inc. on Docket No. 2004P-0365:
Abbreviated New Drug Applications for Agrylin® (anagrelide
hydrochloride) Capsules**

Dear Sir or Madam:

Mylan Pharmaceuticals Inc. ("Mylan") submits these comments in response to the above-referenced Citizen Petition filed by Arnall Golden Gregory LLP, on behalf of Shire US, Inc. ("Shire" or "Petitioner") on August 13, 2004 (the "Petition").

Mylan has an interest in the Petition, because Mylan has submitted an abbreviated new drug application ("ANDA") for Anagrelide Hydrochloride Capsules, and the Petitioner has requested the Food and Drug Administration ("FDA" or "Agency") to refrain from approving any ANDA for Anagrelide Hydrochloride Capsules that fails to: (i) include the monitoring of an active metabolite of Agrylin®, 3-hydroxy anagrelide, in bioequivalency testing to ensure that a similar exposure to the active metabolite is achieved; and (ii) include active metabolite monitoring under fed and fasting test conditions.

I. INTRODUCTION

Based on Shire's interpretation of FDA's General Guidance on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products ("Guidance"), Shire requests that generic Agrylin® applicants be required to monitor the 3-hydroxy anagrelide metabolite in order to provide assurance that there is not an unexpected exposure to this metabolite. Shire proposes that the monitoring of such metabolite should be a prerequisite for approval of generic anagrelide hydrochloride capsules.

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Mylan respectfully requests that the Agency deny the Petition for at least the following reasons. *First*, while the Guidance suggests monitoring the active metabolite if it is formed as a result of presystemic metabolism and contributes meaningfully to safety and/or efficacy, the Guidance only requires that the parent drug meet bioequivalence criteria, as a prerequisite for approval. *Second*, the studies upon which the Petitioner relies do not conclusively demonstrate that the 3-hydroxy anagrelide metabolite is formed presystemically. *Lastly*, if two formulations are essentially equivalent, rapidly dissolving, and the parent compound meets the established standards for demonstration of bioequivalence, it can be inferred that the active metabolite is also equivalent.

II. THE CITIZEN PETITION DOES NOT DEMONSTRATE ANY NECESSITY TO MODIFY THE LONGSTANDING REQUIREMENTS AND STANDARDS FOR DEMONSTRATING BIOEQUIVALENCE TO AGRYLIN®

A. Shire interprets FDA’s general guidance on bioavailability and bioequivalence as requiring the measurement of the 3-hydroxy anagrelide as a prerequisite for approval.

In March 2003, FDA revised its Final Guidance on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (“Final Guidance”). In that Final Guidance, FDA recommends measuring an active metabolite only if it is formed as a result of gut wall or other presystemic metabolism and contributes meaningfully to safety and/or efficacy. *See Final Guidance*, at Section VI, paragraph B. However, the Final Guidance clearly states that it is the parent drug which must be measured in bioequivalency studies and analyzed using a confidence interval approach and not the active metabolite. *Id.* Because the parent drug is more sensitive to changes in formulation performance than a metabolite, the data from the measurement of an active metabolite can be used as supportive evidence of equivalency. *Id.*

Shire interprets the Final Guidance to mandate the measurement of an active metabolite of Agrylin®, 3-hydroxy anagrelide, as a prerequisite for approval of generic anagrelide hydrochloride capsules. The Final Guidance, however, is clear that only the parent drug must be demonstrated to be bioequivalent. *Id.* Data from measurement of an active metabolite is limited to providing “supportive evidence of comparable therapeutic outcome”. *Id.* As a result, the bioequivalency requirement for the approval of generic anagrelide hydrochloride is based upon an evaluation of the parent compound and not the measurement of its active metabolite. Accordingly, applicants for generic anagrelide hydrochloride capsules, who have demonstrated the parent compound to be bioequivalent, should be eligible to receive final approval upon the expiration of Shire’s pediatric exclusivity.

B. Shire requests the Agency to withhold approval of ANDAs for anagrelide hydrochloride capsules based upon indirect evidence of first pass metabolism.

The Petitioner relies upon studies which suggest that Agrylin® may undergo first pass metabolism in the formation of its active metabolite. However, the following points should be taken into consideration:

First, Shire relies on the C14 data as proof of complete absorption, but as the study by Gaver et al. [4] indicates, unchanged anagrelide was never assessed in feces. Since only up to ~78% of radioactivity was accounted for in urine, it may be possible that up to 20% of the dose might have been unabsorbed and excreted in feces. In addition, evidence is said to have been provided that Agrylin® remains relatively unchanged in the presence of a human faecal preparation, which also supports the notion that a part of the oral dose could be eliminated intact without being absorbed, thus accounting for a large portion of the fraction of drug alleged to be subject to first-pass metabolism.

Second, Shire also relies upon a bioavailability study conducted in minipigs to suggest evidence of first pass metabolism. The study relied upon by the Petitioner indicates that two Agrylin® capsules (2 x 0.5mg) were administered to female minipigs with 20mL of water. It is unknown whether the species of minipig used absorbs and metabolizes anagrelide in a similar manner as humans. In addition, there is no 3-hydroxy anagrelide data presented for the minipig study. The mini-pig study simply provides an assessment of absolute bioavailability in mini-pigs. However, from the data summarized, one can not dismiss the possibility that orally-administered anagrelide could have been excreted unabsorbed in feces.

Third, Shire claims that the similarity of profiles of 3-hydroxy anagrelide and Agrylin®, in a study of 38 healthy volunteers, is supportive of a first pass effect. Such profiles could also be representative of drugs with no first pass effect, in which appearance of metabolite is formation-rate limited.

Fourth, Shire also claims that because the most likely site of presystemic metabolism of a drug is the liver by CYP1A2 enzymes, this indicates that the liver is solely responsible for the biotransformation of anagrelide. Since CYP1A2 enzymes are reported to be located in various extrahepatic tissues such as the lungs, esophagus, stomach, and colon [1-3], these additional sites of post systemic metabolism could contribute to the formation of 3-hydroxy anagrelide. These sites of metabolism are not generally associated with first-pass metabolism and thus, if not accounted for, could inflate the estimate of anagrelide's extent of first pass metabolism.

Fifth, Shire relies on theory and assumptions to estimate bioavailability limited by first pass. The equation provided by the Petitioner is based upon assumptions which cannot be verified.

Sixth, Shire concedes that the food-effect study does not provide a straightforward relationship. The food-effect study contradicts the currently approved labeling for Agrylin®, and thus, the results of the study do not conclusively support the notion of first pass metabolism.

Lastly, the summary basis of approval (“SBOA”) for Agrylin® includes a dose proportionality study, which suggests that the pharmacokinetics of anagrelide are linear over the dosage range of 0.5 to 2 mg. If a first pass effect were present, it would be potentially subject to saturation and consequently non-linear kinetics. However, the dose-proportionality data do not support this.

Without taking into consideration these factors, the Petitioner cannot definitively conclude that Agrylin® undergoes first pass metabolism in the formation of the 3-hydroxy anagrelide metabolite. Because the Final Guidance does not require the measurement of the active metabolite unless it is formed as a result of gut wall or other presystemic metabolism, generic applicants for anagrelide hydrochloride should not be required to provide additional data of equivalency.

C. Because the parent compound is shown to be bioequivalent, it can be inferred that the 3-hydroxy anagrelide is also equivalent.

If two formulations are essentially equivalent, rapidly dissolving, and the parent compound is shown to be bioequivalent, it can be inferred that the active metabolite is also equivalent. The Petitioner suggests that at physiologic pH (and presumably physiologic temperature) anagrelide has a solubility of 1.5ng/mL. This suggests that it would take ~667 liters of physiologic fluid to dissolve a single 1 mg tablet. However, as is shown in dissolution data in Shire’s SBOA¹, a 1 mg capsule will dissolve ~100% in 0.9 liters within 15 min at a physiologic pH associated with the human stomach. Thus, as complete dissolution appears to occur relatively fast in vivo, the impact of minor differences in formulations on absorption would essentially be abolished, as the drug formulation rapidly dissolves. Therefore, in the vast majority of patients, differences between test and reference formulations are analogous to absorption of a solution of anagrelide on two different occasions.

In addition, review of the limited data provided by Shire indicates that the rate of formation of 3-hydroxy anagrelide appears to proceed in parallel with the absorption of the parent drug. It should be noted, that influence of protein binding of 3-hydroxy metabolite is unclear, which may affect the presence of free metabolite and corresponding clearance. Overall, the disposition of 3-hydroxy anagrelide appears to mimic the parent drug. Further support comes from the data reported by Gaver et al. in 1981 [4], where it is shown that following an oral dose of C14-labelled anagrelide, total radioactivity (parent plus metabolites) and parent in plasma exhibit parallel disposition on log scale. Thus, the appearance of 3-hydroxy anagrelide in plasma appears to be limited by its formation and the concentration-time profile of this metabolite essentially mirrors the parent profile. This relationship is evident from the near identical profiles presented

¹ Roberts Pharmaceutical Corporation obtained NDA approval and was subsequently acquired by Shire.

for anagrelide and 3-hydroxy anagrelide in the examples provided in the Petition. Therefore, one may expect that since the 3-hydroxy anagrelide metabolite follows an identical pattern to the parent compound, any bioequivalence results for the parent compound would also correspondently have a similar result for the 3-hydroxy anagrelide metabolite.

III. CONCLUSION

For all of the foregoing reasons, the Petition should be denied immediately.

Respectfully submitted,



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Reference:

- 1) Ding X and Kaminsky LS. Human extrahepatic cytochromes P450: Function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. *Annu Rev Pharmacol Toxicol.* 43: 2003, 149-173.
- 2) Wei C, Caccavale RJ, Kehoe JJ, Thomas PE, Iba MM. CYP1A2 is expressed along with CYP1A1 in the human lung. *Cancer Let.* 171: 2001, 113-120.
- 3) Mercurio MG, Shiff SJ, Galbraith RA, Sassa S. Expression of cytochrome P450 mRNAs in the colon and the rectum in normal human subjects. *Biochem Biophys Res Comm.* 210(2): 1995, 350-355.
- 4) Gaver RC, Deeb G, Pittman KA and Smyth RD. Disposition of anagrelide, an inhibitor of platelet aggregation. *Clin Pharmacol Ther.* 29: 1981, 381-386.