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BY HAND DELIVERY

Dockets Management Branch
U.S. Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852

Re: Docket No. 02P-0170/supplement 1

The undersigned, on behalf of Amarin Pharmaceuticals Inc. ("Amarin"), submits these supplemental comments in support of Amarin's citizen petition of April 19, 2002 (Docket No. 02P-0170) (the "Petition") and in response to the June 10, 2002 submission of Teva Pharmaceuticals USA ("Teva") in opposition to the Petition. Following is a brief response to certain points raised in Teva's submission (the paragraph numbers correspond to those in the Teva submission).¹

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¹ As noted in the Amarin citizen petition, Amarin has not had access to the Permax NDA. Information contained therein may have bearing on the issues discussed here.

1. In Vitro Bioequivalence for All Dosage Strengths.

Teva attempts (p. 1) to dismiss the bioequivalence issues raised in the Petition by asserting that pergolide mesylate has linear kinetics, and that therefore “*if* the formulations of the three strengths are proportionally similar *and* exhibit similar dissolution behavior, in vivo bioequivalence studies for all strengths are not required by FDA guidance.” (emphasis added) As Teva acknowledges, it is only appropriate to allow such a waiver where (1) the drug has linear elimination kinetics over the therapeutic dose range; (2) the higher strength dosage form is proportional to the lower strength; and (3) comparable dissolution is demonstrated using appropriate testing criteria. Teva’s ANDA must meet each of these criteria.

First, although Teva states that it is “known” that pergolide mesylate has linear pharmacokinetics, it does not cite any reference for its assertion. In fact, the complex metabolic pathways and the need for extremely careful dose titration, as documented in the approved Permax labeling, suggest that pergolide mesylate may not have linear elimination pharmacokinetics.

Second, whether or not pergolide mesylate exhibits linear pharmacokinetics, Teva’s response does not establish that the three pergolide mesylate dosage strengths have dosage form proportionality. Teva simply states that if there is dosage form proportionality, a waiver may be granted.

Third, Teva states that if the different strengths have comparable dissolution, a waiver may be granted, but does not demonstrate that the three strengths actually have comparable dissolution. It is critical not only that comparable dissolution be demonstrated, but that appropriate criteria be employed to assess the comparability of the dissolution profiles. There is no compendial dissolution test for pergolide mesylate. FDA must therefore take independent steps to ensure that whatever dissolution test is used is appropriately precise, validated and acceptable in order for the waiver to be justified.

2. Bioequivalence for Pergolide Metabolites

Amarin agrees that there are no available data regarding whether the formation of pergolide mesylate metabolites occurs as a result of gut wall or presystemic action. Teva is incorrect, however, in stating that no potential safety issues have been raised regarding the metabolites. As addressed more fully in the Amarin citizen petition (pp. 9-10), two of the known metabolites of pergolide mesylate -- pergolide sulfoxide and pergolide sulfone -- have pharmacological activity as dopamine agonists in animal models and may therefore have activity in humans. Animal data further suggest that the sulfoxide may be more toxic than the parent drug. Thus, the presence of these metabolites may play an important role in the safety and effectiveness of a particular pergolide formulation. These points should be considered in evaluating whether there is a need for ANDA applicants to establish bioequivalence as to the pergolide metabolites.

3, 4, 5. Safety, Stability and Acceptance Criteria Issues

As indicated above, there is no compendial monograph for pergolide mesylate tablets. It is critical, as a matter of good science and the public health, that appropriate acceptance criteria be established not only to ensure that degradation of the parent drug does not result in an improper loss of potency, but also to ensure that degradation does not produce an unacceptable level of impurities such as pergolide sulfoxide. It is not necessarily sufficient that the degradation and or concentration of the active drug be within existing specifications for the reference listed drug. Any pergolide mesylate ANDA must also ensure that the specifications for any resultant impurity fall within appropriate limits for that product. This is important given the potential toxicity of the pergolide sulfoxide, especially if present above the NDA specifications.

6. Photostability

FDA policy requires photostability testing for new molecular entities and new drug products. FDA Guidance for Industry, Q1B Photostability Testing of New Drug Substances and Products (Nov. 1996). While it is our understanding that generally FDA does not require photostability testing in ANDAs, based on the known photostability issues associated with manufacture of pergolide mesylate formulations (see the Petition, p. 12), FDA should require photostability testing in any pergolide mesylate ANDA. Teva's proposed labeling (p. 3) (advising that the drug be dispensed in a "light-resistant container") may satisfy FDA's usual regulatory requirements. In this case, however, there is a further risk that patients will not always keep their medication in the packaging of the supplier or even of the pharmacy, and that in the absence of a photosensitivity stabilizer, pergolide mesylate tablets will be exposed to light and will degrade, thereby potentially affecting both safety and efficacy.

Conclusion

We appreciate your consideration of these additional points.

Respectfully submitted,

AMARIN PHARMACEUTICALS, INC.



Michael Wess, MD

Vice President, Scientific & Medical Affairs

cc: Gary J. Buehler, Director, Office of Generic Drugs