



NOV 26 2002

Michael Wess, M.D.  
Amarin Pharmaceuticals, Inc.  
Two Belvedere Place, Suite 330  
Mill Valley, CA 94941

Re: Docket No. 02P-0170/CP1 & SUP1

Dear Dr. Wess:

This responds to your citizen petition (Petition), dated April 19, 2002, and supplement dated July 8, 2002, requesting that the Food and Drug Administration (FDA) take certain action with respect to the abbreviated new drug applications (ANDAs) filed by Teva Pharmaceuticals (Teva) and Ivax Pharmaceuticals (Ivax) for the generic formulation of Permax (pergolide mesylate). Specifically, you request that the FDA not approve ANDAs for a generic formulation of pergolide mesylate without the following:

1. appropriate data to demonstrate in vivo bioequivalence to Permax for all dosage strengths, including lower dosage strengths with a high active ingredient to excipient ratio
2. appropriate acceptance criteria for key pergolide mesylate degradation products
3. demonstration of acceptable stability for all dosage strengths

In reaching a decision, the FDA has considered all of the information in your Petition and the supplement, the declaration of Nicholas M. Fleischer, R.Ph. Ph.D., dated May 3, 2002, the comments by Teva dated June 10, 2002, and other information available to the Agency. For the reasons set forth below, your Petition is denied in part and granted in part.

## I. BACKGROUND

We approved the original new drug application (NDA) for Permax tablets (0.05-milligram (mg), 0.25-mg, and 1-mg strengths) on December 30, 1988. Pergolide mesylate is an ergot derivative and acts as a dopamine receptor agonist at both the D1 and D2 receptor sites. Permax is indicated as adjunctive treatment to levodopa/carbidopa for symptomatic treatment of Parkinson's disease. Individualized dosing regimens are established by slow, careful titration.<sup>1</sup> Eli Lilly and Company (Lilly) holds the NDA for

<sup>1</sup> The recommended initialization regimen is a daily dosage of 0.05 mg for the first 2 days. The dosage should be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day every third day until an optimal therapeutic dosage is achieved (average daily doses of 3 mg/day in clinical trials). Permax is usually administered in divided

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Permax (NDA 19-385), and Amarin Pharmaceuticals, Inc. (the petitioner) has the exclusive right to market the product in the United States. You state that you do not have access to the information contained in the NDA and acknowledge that such information may be relevant to the issues raised in the Petition (Petition at 1).

## II. DISCUSSION OF ISSUES

### A. Bioequivalence

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the current ANDA approval process. An ANDA applicant does not have to submit evidence on the safety and effectiveness of the drug product because an ANDA relies on FDA's previous finding that the reference listed drug is safe and effective. Instead, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the reference listed drug as required by section 505(j)(2)(A)(iv) of the Act.<sup>2</sup> The scientific premise underlying the Hatch-Waxman Amendments is that, when other aspects of the drug products (e.g., active ingredient, strength, dosage form, labeling) are the same, bioequivalent drug products may be substituted for each other. A generic drug is bioequivalent to the listed drug if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses. . .<sup>3</sup>

#### 1. *Appropriate Assay and Dosage Strength*

You claim that bioequivalence for the generic formulation of pergolide mesylate must be established at all dosage strengths by use of an appropriate assay (Petition at 7). You express your concern that ANDA applicants will not be able to make the required bioequivalence showing because of the lack of an established assay for measuring pergolide bioavailability (Petition at 7).<sup>4</sup> In addition, you state that because the 0.05-mg dosage strength has a high excipient to drug ratio and due to the associated stability/degradation concerns, in vivo bioequivalence should be established for all dosage strengths (Petition at 7).

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doses three times per day. During dosage titration, the dosage of concurrent levodopa/carbidopa may be cautiously decreased.

<sup>2</sup> A generic drug that establishes bioequivalence as well as pharmaceutical equivalence is rated as therapeutically equivalent to the reference drug in FDA's *Approved Products with Therapeutic Equivalence Evaluations*, commonly referred to as the *Orange Book*.

<sup>3</sup> 21 U.S.C. 355(j)(8)(B)(i); see also 21 CFR 320.1(e) and 320.23(b).

<sup>4</sup> The Permax labeling states that pharmacokinetic information on the bioavailability of pergolide is unavailable because there is not a "sufficiently sensitive assay to detect the drug after the administration of a single dose."

We agree that the bioequivalence of pergolide mesylate tablets should be established using an appropriate assay. We expect that analytical methods used by ANDA applicants for the generic version of pergolide mesylate will be reliable, sensitive, and validated. With respect to bioequivalence testing for all dosage strengths, we require in vivo bioequivalence to be established for only one dosage strength of an immediate release (IR) tablet if the formulations between the test and reference tablets are proportionally similar and the other dosage strengths meet an appropriate in vitro dissolution test.<sup>5</sup> Bioequivalence is generally established by in vivo methodology between the highest strength of the generic and reference drugs.<sup>6</sup> The three strengths for Permax (0.05 mg, 0.25 mg, and 1 mg) were considered similar in composition in the NDA approval. Since these three strengths exhibited comparable and adequate dissolution, an in vivo bioavailability study comparing these three tablet strengths was not requested. (See FDA letter to Lilly, dated November 23, 1988.) All three strengths of Permax have a tablet weight of 300 mg and contain 0.05, 0.25, or 1 mg of pergolide. Therefore, not only the 0.05-mg strength but also the other two strengths have a high excipient to active ingredient ratio.

As a result, the FDA disagrees with your analysis that bioequivalence should be established between all dosage strengths of the generic and the reference pergolide mesylate tablets. Because Permax is proportionally similar for all dosage strengths according to the definition provided in the BA/BE guidance, we expect that ANDA products for pergolide mesylate would also be proportionally similar. Therefore, we deny your request to require in vivo bioequivalence testing for all dosage strengths of generic versions of pergolide mesylate.

## 2. *Establishing Bioequivalence for the Pergolide Metabolites*

You also ask the Agency to require a showing of bioequivalence for the two metabolites of pergolide (sulfoxide and sulfone), as well as for the parent compound (pergolide). You point out that our approval of the Permax NDA states that once an appropriate assay is available to measure pergolide, the assay should be used to determine the bioavailability of both pergolide and its metabolites (Petition at 9). The Clinical Pharmacology section of the approved labeling for Permax states that both pergolide sulfoxide and pergolide sulfone are dopamine antagonists in animals (Petition at 9). In

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<sup>5</sup> Guidance for Industry: *Bioavailability and Bioequivalence for Orally Administered Drug Products – General Considerations* (October 2000) (BA/BE guidance). A revision to the BA/BE guidance was published in draft in July 2002. See also 21 CFR 320.22(d)(2).

<sup>6</sup> Due to safety concerns, FDA accepted bioequivalence study protocols for pergolide mesylate tablets in which a single 0.1-mg dose given as two 0.05-mg tablets is administered to healthy subjects. However, in December 2000, the reference listed drug (RLD) was officially changed from the 1-mg tablet to the 0.05-mg tablet (See Orange Book, 20<sup>th</sup> edition, Supplement 12). The Agency recommended to sponsors of ANDAs that in vivo bioequivalence studies be conducted with a 0.1-mg dose given as two 0.05-mg tablets. In vivo BE studies were waived for the higher strengths, 0.25 mg and 1 mg, based on in vivo bioequivalence studies on the 0.05-mg tablets, as well as, comparative dissolution data and formulation proportionality. It should be noted that the Agency does not currently recommend that normal, healthy volunteers be used in bioequivalence studies for pergolide mesylate tablets. At the time recommendations were provided to potential ANDA sponsors, the enrollment of healthy subjects was suggested.

addition, animal toxicity studies in the Permax investigational new drug application (IND) and referenced in FDA's Pharmacology and Toxicology review of the Permax NDA indicated that the sulfoxide presented greater acute toxicity than the parent drug (Petition at 9). You claim that pergolide mesylate forms metabolites with the potential for clinically relevant activity and once a validated assay is available for pergolide, consideration can then be given to whether the metabolites form presystemically (Petition at 10).

Regarding the animal toxicity studies in the Permax IND, the doses used in the acute toxicology study in mice, where oral administration of the sulfoxide metabolite was shown to be slightly more acutely toxic than oral administration of pergolide, were 1,100 to 4,200 times higher on a kilogram (kg) basis than the highest human Permax dose used in the clinical efficacy trials (total dose of 5-mg/day = 0.07 mg/kg based on a 70-kg body weight). Consequently, it is not clear that this metabolite contributes meaningfully to the safety or efficacy of pergolide mesylate therapy.

As noted in the Permax labeling, at least ten metabolites have been detected, including N-despropylpergolide, pergolide sulfoxide, and pergolide sulfone. The other detected metabolites have not been identified, and it is not known whether any other metabolites are active pharmacologically. Based on the BA/BE guidance, we recommended measuring the parent compound and not the metabolites for ANDAs referencing pergolide sulfone. This is due to the fact that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which, in turn, is more reflective of metabolite formation, distribution, and elimination.

According to the BA/BE guidance, major pharmacologically active metabolites that are formed presystemically and contribute meaningfully to safety and/or efficacy should also be measured. With respect to pergolide, it is not known if the metabolites are formed presystemically and it is also unclear if they have any pharmacological activity in humans. From a pharmacokinetic perspective, it is sufficient to establish bioequivalence between generic and reference products of the immediate release pergolide mesylate formulations based on pergolide plasma concentrations alone. Therefore, the FDA denies your request to measure the pergolide metabolites.

## **B. Stability and Degradation**

### *1. Stability*

In the Petition, you explain that pergolide mesylate formulations can degrade upon exposure to light and air (Petition at 10). Additionally, oxidation is a concern for the 0.05-mg formulation because of the high excipient to drug ratio (Petition at 10). To maintain stability and prevent degradation, all Permax formulations are made with povidone and the 0.05-mg formulation is made with methionine (Petition at 10). To demonstrate your safety concerns, you provided studies indicating that when the 0.05-mg formulation is manufactured with and without the stabilizer methionine, there is only 0.71 percent pergolide sulfoxide in the methionine formulations compared to 6.9 percent

pergolide sulfoxide in the formulations without methionine (Petition at 10). Studies also show that the absence of povidone can lead to a loss of more than 20 percent pergolide content and a 500 percent increase in pergolide sulfoxide content (Petition at 10).

You emphasize that the stability and degradation issues are most prominent in the 0.05-mg strength because of its role in titration (Petition at 11). You suggest that because of these stability issues, the FDA or the generic firms might omit from the labeling either the dosage itself or the dosage and administration information for the 0.05-mg strength.

The ANDA applicants' paragraph IV notices state that the proposed generic formulations contain no stabilizers (Teva) or do not contain stabilizers equivalent to those in the Permax formulations (Ivax). Thus, you argue, if the generic formulations do not include effective stabilizers, then they will be susceptible to a loss of pergolide content upon exposure to air or light (Petition at 10). You maintain that this could alter the effectiveness of the formulations and affect the safety and effectiveness of dose titration. Furthermore, sulfoxide may be present in substantially larger quantities in the generic formulations than in Permax (Petition at 10). This increased concentration of an apparent dopamine agonist, at levels in excess of approved product specification, could be a potentially toxic agent and could cause the generic formulations to exhibit a different therapeutic profile from that of Permax (Petition at 11).

We recognize your concern about the stability of generic versions of pergolide mesylate. Drug product stability is always addressed during the review of any ANDA submission. The Agency requires information that describes the stability characteristics, including the formation and extent of degradation products, of any drug product submitted in an ANDA. ANDA sponsors are required to investigate degradants and/or impurities in the drug product. Stability data submitted by the ANDA applicants for generic versions of a reference listed drug are examined to ensure that the generic formulation is within specifications.

As with any ANDA submission, sponsors of ANDAs for pergolide mesylate must provide suitable information regarding the stability (including degradation of active ingredient) of their proposed products, including the 0.05-mg strength, to support approval of their applications. We agree that the labeling for ANDAs must be the same as the labeling approved for the reference listed drug. Only the limited variations permitted under § 314.94(a)(8)(iv) will be acceptable in an ANDA for pergolide mesylate.

## *2. Acceptance Criteria and Expiration Dating*

In the Petition, you request that we establish acceptance criteria for the sulfoxide in pergolide ANDAs (Petition at 11). You assert that such criteria will guard against the adverse clinical implications that could arise from degraded generic formulations with elevated levels of pergolide sulfoxide (Petition at 11). You state that FDA's approval of Permax required Lilly to develop appropriate analytical methods for establishing the content of pergolide mesylate and pergolide sulfoxide in Permax tablets. Accordingly,

you request that we impose the same requirements on the ANDA sponsors and set appropriate acceptance criteria for the sulfoxide content in the generic formulations.

We agree that levels of degradants must meet specifications and appropriate stability data that supports expiration dating must be submitted. We also note that stability data for the ANDA product may demonstrate that stabilizing agents are not necessary to prevent the degradation of the product. For any ANDA submission, FDA requires that stability data be submitted to support the proposed expiration dating periods for a product. Formulation specific information is reviewed and evaluated to determine acceptable specifications and expiration dating periods. Any ANDA, regardless of formulation of product, must include adequate proposed specifications and supporting data to qualify for approval.

### 3. *Photostability*

You point out that the proposed generic formulations of Permax, as described in the paragraph IV notices, differ from Permax in that they lack povidone or an equivalent stabilizer (Petition at 12). Additionally, studies indicate that pergolide formulations are unstable upon exposure to light (Petition at 12). On the basis of the information in the paragraph IV notices, you argue that approval of the ANDAs referencing Permax should require photostability data (Petition at 12). Moreover, data should be provided for all of the dosage strengths because of the differences in ingredients for the different dosage strengths (Petition at 12). In support of your request to require photostability data, you cite our draft guidance for industry *Stability Testing of Drug Substances and Drug Products* (June 1998) (Petition at 12).

According to our draft guidance on stability testing, photostability testing is primarily intended to determine photostability of a drug substance and to serve as a guide in subsequent testing for acceptable stability. In the absence of other data, extensive testing may be necessary. However, if a drug substance is known to be sensitive to light, a demonstration that the packaged product has satisfactory stability may be sufficient. As mentioned above, any ANDA must include stability information, including adequate proposed specifications and supporting data, to qualify for approval.

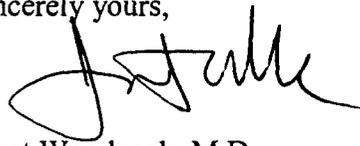
### III. CONCLUSION

For the reasons discussed above, your Petition is denied in part and granted in part. We deny your requests that the Agency require in vivo bioequivalence be established for all dosage strengths and for the two metabolites (pergolide sulfoxide and pergolide sulfone).

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We agree that bioequivalence of pergolide mesylate should be established using an appropriate assay. We will address stability and degradation issues as part of our review of the ANDAs.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'J. Woodcock', written in a cursive style.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research