



April 19, 2002

BY HAND DELIVERY

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

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CITIZEN PETITION

Amarin Pharmaceuticals Inc. ("Amarin") submits this petition under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 C.F.R. § 314.94(a), 21 C.F.R. part 320, and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs consider important bioequivalence, safety, degradation, and stability issues raised by abbreviated new drug applications ("ANDAs") that Teva Pharmaceuticals ("Teva") and Ivax Pharmaceuticals, formerly known as Zenith Goldline Pharmaceuticals ("Ivax") (collectively "ANDA applicants"), have submitted in reliance on Permax® (pergolide mesylate) as the reference listed drug.¹ As explained below, these ANDAs present special review issues due to the difficulty of measuring the systemic absorption of pergolide mesylate, and due to the degradation and instability of formulations of the drug. These issues must be addressed to ensure that any generic pergolide mesylate formulation will have the same clinical effects and safety as Permax, and will be stable.

Pergolide formulations present a number of review challenges. Pergolide is associated with various adverse reactions, as listed in the approved labeling. The labeling calls for sensitive dose titration, beginning at 0.05 mg and titrating up to an average daily dose of 3.0 mg, or a factor of 60x, in a matter of weeks. To date it does not appear that FDA has reviewed and accepted an assay that can

¹ Eli Lilly & Company ("Lilly") holds the new drug application ("NDA") for Permax (NDA 19-385), and Amarin has exclusive rights to market Permax in the United States. Amarin has not had access to the Lilly NDA. Information in the NDA may bear on the issues raised in this Citizen Petition.

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measure pergolide bioavailability, particularly at lower dosage strengths. At the same time, while the bulk drug itself is stable, once formulated into a pharmaceutical preparation, pergolide formulations can be quite unstable. In the absence of stabilizing ingredients or other measures, pergolide formulations can degrade immediately and significantly in the presence of both light and air. This is especially true for the 0.05 mg tablet, which is critical for proper dosing titration. One of the primary degradation products is also a metabolite, and has been shown to have pharmacologic activity and potential toxicity at levels in excess of current permitted product specifications under the Permax NDA.

Given the complex dosing profile required by current product labeling and the need for careful titration of the drug to avoid potential toxicity, it is extremely important to ensure that any generic formulation is supported by compelling bioequivalence data, and that the formulation does not degrade. Two critical stabilizers are used in the Permax formulations to prevent degradation, one in all strengths and another only in the important 0.05 mg strength. According to the paragraph IV notice made by Teva its proposed generic pergolide formulations do not contain any stabilizing agent. Ivax asserts in its Paragraph IV notice that its proposed generic formulations do not contain any stabilizers equivalent to those in Permax.² To the extent that the generic formulations may attempt to address the degradation issue through some other means, it is not clear that any other means would be effective. The absence of a validated assay to measure pergolide bioavailability also calls into question how bioequivalence can be established for the generic formulations, including in particular the 0.05 mg dosage strength. Review of the ANDAs must take these issues into account to ensure that any patient dispensed a generic pergolide formulation truly is receiving equivalent therapy to Permax.³

Action Requested

Amarin requests that FDA ensure that ANDAs relying on Permax as the reference listed drug not be approved in the absence of (1) submitting 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) establishing

² Any discussion of “equivalence” in this petition relates solely to issues concerning Ivax’s ability to meet FDA requirements of bioequivalence, stability, and degradation, and has no bearing on the question whether Ivax’s product infringes Lilly’s patents under the doctrine of equivalents or on any other issue.

³ We will be submitting subsequently an expert declaration from Nicholas M. Fleischer, R.Ph. Ph.D. in support of this Citizen Petition. Dr. Fleischer is the Director of Biopharmaceutics at THE WEINBERG GROUP, INC., and was formerly Director of the Division of Bioequivalence in the Office of Generic Drugs at the Center for Drug Evaluation and Research.

and meeting appropriate acceptance criteria for key pergolide mesylate degradation products, and (3) demonstrating acceptable stability for all dosage strengths.

Statement of Grounds

I. Background

A. General

Permax was originally approved by FDA in December 1988. The active ingredient in Permax is pergolide mesylate, an ergot derivative dopamine agonist. Permax is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease. It is believed that pergolide mesylate exerts its therapeutic effect by stimulating postsynaptic dopamine receptors in the nigrostriatal system and providing the dopamine response lacked by patients with Parkinson's disease. Permax is supplied in 0.05 mg, 0.25 mg, and 1 mg tablets.

Pergolide mesylate requires specific titration to produce efficacy and minimize adverse events. Dosage must be titrated gradually and with ongoing monitoring, beginning with administration of the 0.05 mg tablets. The approved labeling for Permax (copy attached as Exh. 1) instructs physicians to initiate therapy with a daily dosage of 0.05 mg for the first two days. Dosage should then be gradually increased by 0.1 or 0.15 mg/day every third day over the next 12 days of therapy. Dosage may then be increased by 0.25 mg/day every third day until optimal therapeutic dosage is achieved. In clinical studies, the mean therapeutic daily dose was 3 mg/day. Permax is usually administered in divided doses three times per day.

There is a risk of adverse reactions during dose titration and at maintenance therapy. In premarketing clinical trials of Permax (Exh. 1, p. 5), 27 per cent of study subjects withdrew from therapy due to an adverse event. The frequently observed adverse reactions identified in the labeling include, among others, hypotension, hallucinosis, and dyskinesia. Some adverse reactions may be dependent on dose and/or blood concentration. Warnings are provided in the Permax labeling for symptomatic hypotension (particularly during initial treatment), hallucinosis, serous inflammation and fibrosis, and fatalities (which occurred in clinical trials but could not be causally associated with pergolide mesylate).

B. Pharmacokinetics

Little is known about the absorption of pergolide mesylate. The approved labeling for Permax (Exh. 1) states that "information on oral systemic bioavailability of pergolide mesylate is unavailable because of the lack of a sufficiently sensitive assay to detect the drug after the administration of a single dose." The labeling states that it is suggested that "a significant fraction" is absorbed based on testing with radiolabeled pergolide, but no data are provided on the rate and extent of

absorption of the drug. There is also no information available on presystemic clearance, if any, or on postabsorption distribution.

When FDA approved Permax, it waived the requirement that bioavailability be established on the condition that work continue to develop and validate an appropriate assay to measure bioavailability. This is reflected in an approvable letter FDA issued for Permax (Exh. 2, p. 3). In 1992, Lilly published an article entitled "Sensitive, specific radioimmunoassay for quantifying pergolide in plasma." Clin. Chem. 1992 Oct.; 38 (10): 1975-80 (Exh. 3). A Canadian group has also apparently been working to develop an assay capable of measuring pergolide in human plasma. This development work was reported in the Proceedings of the 49th ASMS Conference on Mass Spectrometry and Allied Topics, Chicago, Illinois, May 27-31, 2001 (Exh. 4). Based on available information, it is not possible to determine whether these assays are properly validated, state of the art, and otherwise reliable and of appropriate quality and sensitivity. They do indicate, however, that it may be possible to develop an assay for measuring pergolide bioavailability. We are not aware of any such assay yet being accepted by FDA for use.

Heightened bioavailability and bioequivalence issues exist for the 0.05 mg dosage strength, which is critical to the proper dosage and administration of Permax. As explained above, Permax therapy must be initiated with a daily dosage of 0.05 mg, and then carefully increased until an optimal therapeutic dose is reached. Dose increases should begin with 0.1 or 0.15 mg/day every third day, and then may increase by 0.25 mg/day. Additionally, Permax is usually administered in divided dosage three times per day, and the 0.05 mg tablet may be essential for divided dosing. Due to the clinical importance of the 0.05 mg dosage strength, an appropriate assay for measuring pergolide content in plasma should be able to detect concentrations of the 0.05 mg dose. This is also important because of the issues that can be raised by the high excipient to active ingredient ratio in the 0.05 mg strength. FDA has recognized that drug products with a high ratio of excipients to active ingredients may raise special bioavailability or bioequivalence issues. 21 C.F.R. § 320.33(e)(5).

Notwithstanding the absence of data on the bioavailability of pergolide mesylate, it is known that pergolide mesylate is extensively metabolized. According to the approved labeling for Permax, at least ten metabolites have been detected, including N-despropylpergolide, pergolide sulfoxide, and pergolide sulfone. FDA's Pharmacology and Toxicology Review of the Permax NDA (Exh. 5, p. 90) explains that the parent drug is oxidized to the sulfoxide by a microsomal enzyme and the sulfoxide is reduced back to pergolide by a reductase in the 100,000 x g supernatant fraction.

Certain of the metabolites exhibit apparent pharmacologic activity. Some of these metabolites are also produced by degradation of pergolide mesylate formulations, as discussed further in the next section. Pergolide sulfoxide and pergolide sulfone are dopamine agonists in animals. Toxicity studies on mice submitted to the Permax IND indicated that the sulfoxide is somewhat more acutely toxic than the parent

drug, and was responsible for clonic convulsions seen in mice. In addition, the median lethal dose in mice for the sulfoxide was lower than for pergolide mesylate (211 mg/kg versus 301 mg/kg). These toxicity studies are referenced in FDA's Pharmacology and Toxicology Review of the Permax NDA (Exh. 5, at pp. 30, 32). The presence of unacceptable levels of these metabolites beyond those permitted in current NDA specifications, including in particular the sulfoxide, could raise potential toxicity concerns.

C. Degradation and Stability

Pergolide mesylate formulations present a number of degradation and stability issues. Pergolide formulations decompose to a sulfoxide species upon exposure to light, which can result in a measurable reduction in potency and raise issues due to the apparent pharmacologic activity of the sulfoxide. As noted above, pergolide sulfoxide is a metabolite of pergolide, but it is also a key degradation product. As part of its approval of Permax, FDA required that Lilly develop appropriate analytical methods to determine the content of pergolide mesylate and pergolide sulfoxide in Permax tablets. This is reflected in FDA's approvable letter for the Permax NDA (Exh. 2, pp. 1, 2).

The addition of polyvinylpyrrolidone (also known as "povidone" or "PVP") has been shown to significantly retard the degradation and decrease in potency of pergolide formulations. This has been shown by studies comparing pergolide content following light exposure of compositions with and without povidone. In one study, the composition without povidone lost nearly 40 percent of its pergolide content, compared to a less than 10 percent reduction for the composition containing the stabilizing benefits of povidone. *See* U.S. patent no. 4,797,405, ex. 1 ("405 patent") (Exh. 6), issued to Lilly, the innovator and NDA holder. In a similar study, the composition without povidone resulted in a loss of more than 20 percent pergolide content, compared to an approximate 6 percent loss of pergolide for the composition containing povidone. *See id.* example 2.

A related study (*id.*) compared levels of the degradant, pergolide sulfoxide, following exposure to light in pergolide compositions with and without povidone, and demonstrated that the povidone composition contained almost no pergolide sulfoxide, compared to a more than 500-percent increase in pergolide sulfoxide content for the composition without povidone. As a result, each dosage strength of Permax contains povidone, which maintains the stability of the active ingredient and helps inhibit formation of the degradation product pergolide sulfoxide.

Pergolide mesylate formulations also degrade to the sulfoxide species during the manufacturing process as a result of oxidation, particularly for tablets with a large excipient to drug ratio such as the 0.05 mg titration dose tablet, which contains approximately 50 mcg of pergolide in a tablet of about 300 mg total weight. Lilly discovered that the addition of methionine significantly reduced the degradation for the

0.05 mg tablets. *See* U.S. patent no. 5,114,948 (“’948 patent”)(Exh. 7). A study comparing pergolide sulfoxide content in tablets prepared with and without methionine showed that tablets manufactured without methionine contain approximately 10 times more sulfoxide than in tablets made with methionine, thus demonstrating the significant stabilizing benefits of methionine. These data are described in the ’948 patent. *See id.*, table 1).⁴

The 0.05 mg dose is critical to the proper dosage and administration of Permax, as explained above. Titration of Permax occurs over a period of weeks to an optimal therapeutic dose which is individualized for each patient. Permax therapy should be initiated with a daily dosage of 0.05 mg, and then carefully increased, beginning with increases of only 0.1 or 0.15 mg/day every third day, and then moving to increases of 0.25 mg/day.

D. Pergolide Mesylate ANDAs

Teva and Ivax have each filed ANDAs for the approval of generic pergolide mesylate products in 0.05 mg, 0.25 mg, and 1 mg strengths. Each ANDA applicant submitted a paragraph IV certification to patents listed for Permax in the Orange Book. In their paragraph IV notices, each ANDA filer states that its product does not contain either of the photosensitivity stabilizer, povidone, or the antioxidant methionine. The Teva paragraph IV notice (Exh. 9) states that its formulation does not contain any excipient which performs the function of a stabilizing agent. The Ivax paragraph IV notice (Exh. 10) states that its tablets do not include any stabilizing agent such as those in Permax. Serious questions are thus raised as to the stability of these proposed formulations, and the levels of the sulfoxide degradation product present in the products. It is also not clear what bioequivalence data each ANDA filer might have submitted for either the parent compound or its key metabolites, given the lack of an assay accepted by FDA that is sufficiently sensitive to measure in vivo bioavailability.

On February 14, 2002, an international patent application from Teva was published under the Patent Cooperation Treaty, WO 02/11727 A1, by which Teva seeks to patent (no patent has issued) a process “whereby substantially stable pergolide mesylate can be manufactured without having to introduce stabilizing additives.” A copy is attached as Exhibit 11. This patent application recognizes and validates that stability and degradation issues are raised by pergolide mesylate formulations and merit consideration. Nothing in the patent application addresses bioavailability or bioequivalence issues.

⁴ These degradation and stability issues are further highlighted in a chapter on pergolide mesylate in *Analytical Profiles of Drug Substances and Excipients*, Vol. 21 (Brittain, Harry G., ed. 1992) (Exh. 8). As explained in the chapter (p. 409), pergolide mesylate is stable as a dry bulk drug substance, but is unstable in water when exposed to light and heat, yielding the sulfoxide and sulfone degradant products.

II. Discussion

A. Bioequivalence Issues

1. **The ANDAs Must Establish In Vivo Bioequivalence to Permax at All Dosage Strengths Based on an Appropriate Assay for Measuring Pergolide Absorption.**

ANDAs relying on Permax as the reference listed drug must include data to show that the proposed generic formulations are bioequivalent to Permax. FDCA § 505(j)(2)(A)(iv); 21 C.F.R. §§ 314.94(a)(7). Bioequivalence is established when there is no significant difference in the rate and extent of absorption of the active ingredient of the generic and reference listed drugs. FDCA § 505(j)(8)(B); 21 C.F.R. § 320.1(e). Under agency policy, no significant difference exists between the bioavailability of a generic and reference listed drug when the rate and extent of absorption of the generic fall within a range of 80 to 125 per cent of the innovator. FDA Guidance for Industry, Statistical Approaches to Establishing Bioequivalence, at 2 (Jan. 2001).

It is unclear how the pergolide ANDA applicants will make the required bioequivalence showing because of the lack of an established assay for measuring pergolide bioavailability. This showing is fundamental, and without it there is no basis for concluding that the ANDAs will be safe and effective. Moreover, in vivo bioequivalence should be established for all dosage strengths. Special issues may be raised by the 0.05 mg dosage strength in light of its high excipient to drug ratio and the associated stability/degradation concerns. This potential is also reflected in FDA's bioequivalence regulations. 21 C.F.R. § 320.33(e)(5). Clinical evidence of in vivo bioequivalence is thus needed for the 0.05 mg strength, and should not merely be extrapolated from data on higher dosage strengths. Assurances of the proper performance of the different Permax dosage strengths is provided by the use of the different dosage strengths in clinical trials and subsequent marketing history. No similar assurance will exist for the different generic pergolide formulations absent the submission of in vivo bioequivalence data for all strengths.⁵

The approved 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." Teva so

⁵ Special concerns may also be raised by bioequivalence testing on the other dosage strengths. For example, given the careful dosage titration that must be followed for pergolide mesylate, it is not clear exactly how bioequivalence testing would be performed in healthy patients on the 1.0 mg dosage strength consistent with prevailing ethical and safety considerations. These ethical considerations are recognized in the literature. *See* Exh. 3 at 1979 ("Single-dose pharmacokinetic studies involving the therapeutic doses of pergolide are not feasible in normal healthy adult volunteers . . .").

acknowledges in its patent application. *See* Exh. 11 at 2 (“information on oral systemic bioavailability of pergolide mesylate is unavailable because of the lack of a sufficiently sensitive assay to detect the drug after the administration of a single dose”). According to the labeling for Permax, the only absorption data available are based on administration of ¹⁴C radiolabeled pergolide mesylate and subsequent recovery of some but not all of the administered radioactivity, “suggesting that a significant fraction of drug is absorbed.” No other information on the rate or extent of absorption is provided. Additionally, the Permax labeling cautions that no conclusions as to the extent of presystemic clearance, if any, can be made based upon the radiolabeled Permax studies. Thus, even if similar studies conducted with the proposed generic formulations result in the same percentages of the administered radioactive pergolide being recovered from urine and expired carbon dioxide, there would be no basis to conclude that the same or similar amount of pergolide was absorbed. That is to say, because there is no means to know how much of the pergolide is cleared presystemically and how much is actually absorbed, the fact that the same amount of administered radioactivity might be recovered from a generic formulation and Permax would in no way indicate that the same amount of pergolide was absorbed in both (particularly in the absence of one or both of the stabilizing ingredients).

Under FDCA § 505(j)(2)(A)(iv), an ANDA must contain information to establish bioequivalence in order to be approved. Therefore, if the ANDA applicants are unable to show that there are no significant differences in the rate and extent of absorption of their formulations compared to Permax, because of the lack of a suitable assay to make such a showing, they should not be approved.

An analogous issue arose in connection with ANDAs for Premarin (naturally occurring conjugated estrogens). There, FDA refused to approve two synthetic versions of Premarin because the ANDA applicants were unable to demonstrate that their products contained the same estrogenic components, and thus the same active ingredients, as Premarin. 62 Fed. Reg. 42562 (1997). The agency explained that the ANDAs could not be approved until the active ingredients of the reference listed drug “have been sufficiently well defined to permit an ANDA applicant to show that” its proposed formulation contained the same active ingredients. *Id.* at 42562. While the Premarin example related to the sameness requirements of section 505(j)(2)(A)(ii)(II), the same logic applies to the bioequivalence requirement. Just as an ANDA applicant cannot establish sameness where the active ingredients have not been adequately identified, an ANDA applicant may not be able to establish bioequivalence where the bioavailability of the active ingredient cannot be adequately measured.

FDA itself recognized the importance of being able to measure bioavailability when it approved the Permax NDA. As reflected in the approvable letter from 1988 (Exh. 2, p. 3), the agency required that Lilly work on the development of an appropriate assay as a condition of approval. If and when an appropriate assay is available, the ANDA applicants should be required to submit bioequivalence data using

that assay. Until that crucial and legally required bioequivalence showing can be made, though, ANDAs should not be approved.

The need to establish bioequivalence is particularly acute here due to the need for careful titration of pergolide. As discussed above, adverse events may be seen within the therapeutic dosing range, and particular care must be taken to titrate an individual's dose in a gradual, stepwise fashion. If generic pergolide formulations are approved and substituted for Permax, and the bioequivalence of the generic formulations are not firmly established within appropriately tight parameters, significant safety or other clinical issues could result. (In the absence of stabilizing ingredients, it is not clear that even the established NDA specifications would be adequate.) Too little drug from the generic formulation might be absorbed to produce a clinical effect, or too much drug might be absorbed and cause one of the numerous adverse events described in the Permax labeling. In either circumstance, patient health could be compromised.

2. Once an Assay is Available, Consideration Should be Given to the Need for Establishing Bioequivalence as to Pergolide Metabolites.

When FDA approved the Permax NDA, it stated (Exh. 2, p. 4) 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*. This requirement is well-founded in light of the apparent pharmacologic activity of the pergolide metabolites.

As noted above, at least two of the metabolites into which pergolide decomposes -- pergolide sulfoxide and pergolide sulfone -- have apparent pharmacologic activity. The Clinical Pharmacology section of the approved labeling for Permax (Exh. 1) states that both “[p]ergolide sulfoxide and pergolide sulfone are dopamine agonists in animals.” In addition, as noted above, animal toxicity studies in the Permax IND (Exh. 5, at pp. 30, 32) indicated that the sulfoxide presented greater acute toxicity than the parent drug, as seen in clonic convulsions in mice and in a lower median lethal dose in mice. The metabolites pergolide sulfoxide and pergolide sulfone thus have apparent pharmacologic activity -- both with respect to dopamine agonist activity and, in the case of the sulfoxide, with respect to toxicity -- and may play an important role in the safety and effectiveness of a particular pergolide formulation.

These issues should be considered for the generic pergolide applicants, consistent with the agency's statement in connection with its approval of Permax that the bioavailability of both pergolide and its metabolites must be established once a specific assay is available. The principles outlined in FDA's Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Oct. 2000) may also come to bear. The guidance provides (p. 19) that measurement of a metabolite is required for a showing of bioequivalence where the metabolite is formed “as a result of gut wall or other presystemic

metabolism” and that “metabolite contributes meaningfully to safety and/or effectiveness.” We know here that pergolide mesylate forms metabolites with the potential for clinically relevant activity. Once a validated assay is available for pergolide, consideration can then be given to whether the metabolites form presystemically.

B. Safety, Stability and Degradation Issues

1. The Statements of the ANDA Applicants that the Proposed Generic Formulations do not Contain Equivalent Stabilizers to Permax Raise Serious Questions About the Stability and thus the Safety of the Generic Formulations.

As explained above, pergolide mesylate formulations can degrade upon exposure to light and upon exposure to air. Oxidation is a particular concern for the 0.05 mg formulation, because of the high excipient to drug ratio. All Permax formulations are thus made with povidone, and the 0.05 mg formulation is made with methionine to maintain stability and prevent degradation. Studies indicate (Exh. 7, table 1) that when the 0.05 mg formulation is manufactured with and without the stabilizer methionine, there is only 0.71 per cent pergolide sulfoxide in the methionine formulations compared to 6.9 per cent pergolide sulfoxide in the formulations without methionine, almost a ten-fold increase. Similarly, studies show (Exh. 6, examples 1 and 2) that the absence of povidone can lead to a loss of more than twenty percent of pergolide content, and a 500-percent increase in pergolide sulfoxide content.

There can be clinical implications if a formulation is not stable and if it forms significant degradation products. The decrease in pergolide content from the lack of stability could compromise the clinical effectiveness of the drug and adversely skew the careful titration that needs to be performed to administer the drug effectively under the approved labeling. If greater levels of the sulfoxide are formed, clinical effects might be caused due to the sulfoxide’s apparent dopamine agonist activity. The presence of higher sulfoxide levels than in approved Permax specifications, at a minimum, could also create safety issues such as those identified in the approved Permax labeling, based on the increased toxicity the sulfoxide presented in mice compared to pergolide mesylate.

These issues are squarely raised by the pergolide ANDAs. The paragraph IV notices that the ANDA applicants made state either that the proposed generic formulations contain no stabilizers (Teva) or do not contain stabilizers equivalent to those in the Permax formulations (Ivax). If the generic formulations do not include effective stabilizers, then the generic formulations may be susceptible to a loss of pergolide content upon exposure to air or light. This could alter the effectiveness of the formulations and affect the safety and effectiveness of dose titration, as discussed above. Similarly, the sulfoxide may be present in substantially larger quantities in the generic formulations than in Permax. This increase in

concentration of an apparent dopamine agonist, which at levels in excess of approved product specifications could be a potentially toxic agent, could cause the generic formulations to exhibit a different therapeutic profile than Permax.

These stability and degradation issues are most pronounced in the 0.05 mg titration strength, which presents particular stability concerns. The 0.05 mg strength and the related dosage and administration information based on the 0.05 mg strength are essential to the current Permax labeling. The labeling for the ANDAs must be the same as the labeling approved for the reference listed drug. FDCA § 505(j)(2)(v); 21 C.F.R. § 314.94(a)(8). Omission of the dosage and administration information related to the 0.05 mg strength from the generic labeling would raise significant legal questions, as well as fundamental safety and efficacy issues. Although certain limited variations between ANDA and NDA labeling are permitted, the omission of key dosage and administration information would not fall within any of the enumerated exceptions. 21 C.F.R. § 314.94(a)(8)(iv) (allowing differences based on a suitability petition, a difference in manufacturer, a difference to address an FDA guidance, and omissions of indications or uses protected by patent or other exclusivity protections). At the same time, it is not clear how the ANDAs could keep the labeling related to use of the 0.05 mg strength without being able to supply the dosage unit called for in their own labeling.

2. The ANDAs Should Establish Acceptance Criteria for Pergolide Sulfoxide.

In order to guard against the adverse clinical implications that could arise from degraded generic formulations with elevated levels of pergolide sulfoxide, the pergolide ANDAs should establish appropriate acceptance criteria for the sulfoxide. When FDA approved Permax, the agency required (Exh. 2, pp. 1, 2) that Lilly develop appropriate analytical methods for establishing the content of pergolide mesylate and pergolide sulfoxide in Permax tablets. The same requirements should be imposed on the ANDA applicants, and appropriate acceptance criteria set for the sulfoxide content in the generic formulations. It is not clear that in the absence of stabilizing ingredients, even the levels contained in the Permax NDA would be adequate.

This requirement would be consistent with FDA's Draft Guidance for Industry, ANDAs: Impurities in Drug Products (Dec. 1998). The guidance states (p. 6) that "[a]ll ANDAs should include proposed acceptance criteria for degradation products expected to occur under recommended storage conditions." Here, the Paragraph IV statements of the ANDA applicants that the generic formulations lack equivalent stabilizers compared to the Permax formulations (Ivax) or contain no stabilizing agents at all (Teva) suggest that the sulfoxide degradation product may be present in substantially higher levels in the generic products under normal storage conditions. Appropriate acceptance criteria should thus be established for the generic formulations and those specifications should be met during manufacturing.

3. The ANDAs Must Contain Stability Data to Support Expiration Dating.

Whether or not acceptance criteria are set for the sulfoxide, the ANDAs must establish stability for purposes of expiration dating. FDA regulations require that a generic applicant provide stability data in the ANDA to support expiration dating. 21 C.F.R. §§ 314.94(a)(9) & 314.50(d)(1). FDA's Draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products at 62-63 (June 1998), provides additional details on this requirement. As discussed, pergolide mesylate formulations can degrade in the presence of air. This potential for degradation due to oxidization is particularly acute for the 0.05 mg tablet. Yet the paragraph IV notices for both the Teva and Ivax ANDAs state that neither of the proposed generic formulations -- including the 0.05 mg formulations -- contains an antioxidizing agent such as methionine.

Methionine is critical to the stability and integrity of pergolide mesylate in the 0.05 mg strength. The absence of methionine or an equivalent agent in the proposed generic products to address the known oxidization of pergolide would raise a serious question as to whether the products are sufficiently stable to support whatever expiration dating is proposed for the ANDAs.

4. The ANDAs Should Establish Photostability.

FDA requires that photostability issues be considered in connection with applications for already approved molecular entities where the new applications are for a different formulation than the previously approved products and prior studies indicate that a stability issue may exist following exposure to light. FDA Draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products at 62-63 (June 1998). This policy applies here. According to the paragraph IV notices made by the ANDA applicants, the proposed generic formulations differ from Permax in that they lack povidone or an equivalent stabilizer (Ivax) (or any other photostabilizer in the case of Teva), and the data are clear that pergolide formulations are unstable upon exposure to light. Approval of the proposed generic products should thus require data on the photostability of the proposed generic formulations. Moreover, data should be provided for all of the dosage strengths because of the differences in ingredients for the different dosage strengths.

Conclusion

Amarin respectfully submits that FDA in reviewing and approving the Teva and Ivax ANDAs should require that the ANDAs (1) establish in vivo bioequivalence to pergolide and potentially its metabolites based upon an appropriate assay for all dosage strengths, (2) establish and meet acceptance criteria to account for pergolide sulfoxide content, and (3) submit stability and photostability data to demonstrate appropriate stability in accordance with the proposed expiration dating and storage and handling instructions.

Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31.

Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

Certification

The undersigned certifies 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.

Respectfully submitted,

AMARIN PHARMACEUTICALS, INC.



Michael Wess, M.D.
Vice President, Scientific & Medical
Affairs

Attachments

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