

Wyeth

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April 8, 2004

VIA HAND DELIVERY

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

Re: Comments to Lachman Consultant Services, Inc.'s Pediatric Waiver Request, Docket Number 03P-0159 (AMD1)

Ladies and Gentlemen:

Wyeth Pharmaceuticals ("Wyeth") is the manufacturer of Effexor[®] XR (venlafaxine HCl) Extended Release Capsules ("Effexor XR"). Wyeth submits these comments in response to the above-referenced Request for Pediatric Waiver (the "Waiver Request"). Lachman Consultant Services, Inc. ("Lachman") submitted the Waiver Request on January 29, 2004 as an Amendment to its Suitability Petition of April 14, 2003 (the "Suitability Petition"). The Suitability Petition seeks FDA's approval to submit an ANDA for extended release tablets in reliance on Effexor XR capsules as the reference listed drug. Wyeth previously submitted comments to the Suitability Petition on August 28, 2003.

The Federal Food, Drug, and Cosmetic Act ("FDCA") as modified by the newly enacted Pediatric Research Equity Act of 2003 (the "PREA") makes clear that suitability petitions requesting a change of dosage form fall under the PREA's requirements for pediatric assessments. Lachman's Waiver Request as submitted does not present sufficient evidence to qualify for a waiver from pediatric assessments under these statutory requirements.

I. The Suitability Petition is Subject to the Requirements of the Pediatric Research Act of 2003.

The PREA created a new section 505B(a)(1) of the FDCA requiring that:

A person that submits an application (or supplement to an application) (A) under section 505 for a new active ingredient, a new indication, new dosage form, new dosing regimen, or new

03P-0159

C2

route of administration . . . shall submit with the application the assessments described in paragraph (2).¹

Paragraph (2) of section 505B(a) requires assessments containing data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate to (i) assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and (ii) support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.²

Lachman's Suitability Petition seeks permission to submit an ANDA for a new dosage form of venlafaxine (extended release tablets). Under the plain terms of section 505(B)(a)(1), the application is required to contain pediatric assessments. The statutory language squarely covers, among other things, any new application submitted under section 505 for a new dosage form. An ANDA is an application submitted under section 505 of the FDCA (specifically section 505(j)), and the Suitability Petition has been submitted for the precise purpose of seeking approval of a new dosage form. The only basis, therefore, for Lachman to avoid these requirements is to meet the statutory criteria for waivers.

If Lachman cannot meet the waiver provisions of the PREA, the suitability petition cannot be approved. In order to comply with the pediatric assessment requirements of the FDCA, most applicants must submit clinical data concerning the safety and effectiveness of the proposed new drug or new formulation in pediatric patients. However, in the case of a suitability petition, this precludes FDA approval. Pursuant to section 505(j)(2)(C) of the FDCA, FDA must deny a suitability petition if it finds that "investigations must be conducted to show the safety and effectiveness of the drug or . . . the dosage form . . . which differ[s] from the reference listed drug." Indeed, under the previous "Pediatric Rule," FDA typically denied suitability petitions requesting changes in dosage form on the ground that investigations were necessary to demonstrate the safety and effectiveness of the new dosage form in pediatric patients."³ As a result, FDA must deny the Suitability Petition unless it qualifies for a waiver from the assessment requirements of the PREA.

¹ 21 U.S.C. § 355c(a)(1).

² 21 U.S.C. § 355c(a)(2).

³ See, e.g., Letter from FDA to Lachman Consulting Services, Inc. (July 9, 2002) (stating that the change in dosage form requested by a Lachman suitability petition is subject to the Pediatric Rule and denying the suitability petition on the ground that investigations are necessary to determine the safety and effectiveness of the new dosage form in pediatric populations).

II. Lachman Has Not Presented Sufficient Evidence to Qualify for a Waiver From the Assessment Requirements of the PREA.

The FDCA, as modified by the PREA, provides for a waiver of the pediatric assessment requirements under certain limited circumstances. Under the Act, a full waiver, as requested by the Suitability Petition, may be granted only under three specified conditions.⁴ Lachman has requested a waiver based on the third of these conditions, which permits the Secretary to grant a waiver only if both of the following apply:

(I) that the drug product (including a change in dosage form) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(II) that the drug product (including a change in dosage form) is not likely to be used in a substantial number of pediatric patients.⁵

With regard to the first prong of this exception, the Waiver Request offers no evidence whatsoever to support Lachman's contention. The Waiver Request only points out that venlafaxine has undergone some pediatric testing. Based on this statement alone, Lachman concludes that "[t]he introduction of a capsule dosage form [sic] of the product is not likely to provide a meaningful therapeutic benefit over existing therapies for pediatric patients nor would it be expected to diminish the knowledge gained by the conduct of pediatric studies already completed."⁶

The fact that venlafaxine has previously undergone some pediatric testing does not preclude the possibility that an extended release tablet formulation of venlafaxine might have a different therapeutic profile than the marketed capsule formulation in some pediatric patients. As set forth in further detail in Wyeth's August 28, 2003 Comment to the Suitability Petition, an extended release tablet formulation of venlafaxine may exhibit different clinical properties from an extended release capsule formulation due to differences in certain pharmacokinetic properties, certain physical properties that are specific to capsules, and intra-subject variability that may be associated with extended release tablet formulations of venlafaxine.⁷ In light of these differences, it is simply not clear what therapeutic properties an extended release tablet formulation of venlafaxine might present for pediatric patients.

⁴ 21 U.S.C. § 355c(a)(1)(4)(A).

⁵ See Waiver Request, p. 1. See also 21 U.S.C. § 355c(a)(1)(4)(A)(iii).

⁶ *Id.* at 2. The Waiver Request indicates that the reference listed drug is a tablet and the Suitability Petition proposes a capsule. In fact, Effexor XR is a capsule. The Suitability Petition proposes a change in dosage form to a tablet.

⁷ See Wyeth Pharmaceuticals, Comments to Lachman Consultant Services, Inc. Suitability Petition, at pp. 3-7 (August 28, 2003) (Docket Number 03P-0159/C1).

Separate and apart from whether there might be a “meaningful therapeutic benefit” associated with venlafaxine extended release tablets, to qualify for a waiver, Lachman must also establish that the product is not likely to be used in a substantial number of pediatric patients. The Waiver Request asserts that the tablet dosage form is not likely to be used in a substantial number of pediatric patients, but offers no support for this assertion. Lachman states only that “based on the labeling of the proposed product, it is not likely to be used in a substantial number of pediatric patients.”⁸ Lachman does not specify what aspect of the labeling it is referring to or why such labeling establishes that the product is not likely to be used in a substantial number of pediatric patients.

Wyeth’s labeling for Effexor XR does contain strong precautions regarding safety in pediatric populations, particularly as used to treat Major Depressive Disorder.⁹ This does not establish, however, that physicians do not or will not prescribe a tablet drug product to substantial numbers of children. In addition to Major Depressive Disorder, Effexor XR is also indicated for treatment of Generalized Anxiety Disorder and Social Anxiety Disorder, conditions which may have substantial pediatric patient populations. Social Anxiety Disorder, for example, affects up to five percent of children and is the third most common psychiatric disorder in children.¹⁰ As a result, it is far from clear that the proposed extended release tablet would not be used in a substantial number of pediatric patients. In light of the lack of evidentiary support Lachman has offered, there is no basis for the findings FDA would have to make in order to grant a waiver request.

III. Conclusion

Major Depressive Disorder, Social Anxiety Disorder, and General Anxiety Disorder are serious conditions affecting a great number of pediatric patients in the United States. The Waiver Request filed by Lachman has failed to establish that a tablet formulation would not have a different therapeutic profile – conceivably representing a “meaningful therapeutic benefit” – for pediatric patients.¹¹ Lachman similarly has failed to establish that an extended release tablet formulation of venlafaxine would not be used in a substantial number of pediatric patients.

⁸ Waiver Request, at 2.

⁹ See Effexor XR, Prescribing Information.

¹⁰ See Cincinnati Children’s Hospital Medical Center, *Conditions and Diagnoses: Social Anxiety Disorder*, available at <http://www.cincinnatichildrens.org/health/info/mental/diagnose/social-anxiety.htm>.

¹¹ To be absolutely clear, this statement is not intended to imply that Wyeth is aware of any evidence that a tablet formulation of venlafaxine XR would represent a benefit of any kind over the existing Effexor XR product. The point is simply that Lachman has offered no evidence at all to exclude the possibility of such benefit, and therefore has not met the conditions for a waiver.

Dockets Management Branch (HFA-305)

April 8, 2004

Page 5

Accordingly, FDA should deny Lachman's request for a waiver of the pediatric assessment requirements of the PREA.

Furthermore, to the extent that the Lachman Suitability Petition is not entitled to a waiver of the PREA requirements, and investigations are necessary to support the safety and effectiveness of the proposed tablet drug product in pediatric patients, FDA should deny the Suitability Petition pursuant to section 505(j)(2)(C)(i).

Respectfully Submitted,



Kenneth Bonk
Director, Worldwide Regulatory Affairs
Wyeth Pharmaceuticals