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BY FEDERAL EXPRESS

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

SUITABILITY PETITION

Re: Suitability Petition; Escitalopram Oxalate Capsules

On behalf of Alphapharm Pty Ltd of Glebe, New South Wales, Australia, the undersigned hereby submits, in quadruplicate, this Suitability Petition pursuant to Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j)(2)(C), and FDA regulations 21 CFR §§ 314.93, 10.25 and 10.30.

**A. Action Requested**

This Suitability Petition requests a declaration by the Commissioner of Food and Drugs, head of the Food and Drug Administration ("FDA"), that an Abbreviated New Drug Application ("ANDA") may be filed for the drug escitalopram in a capsule dosage form.

**B. Statement of Grounds**

• An ANDA may be filed for the approval of a new drug that is the same as a reference listed drug ("RLD"). 21 U.S.C. § 355(j)(2)(A). An ANDA may also be filed for a new drug which is the same as an RLD except for a difference in dosage form, provided that FDA has granted permission to file such an ANDA upon the submission and approval of a pertinent "suitability" petition. 21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93(b). FDA is authorized to approve a suitability petition seeking a change in dosage form from an RLD. Id.

• The specific RLD upon which this Petition is based is Lexapro®

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(escitalopram oxalate ("escitalopram")) tablets, a prescription drug which is indicated in its FDA-approved labeling for the treatment of major depressive disorder and generalized anxiety disorder. (See Attachments 1 and 2 hereto). The approved NDA for the RLD (#021-323) is held by Forest Laboratories, Inc. *Id.*

- The proposed drug product will contain the same active ingredient as the RLD (escitalopram), and will have the same strengths (10 mg and 20 mg) and the same route of administration (oral) as the RLD. The proposed drug product will differ from the RLD only in its dosage form -- a capsule rather than a tablet.

- The labeling of the proposed drug product will also be the same as the currently approved labeling for the RLD, except for changes which are required because of the difference in manufacturer, and the difference in dosage form proposed under this Petition (see proposed labeling in Attachment 3).

- The FDA has previously approved a number of ANDA suitability petitions allowing a change in dosage form from a tablet to a capsule. For example, FDA has approved a suitability petition for a capsule dosage form of the antidepressant drug ZOLOFT (sertraline hydrochloride), which was previously only available in a tablet dosage form.

- The petitioner is seeking the change in dosage form from a tablet to a capsule in an effort to make an alternative dosage form of escitalopram available to patients, particularly to those individuals who may have difficulty in swallowing a tablet or who prefer a capsule dosage form.

- In view of the above, and since Lexapro® brand of escitalopram tablets has been marketed in the United States for nearly two years with an established safety and effectiveness profile (see Attachments 2 and 4), there is no reason to question the safety and effectiveness of the proposed escitalopram capsules for their labeled uses.

- *On December 9, 2003, the undersigned, also on behalf of Alphapharm Pty Ltd, filed a suitability petition for permission to submit an ANDA for the antidepressant drug citalopram in a capsule dosage form. Since escitalopram is the active isomer of racemic citalopram, this suitability petition for escitalopram should be granted if the suitability petition for citalopram is granted. **This position is supported by the fact that FDA has granted pediatric exclusivity to Lexapro® brand of escitalopram on the basis of pediatric studies conducted on citalopram (see pediatric checklist for Lexapro®, in Attachment 5).***

**C. Pediatric Assessment Waiver Request**

Pursuant to the Pediatric Research Equity Act of 2003 (“PREA”), 21 U.S.C. § 355B(a)(4)(ii), a full waiver of the requirement to submit an assessment of escitalopram oxalate in a capsule dosage form in a pediatric population is requested, on the grounds that:

- (1) There is evidence strongly suggesting that escitalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant drug indicated for major depressive disorder (MDD), would be unsafe in pediatric age groups, based on reported data indicating that SSRI antidepressant drugs have produced suicidality adverse events in pediatric populations with MDD;
- (2) There is additional evidence strongly suggesting that escitalopram would be ineffective in pediatric age groups.

1. Lack of Safety

In a Public Health Advisory recently issued to health care professionals on October 27, 2003 (see Attachment 6), FDA informed health care professionals that clinical studies conducted to date on eight antidepressant drugs, *including citalopram, of which escitalopram is the active isomer*, suggest an excess of reports of suicidality (both suicidal ideation and suicidal attempts) in pediatric patients with MDD treated with such drugs as compared to placebo.

In addition, at the Joint Meeting of FDA’s Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the agency’s Anti-Infective Drugs Advisory Committee, recently held on February 2, 2004, these Committees recommended that FDA re-analyze existing pediatric data on SSRI antidepressant drugs, *including data on citalopram, of which escitalopram is the active isomer*, to determine whether other reported adverse events, such as “stimulation” or “activation” syndrome, including symptoms of agitation, restlessness, hyperactivity and disinhibition, could also be events indicative of suicidal behavior in children taking these drugs (see Attachment 7).<sup>1</sup>

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<sup>1</sup> Suicidal ideation associated with SSRIs in pediatric MDD patients has also been reported in the medical literature. Veneman J, Lahuus B, Buitelaar JK. SSRIs associated with behavioral activation and suicidal ideation, *J.Am.Ac.Ch.Adol.Psych.*, 40 (12):1364-65 (2001) (see Attachment 8).

Further, Solomon Iyasu, M.D., Lead Medical Officer of FDA's Division of Pediatrics Drug Development, made a presentation at the above-noted Joint Meeting on adverse events reported in pediatric patients during the One-Year Post-NCE Exclusivity Adverse Event Review for Celexa® brand of citalopram, *of which escitalopram is the active isomer* (pertinent pages of meeting transcript annexed as Attachment 9). Dr. Iyasu stated that: (a) citalopram is the fourth most commonly used SSRI antidepressant drug in children; (b) such use has been increasing in recent years; (c) there were *26 unduplicated adverse event reports for citalopram within the one-year post-NCE exclusivity period alone*, including, in addition to suicidality, labeled adverse events of cognitive impairment, aggression, agitation, mania, delusions, and psychotic reaction. Age distribution was 6-16.

Based on these developments, FDA very recently requested manufacturers for 10 antidepressant drugs, including Forest Laboratories, manufacturer of Lexapro® brand of escitalopram, to *add a labeling warning recommending close monitoring of both adult and pediatric patients for suicidal behavior*. A trade press article reporting FDA's request is annexed as Attachment 10. Forest has added this warning to the labeling of Lexapro® (see Attachment 2).

## 2. Lack of Efficacy

In the same October, 2003 Public Health Advisory to noted above, the FDA stated as follows: "FDA emphasizes that, for the 7 [antidepressant] drugs evaluated in pediatric major depressive disorder (MDD), data reviewed by FDA were adequate to establish effectiveness in MDD for only one of these drugs, Prozac (fluoxetine)" (see Attachment 6).<sup>2</sup> This is also evidenced by the fact that escitalopram received a pediatric exclusivity period (see pertinent Electronic Orange Book entry in Attachment 11), but was not awarded a three-year exclusivity period for a pediatric MDD labeling indication.

Accordingly, existing data strongly suggest that the marketed tablet dosage form of escitalopram is neither safe nor effective in a pediatric population. Indeed, the FDA-approved labeling for Lexapro® brand of escitalopram explicitly discloses: "Safety and effectiveness in pediatric patients have not been established" (see Attachment 2).

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<sup>2</sup> Celexa® brand of citalopram, *of which escitalopram is the active isomer*, was one of the antidepressant drugs which were evaluated in an MDD pediatric population, but found ineffective. *Id.*

Moreover, Lexapro® brand of escitalopram is being allowed to continue on the market with this pediatric disclosure labeling statement, without (to petitioner's knowledge) a request for a pediatric assessment under the Pediatric Research Equity Act, 21 U.S.C. § 355B(b). Generic escitalopram formulations are also eligible for approval with the same pediatric disclosure statement, under the Hatch-Waxman "same labeling" provision.

Finally, *a mere change in dosage form from tablets to capsules*, the type of request in the instant Suitability Petition, is routinely granted *because there is no safety issue*. It would be contrary to the intent of both Hatch-Waxman and PREA, to allow escitalopram tablets to be marketed but not escitalopram capsules.

A full waiver from a pediatric assessment is therefore warranted.

**D. Environmental Impact**

Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

**E. Economic Impact**

Pursuant to 21 C.F.R. § 10.30 (b), economic impact information is to be submitted only when requested by the Commissioner following review of this Petition.

**F. Certification**

The undersigned certifies that, to their best knowledge and belief, this Suitability Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to the Petition.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By   
Charles J. Raubicheck

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cc(w/attachments):  
Gary J. Buehler (Director, FDA Office of Generic Drugs)

Attachments:

1. Approved Drug Products with Therapeutic Equivalence Evaluations (“the Electronic Orange Book”, current through May 20, 2004): Lexapro® (escitalopram oxalate) tablets, 10 mg and 20 mg.
2. Approved labeling for Lexapro® (escitalopram oxalate) tablets.
3. Proposed labeling for escitalopram oxalate capsules, 10 mg and 20 mg.
4. NDA approval letter for Lexapro® (escitalopram oxalate) tablets, 10 mg and 20 mg.
5. Lexapro®: FDA’s Pediatric Exclusivity Checklist.
6. FDA Public Health Advisory: “Reports of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD)”, October 27, 2003.
7. FDA: Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee,” February 2, 2004.
8. Veneman J, Lahuus B, Buitelaar JK. SSRIs associated with behavioral activation and suicidal ideation, *J.Am.Ac.Ch.Adol.Psych.*, 40 (12):1364-65 (2001).
9. Transcript: FDA: Psychopharmacologic Drugs Advisory Committee with the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee,” February 2, 2004, pp.195-215.
10. “FDA Requests Antidepressant Labeling Add Suicidality Warning,” F-D-C Reports, The Pink Sheet, March 29, 2004, at 22.
11. Electronic Orange Book, Lexapro®, Patent and Exclusivity Data.