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VIA FEDERAL EXPRESS

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: **Docket No. 03P-0551/CP1**
Citalopram Hydrobromide Capsules 10, 20 and 40 mg

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In response to the letter from Gary J. Buehler dated April 16, 2004 (copy annexed as Exhibit A hereto), this is an amendment (submitted in quadruplicate) to the above-referenced Suitability Petition, requesting a full pediatric assessment waiver.

The original Suitability Petition, filed on December 9, 2003, is annexed (minus exhibits) as Exhibit B.

* * *

Pursuant to the Pediatric Research Equity Act of 2003 ("PREA"), 21 U.S.C. § 355B(a)(4)(ii), the undersigned, on behalf of petitioner Alphaharm Pty Ltd. of Glebe, New South Wales, Australia, hereby requests the Commissioner of Food and Drugs to grant a full waiver of the requirement to submit an assessment of citalopram hydrobromide in a capsule dosage form in a pediatric population, on the grounds that:

(1) There is evidence strongly suggesting that citalopram hydrobromide, 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; and

(2) There is additional evidence strongly suggesting that citalopram hydrobromide would be ineffective in pediatric age groups.

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1. Lack of Safety

In a Public Health Advisory recently issued to health care professionals on October 27, 2003 (copy annexed as Exhibit C), FDA informed health care professionals that clinical studies conducted to date on eight antidepressant drugs, including citalopram, 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, 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 Exhibit D).¹

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 (pertinent pages of meeting transcript annexed as Exhibit F). 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 Celexa® brand of citalopram, 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 Exhibit G. Forest has added this warning to the labeling of Celexa® (see annexed Exhibit H).

¹ Suicidal ideation associated with SSRIs in pediatric MDD patients has also been reported in the medical literature. Veneman J, Lahuis B, Buitelaar JK. SSRIs associated with behavioral activation and suicidal ideation, *J.Am.Ac.Ch.Adol.Psych.*, 40 (12):1364-65 (2001) (copy annexed as Exhibit E).

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 Exhibit C).² This is also evidenced by the fact that citalopram received a pediatric exclusivity period (see pertinent Electronic Orange Book entry in annexed Exhibit I), 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 citalopram hydrobromide is neither safe nor effective in a pediatric population. Indeed, the FDA-approved labeling for Celexa® brand of citalopram explicitly discloses: "Safety and effectiveness in pediatric patients have not been established" (see Exhibit J).

Celexa® brand of citalopram 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 citalopram formulations are also eligible for approval with the same pediatric disclosure statement, under the Hatch-Waxman "same labeling" provision. And it is clear that a mere change in dosage form from tablets to capsules, the type of request in the instant Suitability Petition which is routinely granted, should not change this regulatory approach. It would be highly anomalous, and contrary to the intent of both PREA and Hatch-Waxman, to allow citalopram tablets to be marketed with the pediatric disclosure statement but not citalopram capsules. A full waiver from a pediatric assessment is therefore warranted.

Based on the foregoing, and on the information provided in the original Suitability Petition, it is requested that the Suitability Petition promptly be granted.

Sincerely yours,



Charles J. Raubicheck

cc: Gary J. Buehler (HFD-600)

² Celexa® brand of citalopram tablets was one of the antidepressant drugs which were evaluated in an MDD pediatric population, but found ineffective. *Id.*