CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-822/S-019
21-046/S-003

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

Supplemental NDA:	20-822 SLR-019, 21-046 SLR-003
This review is also filed under NDA:	21-323, 21-365 (for Lexapro™/escitalopram)
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug:	Celexa™ tablets (NDA 20-822) and oral solution (NDA 21-046)
Dates of Submission:	9/30/02 Date received: 10/29/02
Materials Reviewed:	Changes Being Effected in the Other Events Observed During …Postmarketing…Celexa" section of labeling
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	11/15/02

I. Background.

The purpose of this review is to assist the Team Leader and Division Director in the regulatory processing of submissions under these NDAs.

The sponsor is providing an updated version of "Other Events Observed During the Postmarketing Evaluation of Celexa" to make this section of Celexa™ labeling more consistent with the corresponding section in the recently approved Lexapro™ (escitalopram) labeling (NDA 21-323). This review is also being filed under Lexapro™ NDAs (for the tablet and oral solution formulations).

II. Summary of Proposed Labeling Changes of the "Other Events Observed During the Postmarketing …" section of labeling proposed for Celexa™ labeling. The sponsor indicates the addition of a number of adverse event terms (denoted by underlining the text) in the "Other Events…" section. The sponsor denotes by strike through, the deletion of "approximately 8" and inserts "over 30" in the first sentence of the section to read as follows: "…over 30 million patients have been treated with Celexa since market introduction." See a copy of the proposed revised section in Attachment 1 of this review.

For the purposes of this review a comparison was made between the "Other Events Observed During the Postmarketing …" section of labeling proposed for Celexa™ (as provided in this sNDA) and the corresponding section of the Lexapro™ labeling in the 8/14/02 Approval Letter (see Attachment 1 for proposed Celexa™ and approved Lexapro™ versions). The following differences are noted based on this comparison:

- The first sentence of the section "It is estimated that over 30 million patients…" appears in the proposed Celexa™ version, but is not included in the approved Lexapro™ labeling.
- The adverse event term "chest pain" appears in the proposed Celexa™ version but no in the approved Lexapro™ labeling.
- Minor changes are proposed in the sentence "Although no causal relationship…" (the second sentence of the section) in Celexa™ version. This

sentence was modified to provide clarification that the events listed in the section are events that "have not been described elsewhere in labeling."

III. Conclusion and Recommendations.

The modified "Other Events Observed During the Postmarketing..." section of Celexa™ labeling that the sponsor proposes is now almost identical to the corresponding section of the recently approved Lexapro™ labeling. One of the differences between these two versions is the addition of "chest pain" for the Celexa™ labeling which does not appear in the Lexapro™ version. Since this change adds additional safety information, it appears to be an acceptable change. Consideration may be given to adding "chest pain" to the Lexapro™ labeling in the corresponding section (the "Events Reported Subsequent to Marketing of Racemic Citalopram" section). However, Approved Lexapro™ labeling includes "tightness of the chest" under "Other Events Observe During the Premarketing ....of Lexapro™." Since this review also pertains to Lexapro™ the review is also being filed under NDAs 21-323 and 21-365 for Lexapro™ (tablet/oral solution, NDAs), as well as the current Celexa™sNDA submissions.

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Attachment 1.

Proposed Changes for Celexa™ Labeling.

Other Events Observed During the ~~Non-US~~ Postmarketing Evaluation of Celexa (citalopram HBr):

It is estimated that ~~approximately 8~~ over 30 million patients have been treated with Celexa since market introduction. Although no causal relationship to Celexa treatment has been found, the following adverse events have been reported to be temporally associated with Celexa treatment ~~in at least 3 patients (unless otherwise noted)~~, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis ~~(3 cases)~~, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis ~~(2 cases)~~, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, Torsades de pointes, and withdrawal syndrome.

The Corresponding Section in Approved Lexapro™ Labeling (refer to the 8/14/02 Approval Letter)

Events Reported Subsequent to the Marketing of Racemic Citalopram
Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of escitalopram or citalopram: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, neuroleptic malignant syndrome, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, serotonin syndrome, spontaneous abortion, thrombocytopenia, thrombosis, Torsades de pointes, ventricular arrhythmia, and withdrawal syndrome.

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/s/

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