

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-763

MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 21-763 orally disintegrating tablets

Sponsor: Biovail Laboratories, Inc.

Drug

Established Name: Citalopram HBr

Chemical Name: (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr

Formulation: 10, 20 and 40 mg orally disintegrating tablets

Indication: New formulation (orally disintegrating tablets) for Major Depressive Disorder (MDD)

Dates of Submission: April 14, 2004

Materials Reviewed: Original NDA 21-763 describes Pharmacokinetic studies on the orally disintegrating tablet (ODT) formulation and 1 bioequivalence study compared Celexa™ to the ODT formulation (1 Pilot and 4 “Definitive” Studies)

Clinical Reviewer: Karen L. Brugge, M.D.

Review Completion Date: 12/21/04

EXECUTIVE SUMMARY

Purpose of this review: The purpose of this review and summary is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-365.

Five PK studies were conducted of which 4 trials are referred to as definitive trials to support proposed labeling in which the sponsor is seeking approval for a new formulation for citalopram, which is an orally disintegrating tablet (ODT) formulation. These trials employed single-dose treatment conditions of 40 mg ODT and 40 mg of the tablet formulation of citalopram. The studies were generally cross-over, non-placebo controlled trials and were conducted on generally healthy 18-58 year old male and female subjects.

Pending confirmation by OCPB, bioequivalence was demonstrated between the ODT and tablet formulations at the 40 mg dose-level. From a clinical perspective the ODT formulation is adequately safe for the MDD population at the recommended treatment regimen (the sponsor does not propose changing the treatment recommendations from that of approved Celexa™ tablets). However, Dr. Ta-Chen Wu expressed OCPB issues regarding the 20 mg ODT, that he finds will need to be resolved, but are not reasons for not granting an approvable action (as understood by the undersigned at the time of this writing).

The PK trials did reveal greater incidence of adverse dropouts in ODT compared to tablet treatment conditions, as well as a greater incidence in decrease blood pressure reported as an adverse event. There were also a greater incidence of adverse dropouts at ≤ 4 hours after ODT compared to the tablet formulation in the single dose trials. These adverse dropouts were generally due to nausea and/or vomiting and often with dizziness or in a few subjects, brief syncopal-like episodes. A few of these subjects had concomitant decreased blood pressure. Other vital sign findings were also observed in both treatment conditions that were generally mild decreases in blood pressure and heart rate that were likely to be in part, influenced by other confounding variables. However, given the temporal relationship between dosing and the events (near T_{max} or as plasma levels were rising to achieve C_{max}) and that some of the adverse events are known to be associated with citalopram and escitalopram, a role of the study drug is considered likely. However, the magnitude of these effects and the presence of clinically significant adverse events (e.g. near syncopal or syncopal episodes) were likely to be confounded by the Phase I study conditions, as well as the higher than recommended starting-dose-level (twice greater than the starting dose, recommended in approved labeling for the tablet and for proposed labeling for the ODT formulation). Without a placebo comparison group it is difficult to interpret observed differences between the ODT and tablet formulations that are described in this review. Furthermore, the magnitude of a potential effect on the above findings is also difficult to establish given the study design of the PK trials. The caveats of interpreting these results are discussed in more detail in the review.

Recommended Action

In conclusion, it is recommended from a clinical perspective that this NDA be given an approvable action.

Key Issues that are Recommended be Resolved before Granting a Final Approval Action
Recommendations for further investigation of a potential signal for syncopal or near syncopal episodes, for potential clinically significant effects on blood pressure and possibly heart rate are provided in the last section of the review, as well as key labeling recommendations. Also, OCPB issues regarding the 20 mg ODT exist that should be resolved before final approval for the 20 mg ODT. Any other CMC or Pharmacology Toxicology issues should be resolved. Although, to the knowledge of the undersigned there are no major CMC or Pharmacology Toxicology issues, at the time of this writing and as understood by the undersigned.

Addendum. In a recent e-mail (in mid-December) the sponsor notified the Division of plans of submitting an amendment submission with results of a Phase I PK study with the 20 mg ODT dose strength. The sponsor sent a synopsis of the study report which described at least one subject with emesis (twice near tmax, at 5 hours post-dose) that may be similar to adverse events, as described above that also occurred near Tmax in the single-dose trial employing a lower dose level of 20 mg. Before granting final approval on this NDA, it is recommended that this recent submission be subject to review and any issues be resolved.

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I. Introduction and Background.

This review is to assist the Team Leader and Director of the Division of Neuropharmacological Drug Products in the regulatory processing of NDA 21-323.

The sponsor is seeking approval for an orally disintegrating tablet (ODT) formulation of citalopram HBr (CT) for treatment of Major Depressive Disorder (MDD). The tablet formulation of CT (Celexa™) is already approved for treatment of MDD, as well as for other indications.

A. Indication and Proposed Direction of Use

The proposed indication is MDD and the recommended dose is the same as that described in approved Celexa™ labeling.

Current approved labeling recommends a daily dose of 20 mg that can be increased to a daily dose of 40 mg. Some patients may require 60 mg daily, as described in current approved labeling.

B. State of Armamentarium for Indication

Since this NDA is for a new formulation rather than for a new chemical entity, this subsection is not applicable.

C. Administrative History

See the next section regarding the NDA history for citalopram.

D. Related Reviews

The approved NDAs 20-822 and 21-046 for Celexa™ (citalopram hydrobromide) tablet and oral solution formulations are two related NDAs. Celexa™ was approved for the MDD indication on 7/17/98.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics, and/or other Consultant Reviews.

The focus of this submission is on a new formulation in which a bioequivalence study (comparing Celexa™ to CT ODT formulations) and other pharmacokinetic (PK) studies were conducted and described in the NDA. Therefore, the NDA is also under review by the Office of Clinical Pharmacology, Biopharmaceutical (OCPB).

The OCPB reviewer (Dr. Ta-Chen Wu) notes that ODT PK trials were only conducted on the 40 mg dose-level (using the 40 mg ODT), yet the sponsor is seeking approval for the 20 mg ODT, as well. Since the 20 mg dose-level is the recommended starting dose (as approved for MDD for Celexa™), it is important from a clinical perspective to have this lower dose-level available in the ODT formulation. The sponsor submitted a response (dated 10/11/04) to the OCPB issue and others outlined in the 74-day letter. The following are key OCPB issues based on communications with Dr. TC Wu (dated 10/11/04 and 12/7/04), as understood by the undersigned. At the time of this writing, the response submission is under review by Dr. T-C Wu who at this time continues to express concern that an *in vivo* bioequivalence study together with *in vitro* dissolution studies are not adequate to support a 20 mg ODT tablet.

The Chemistry Manufacturing and Controls (CMC) information is under review by Dr. Lyudmila Soldatova. Dr. Soldatova has not expressed any major CMC issues at the time of this writing.

Preclinical Pharmacology and Toxicology (PPT) information is under review by Dr. Linda Fossom who has no preclinical issues, at the time of this writing.

III. Human Pharmacokinetics and Pharmacodynamics

A. Human Pharmacokinetics

See Section IV for a listing of PK studies with the ODT formulation. Since the focus of this Clinical review is regarding safety of the ODT formulation, the PK results of the PK studies are summarized in this section, while a more detailed description will be provided in the OCPB review.

The following outlines PK properties of the ODT formulation (see studies outlined in Section IV of this review):

- No food effects observed on rate or extent of absorption, as described by the sponsor. Yet, the OCPB Reviewer, Dr. Wu, noted (in a 12/7/04 telephone conversation, as understood by the undersigned) some evidence for some food effects on T_{max} (a delay of approximately one hour in the fed compared to fasted condition).
- Administration with or without water results in similar PK values
- Bioequivalence with Celexa™ was observed in a SD 40 mg study (given in fasted conditions).

Refer to the previous section for key OCPB issues, at the time of this writing.

B. Pharmacodynamics

The submission does not contain any new information on the pharmacodynamics of SCT.

IV. Description of Clinical Data and Sources

A. Overall Data: Materials from NDA/IND

The following items were utilized during the course of this clinical review:

Documents Utilized in Clinical Review	
DATE	DESCRIPTION
4/14/04	NDA 21-763 electronic submission: includes an Integrated Safety Section and study reports of PK studies (outlined in Section IV of this review) and proposed labeling. Case Report Tabulations, Case Report Forms, Financial Disclosure information, Foreign Marketing information is included, as well as CMC and PPT sections (under review by other CMC and PPT reviewers)
10/11/04	An amendment submission in response to clinical and OCPB inquiries.

B. Tables Listing the Clinical Trials

The following tables outline the studies described in the submission (as provided by the sponsor). Four studies referred by the sponsor as “definitive,” were conducted to examine the following: a comparison of the ODT with a reference drug (Study 2730), potential food effects (Study 2731), effects of water (Study 2732) and a bioequivalence study comparing ODT to Celexa™ (Study 2750). One study (Study 26022) used a prototype ODT formulation, as a pilot

study. These studies were open-label, SD studies using 40 mg dose-level in which generally healthy male and female subjects were randomized to a sequence of treatment conditions in a cross-over design. The table outlines each study.

Table 1 Overview of Citalopram HBr ODT Clinical Program

Study Number	Title
Pilot	
26022 B00-508PK-PRKN11	A Pilot Three-Way Cross-Over Single-Dose Open-Label Fasting Comparative Bioavailability Study of Citalopram 40 mg Flash Dose Tablets vs. Celexa™ 40 mg (Citalopram Hydrobromide) Tablets in Normal Healthy Non-Smoking Male Volunteers
Definitive	
2730 (B03-635PK- N11F1)	A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Comparative Bioavailability Study of Citalopram Hydrobromide 40 mg ODT, Versus Celexa™ 40 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects
2731 (B03-636PK- N11F1)	A Two-Way, Crossover, Open-Label, Single-Dose, Food Effect Study of Citalopram Hydrobromide 40 mg ODT in Normal Healthy Non-Smoking Male and Female Subjects
2732 (B03-637PK- N11F1)	A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Comparative Bioavailability Study of Citalopram Hydrobromide 40 mg ODT, Without and With Water in Normal Healthy Non-Smoking Male and Female Subjects
2750 (B03-638PK-N11F1)	A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Equivalence Study of 4 x Citalopram Hydrobromide 10 mg ODT Versus 1 x Citalopram Hydrobromide 40 mg ODT in Normal Healthy Non-Smoking Male and Female Subjects

Tables below show additional information regarding the 5 PK studies, including the number of subjects in each study. The number of subjects completing the trials is also provided in the summary table. The first table below indicates abbreviations used for the summary table of the “pilot” and “definitive” PK trials that follows (all tables were provided in the submission).

Table of Abbreviations Used in Subsequent Summary Tables of PK Studies

Section	Abbreviation and/or Term
Study Design	CO = Crossover O = Open-Label R = Randomized
Treatment Groups	ODT = Orally disintegrating tablet
Participants	E = Enrolled R = Randomized S = Safety population C = Completed P = Prematurely Discontinued (Dropout)
Regimen	QD = Once daily

Summary Tables of Each of the 5 PK Studies

Report (Protocol) Number/ Start Date Location	Investigator	Study Design	Treatment Group	Unit Dose (mg)	Regimen	Formulation	Participants					Age (yrs) Mean±SD Range	Gender (N) Male/ Female
Report/Lists/CRFs							E	R	S	C	F		
I. Pilot Study - Single Dose Comparison with Reference Drug: Fasted With Water Versus Fed With Water													
26022 (B00-508PK-PRKN11) May 07, 2001		CO, O, R	All Subjects				18	18	18	18	0	28±6 20-42	18/0
Item 11			Citalopram HBr ODT	40	1 x 40 mg fasted	GMP245							
Item 12			Citalopram HBr ODT	40	1 x 40 mg fed	GMP245							
			Celexa™	40	1 x 40 mg fasted	PO3278							
II. Definitive Studies													
II.A. Single Dose Comparison with Reference Drug: Fasted With Water													
2730 (B03-635PK-N11F1) August 01, 2003		CO, O, R	All Subjects				36	36	36	28	8	35±10 20-51	12/24
Item 11			Citalopram HBr ODT	40	1 x 40 mg fasted	0306011							
Item 12			Celexa™	40	1 x 40 mg fasted	M0201J							
II. Definitive Studies													
II.B. Single Dose Evaluation of the Effect of Water: Fasted													
2732 (B03-637PK-N11F1) August 07, 2003		CO, O, R	All Subjects				34	34	34	28	6	34±8 18-50	13/21
Item 11			Citalopram HBr ODT w/ water	40	1 x 40 mg fasted	0306011							
Item 12			Citalopram HBr ODT w/o water	40	1 x 40 mg fasted	0306011							
II.C. Single Dose Evaluation of the Effect of Food: Fasted With Water Versus Fed With Water													
2731 (B03-636PK-N11F1) August 14, 2003		CO, O, R	All Subjects				35	35	34	31	3	34±11 18-58	23/11
Item 11			Citalopram HBr ODT	40	1 x 40 mg fasted	0306011							
Item 12			Citalopram HBr ODT	40	1 x 40 mg fed	0306011							
II.D. Single Dose Dosage Form Bioequivalence: Fasted With Water													
2750 (B03-638PK-N11F1) February 27, 2004		CO, O, R	All Subjects				36	36	36	28	8	31±8 19-48	27/9
Item 11			Citalopram HBr ODT	40	1 x 40 mg fasted	0306011							
Item 12			Citalopram HBr ODT	40	4 x 10 mg fasted	0307015							

See Section VIIC for a further breakdown of subjects, for treatment exposure and for disposition of the subjects.

C. Post-Marketing Experience

CT ODT is not approved in any country and the sponsor has not submitted applications for approval to regulatory authorities in any foreign country (as clarified upon inquiry in a 10/11/04 submission).

D. Literature Review

The sponsor summarizes a review of the literature for citalopram in Section 18.1 of the ISS. See Section VII M for a summary.

V. Clinical Review Methods

A. Materials Reviewed.

The focus of this review is on safety results of the PK studies, as previously described (refer to Section IV for a listing of studies and other previous sections for the NDA contents).

B. Adequacy of Clinical Experience.

From a clinical safety perspective, the clinical experience with the new formulation, together with previous experience of the approved Celexa™ tablet formulation (refer to current approved labeling for details) are adequate for the purposes of this review (refer to Section IV for an outline of PK studies with the ODT formulation and enumeration of exposed subjects). Refer to Section II of this review regarding OCPB issues, at the time of this writing, as the data provided in the submission are not considered adequate for supporting the 20 mg strength of the ODT formulation (based on communications with the OCPB reviewer).

C. Data Quality and Completeness

Overall, the quality and completeness of this NDA appears adequate on the basis of finding no remarkable problems while reviewing the submission. This conclusion is also based on comparisons between arbitrarily selected narratives and summary tables of adverse dropouts, as described in more detail in the following paragraph.

Narratives of arbitrarily selected adverse dropouts (subject numbers 2732-27, 2730-04, and 2730-26) were compared to corresponding summary tables in the ISS (Tables 20-22). The comparisons were conducted to determine if Preferred Term adverse events and demographic information found in the narratives matched this information provided in the summary tables (the items for making comparisons were generally selected on an arbitrary basis). The comparisons revealed all items in each of the 3 selected narratives matched the summary table that listed the given subject.

D. Evaluation of Financial Disclosure

~~_____~~ MD are listed as the investigators of one or more of the PK studies (a total of 5 studies, outlined under Section IV of the review). Dr. Greg Szpunar of Biovail Technologies, Inc certified that these investigators had no financial information requiring disclosure (as defined in 21 CFR 54.2a) and that there were no financial arrangements between these investigators and the sponsor (as certified on Form FDA 3454 in the submission).

Financial disclosure information was not provided for subinvestigators. Upon request, the sponsor provided a listing as follows, to include all subinvestigators, as shown below (provided in a 10/11/04 submission). The sponsor resubmitted the Form FDA 3454 to include these subinvestigators, which certified that they had no disclosable financial arrangements.

Citalopram Hydrobromide Orally Disintegrating Tablets NDA 21-763 Principal Investigators and Sub-investigators		
Principal Investigator / Sub-Investigators	Study Site	Study No
		800-508PK- PRKN11
		2730
		2731
		2732
		2750

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VI. Integrated Review of Efficacy

This submission contains no new information on efficacy.

VII. Integrated Safety Information

A. Synopsis

The focus of this review is on deaths, SAEs and ADOs in the 5 PK studies. No deaths or SAEs were observed. The incidence of adverse dropouts (ADOs) was greater after treatment with the ODT formulation compared to the Celexa™ formulation (9% and 4%, respectively). These 5 PK trials employed single-dose treatment conditions of 40 mg of the ODT or the Celexa™ formulations (155 and 50 ITT safety subjects given each formulation, respectively). These trials did not include placebo groups.

The majority of the ADOs were due to dizziness±syncope or loss of consciousness and/or nausea±vomiting and/or decreased blood pressure in which the incidence of ITT safety subjects was 6.5% (10/155 subjects) after ODT formulation compared to only 2% (1/50) subjects after the Celexa™ formulation. All but one of these ADOs occurred within 4 hours and one occurred between 4-12 hours. Several of these ADOs included adverse events of syncope, loss of consciousness but the incidence between ODT and tablet formulation treatment conditions was similar (1.9%; 3/155 subjects post-ODT, 2%; 1/50 subjects post-tablet). The incident of subjects with vital sign-related related AEs of decreased blood pressure was numerically greater

in ODT treated subjects (7.1%; 11/155 subjects) compared to subjects after Celexa™ treatment (2%, 1/50 subjects). Mean decreases from baseline to post-dose time-points was observed in blood pressure and heart rate in the one PK study (Study 26022) that conducted vital sign assessments near Tmax. These decreases were generally mild and generally and occurred over a duration of approximately 1-7 hours post-dose. Numerical differences in these mean decreases were not consistently observed between ODT and tablet treatment conditions. See the conclusion subsection K for overall conclusions. Sections VIIK and XI of this review discusses the potential caveats in interpreting these results and provides conclusions and recommendations for the NDA. Key labeling recommendations are also provided in Section XI.

B. Background Information

The sponsor has information on deaths, serious adverse events and adverse dropouts (ADOs) in the Integrated Safety of Summary (ISS) for all 5 PK studies, combined. The narratives of ADOs are provided in an Appendix E of the ISS which were reviewed. Study reports of each PK study are provided in the submission.

The primary focus of this review is on deaths, SAEs and ADOs, given that Celexa™ is already approved and given the ample experience with the tablet formulation. However, given the ADOs of events that included syncopal or near syncopal episodes and in some cases decreased blood pressure the review also focuses on additional safety information relevant to these adverse events.

B. Demographic Characteristics

The table below summarizes the demographic features of the population in the 5 PK studies, combined.

Reviewer Comments. Since the studies were all Phase I trials that involved similar populations (generally healthy, 18-58 year old subjects) integration of this information is considered by this reviewer to be appropriate.

However, one should note that one study, Study 20622 used an ODT prototype (all other studies used the proposed to-be-marketed ODT tablet). Additional caveats are provided later.

Demographic Features of Subjects of 5 PK Studies, Combined

Variable	Citalopram HBr ODT 40 mg (N=155)	Celexa™ 40 mg (N=50)
Gender [n (%)]		
Male	92 (59.4)	28 (56.0)
Female	63 (40.6)	22 (44.0)
Age (years)		
Mean ± SD	32.8±9.12	33.0±9.07
Median	30	31
Range	18-58	20-51
Race/Ethnic Origin [n (%)]		
Caucasian	119 (76.8)	45 (90.0)
Black	22 (14.2)	2 (4.0)
Asian	13 (8.4)	3 (6.0)
Other	1 (0.6)	0 (0.0)

C. Extent of Exposure

The table below enumerates the number of randomized subjects with at least one dose of the study drug in each treatment group/condition of each study (as provided by the sponsor).

Enumeration of Subjects in Each Study

Study Number	All Subjects	Citalopram HBr ODT 40 mg				Celexa™ 40 mg Fasted with water
		All Citalopram Subjects	Fasted with water	Fasted without water	Fed with water	
Pilot						
26022 B00-508PK-PRKN11	18	18	18		18	18
Definitive						
2730 (B03-635PK- N11F1)	36	33	33			32
2731 (B03-636PK- N11F1)	34	34	33		32	
2732 (B03-637PK- N11F1)	34	34	33	29		
2750 (B03-638PK-N11F1)	36	36	33			31
Total	158	155				50

Reviewer Comment: It is important to note the following with respect to safety findings later in comparing the ODT formulation to the Celexa™ formulation. The studies, which were crossover trials, were generally unbalanced with respect to ODT compared to Celexa™ tablet exposure, as described in the following. As shown in the above table, the majority of subjects underwent multiple single-dose ODT treatment conditions, given the cross-over study design employed, while fewer subjects were given Celexa™ tablet treatment which was only given once in a given subject in only 2 of the 5 trials. The pilot prototype and the pivotal ODT bioequivalence studies, Studies 26022 and 2730, were the only studies comparing Celexa™ tablet treatment to the ODT treatment. In Study 26022 subjects received 2 treatment conditions with the ODT prototype, while the definitive ODT bioequivalence study, Study 2730 had one ODT condition and one Celexa™ condition. Note that despite the multiple single-dose conditions, washout periods between treatment conditions were 2-4 weeks in a given trial.

Study 20622 (the study that used an ODT prototype compared to Celexa™ tablet) was the only study to include vital sign measures near Tmax, while none of the trials had ECG data near Tmax.

The following washout intervals between treatment conditions were employed as follows:

- 2 weeks in the pilot ODT prototype bioequivalence study, Study 26022,
- 4 weeks in the pivotal ODT bioequivalence study, Study 2730,
- 4 weeks for ODT PK studies: 2731, 2732 and 2750

The following table shows the disposition of these subjects (as provided by the sponsor).

Disposition of Subjects

Disposition	Citalopram HBr ODT 40 mg	Celexa™ 40 mg
	n	n
Received at least one dose of study drug	155	50
Premature Termination	22	3
Primary Reason for Discontinuation ^a		
Adverse Event	14	2
Administrative Reasons	5	1
Personal Reasons (subject's decision)	7	0

^a A subject could have prematurely terminated for more than one reason.

D. Deaths

There were no deaths reported in any of the 5 PK studies.

E. Serious Adverse Events (SAEs)

There were no SAEs reported in any of the 5 PK studies

F. Dropouts due to Adverse Events

The incidence of adverse dropouts (ADOs) was as follow after each treatment condition as specified:¹

- 40 mg ODT treatment: 9% (14 out of 155 subjects of the ITT safety population)
- 40 mg Celexa™ treatment: 4% (2 out 50 ITT safety subjects).

The majority of ADOs occurred at ≤ 4 hours post-dose (1 subject after Celexa™ and 9 subjects after ODT CT), 1 ADO occurred between 4-12 hours after ODT CT and the remainder 4 ADOs (1 after Celexa™ and 3 after ODT) occurred after 24 hours post-dose. See the following summary tables listing these ADOs for each of these three post-dose time-intervals (<4 hours, 4-12 hours and >24 hour post-dose time of occurrence, as provided by the sponsor).

¹ ITT Safety population = Intent to Treat safety population defined as randomized subjects who had at least one dose of study drug.

Table 20 Subjects Who Prematurely Terminated Due to Adverse Event: Onset of First Adverse Event Leading to Premature Termination ≤4 Hours After Study Drug Administration

Study Drug/ Study/ Subject Identifier	Gender/ Age/Race	Preferred Term	T _{max} ^a (h)	C _{max} (ng/mL)	AUC (ng·h/mL)
Celexa™	2730-04 Female/ 33/Caucasian	Asthenia	1.0	12.7	7
		Blood pressure decreased			
		Body temperature decreased			
		Dizziness			
		Dyspepsia			
		Feeling cold			
		Feeling hot			
		Loose stools			
		Loss of consciousness			
		Nausea			
		Pallor			
		Respiratory rate increased			
		Tremor			
Vomiting NOS					
Citalopram	2732-06 Female/ 42/Caucasian	Nausea	7.0	40.8	1727
		Dizziness			
	2732-08 Female/ 39/Other	Nausea	5.0	37.6	1564
		Dizziness			
		Loose stools			
	2732-27 Male/ 30/Caucasian	Vomiting NOS	2.0	53.1	1738
		Nausea			
	2732-36 Female/ 39/Caucasian	Syncope	4.0	50.9	2655
		Dizziness			
		Tremor			
		Pallor			
	2750-14 Female/ 31/Caucasian	Vomiting NOS	2.0	54.5	161
		Nausea			
2750-15 Male/ 24/Caucasian	Nausea	4.0	31.0	92	
	Vomiting NOS				
2750-26 Male/ 28/Caucasian	Dizziness	4.0	45.1	109	
	Blood pressure decreased				
	Nausea				
	Vomiting NOS				
2750-34 Male/ 32/Black	Nausea	4.0	32.2	82	
	Vomiting NOS				
2750-36 Male/ 42/Caucasian	Blood pressure decreased	4.0	29.8	243	
	Cold sweat				
	Dizziness				
	Loss of consciousness				
	Pallor				
	Sweating increased				
	Tremor				

^a Values are underestimated for profiles.

Source: ISS Appendix F.4, and Final Report for Study 2730 (B03-635PK-N11F1), Appendix 2.4; Final Report for Study 2732 (B03-637PK-N11F1), Appendix 2.4; and Final Report for Study 2750 (B03-638PK-N11F1), Appendix 2.4.

Table 21 Subjects Who Prematurely Terminated Due to Adverse Event: Onset of First Adverse Event Leading to Premature Termination >4 to 12 Hours After Study Drug Administration

Study Drug/ Study/ Subject Identifier	Gender/ Age/Race	Preferred Term	T _{max} (h)	C _{max} (ng/mL)	AUC (ng·h/mL)
Citalopram 2732-03	Male/ 35/Caucasian	Dizziness Sweating increased Syncope	7.0	38.8	1340

Source: ISS Appendix F.4. and Final Report for Study 2732 (B03-637PK-N11F1), Appendix 2.4.

Table 22 Subjects Who Prematurely Terminated Due to Adverse Event: Onset of Adverse Event >24 Hours After Study Drug Administration

Study Drug/ Study/ Subject Identifier	Gender/ Age/Race	Preferred Term	T _{max} (h)	C _{max} (ng/mL)	AUC (ng·h/mL)
Celexa™ 2730-23	Female/ 46/Caucasian	Haemoglobin decreased	6.0	53.6	3138
Citalopram 2730-26	Female/ 47/Caucasian	Haemoglobin decreased	5.0	51.3	3619
2731-08	Female/ 21/Caucasian	Nausea	5.0	62.8	2782
2750-20	Female/ 22/Caucasian	Haemoglobin decreased	3.0	54.9	2489
2750-30	Male/ 30/Caucasian	Haemoglobin decreased	3.0	39.8	1040

Source: ISS Appendix F.4. and Final Report for Study 2730 (B03-635PK-N11F1), Appendix 2.4; Final Report for Study 2731 (B03-636PK-N11F1), Appendix 2.4; and Final Report for Study 2750 (B03-638PK-N11F1), Appendix 2.4.

Reviewer Comment: Note that the incidence of ITT safety subjects who were ADOs due to dizziness±syncope or loss of consciousness and/or nausea±vomiting was 6.5% (10/155 subjects) compared to only 2% (1/50) subjects after Celexa.™ All but one of these ADOs occurred within 4 hours and one occurred between 4-12 hours.

Refer to the Synopsis and Conclusions subsections (A and K) and to Section IX regarding the interpretation of these results and key caveats.

A more detailed discussion of ADOs of syncope or loss of consciousness is provided in a subsection below.

Note that 4 out of the 5 ADOs at >24 hours post-dose were due to decreased hemoglobin (the 5th ADO was due to nausea) but the incidence of subjects with ADOs due to decrease hemoglobin was similar with each formulation (2% of subjects after ODT and 2% of subjects after Celexa™).

Upon request the sponsor provided additional information on these ADOs. The low hemoglobin levels were revealed after approximately 28 days of washout (the washout period before the next single-dose treatment period). Furthermore, all 4 subjects had normal levels within a 7-11 day follow-up assessment. It is not likely that these ADOs were drug-related given the temporal relationship with only a single dose of citalopram. There were no other remarkable observations regarding these subjects. Three of these four subjects had baseline values that were at the low end of the normal range (low normal: 115 g/l and 135 g/l in females and males, respectively). The magnitude of the decrease was no greater than a 20 g/l in any given subject, and were uneventful (no related AEs reported and as above, values were normal at the 7-11 follow-up assessment). The low hemoglobin is likely due to multiple blood sampling and other non-drug related factors (subjects may have donated blood, despite their participation in the Phase I trial).

ADOs involving Syncope or Loss of Consciousness and Related ADOs

Given the higher incidence of ADOs in subjects near T_{max} after ODT treatment compared to the incidence in subjects after Celexa,TM and that several of these ADOs involved syncope and/or loss of consciousness (LOC) the following describes these events in more detail.

ODT and CelexaTM treatment conditions showed similar incidence of ADOs due to LOC or syncope (1.9%; 3/155 subjects post-ODT, 2%; 1/50 subjects post-tablet). Two of these subjects (1 after ODT and 1 after CelexaTM) also had decreased blood pressure.

Additional AEs are listed in the summary table of ADOs, as well as decreased blood pressure in one of the subjects with dizziness who did not experience syncope or LOC (see the previous summary tables of ADOs at <4 hours post-dose and 4-13 hours post-dose). Nausea and/or vomiting and sometimes cold sweat, pallor, sweating, tremor, loose stools were also reported in several subjects (T_{max} generally occurred within 1-7 hours among these ADOs). *Note that nausea was sometimes reported with dizziness and/or syncope.*

Some of the ADOs were also listed as also having AEs of decreased blood pressure in a summary table in the ISS listing subjects with decreased blood pressure, as a reported AE (Table 36 which is a summary table of vital sign-related AEs in the ISS section of the submission, found on page 57-8, Item 8H). Subjects 2732-36, 2750-26, 2750-36 after ODT treatment and subject 2730-04 after CelexaTM treatment are subjects with ADOs of syncope or LOC that are also listed in Table 36 as having decreased blood pressure reported as an AE. However, these 4 subjects were not listed as having vital sign values of potential clinical significance in Table 37 (page 59) of the ISS. Results on AEs involving a safety parameter and results on vital sign outliers (such as results of Tables 36 and 37) are discussed later in this review.

Upon request additional information was provided by the sponsor on the ADOs in Tables 20 and 21 in the original submission and as listed above (subjects with LOC and/or syncope and/or nausea or related events). The sponsor provided this additional information in a 10/11/04 submission. The following summarizes reviewer conclusions, upon review of the sponsor's summary of the events and narratives of subjects with LOC, syncope or dizziness and upon review of narratives of subjects with LOC or syncope.

The events of LOC and syncope were likely associated with a vasovagal response, as suggested by the sponsor. These subjects were undergoing multiple blood sampling (sometimes following an overnight, 10 hour fast). In many cases the episodes occurred shortly after a blood draw, were associated with vasovagal-like signs/symptoms (pallor, sweating, nausea and others). Subjects were healthy with generally no identifiable risk factors. The longest syncopal episode was reported as 5 seconds. Vital signs were monitored in the 4 subjects with syncopal episodes (see above summary tables for subject numbers) at multiple time-points shortly after events of syncope and LOC and were generally stable except one subject had elevated blood pressure (systolic of approximately 150 mmHg) and another subject had markedly low blood pressure (80/40 mmHg) within minutes of the syncopal episode (a third subject also had low systolic blood pressure of 90 mmHg). The adverse events associated with these syncopal episodes resolved generally within minutes or within approximately an hour. Although, some subjects had a recurrence of dizziness and other vasovagal-like signs or symptoms later in the day (e.g. as PK sampling continued and shortly after a given blood draw). ECGs were not conducted during these events, but arrhythmias were not noted during vital sign monitoring and subjects did not report palpitations. Finally, plasma levels of citalopram in these 4 subjects did not exceed group mean levels (mean+1SD) during the time of the events of LOC or syncope (only one subject exceeded the mean+1SD by only a few ng/ml which was transient at a time-point that did not coincide with the event).

While most of the ADOs near Tmax were likely associated with vasovagal-like in nature in subjects undergoing multiple blood sampling (sometimes following a 10 hour fast), a potential contributory role of the study drug should be considered. Furthermore, additional safety findings of decreased blood pressure and heart rate near Tmax in the only trial that conducted vital sign measures near Tmax. A subsection below also describes results of AEs of decreased blood pressure that were reported in a numerically greater incidence of subjects following ODT compared to the incidence following Celexa™.

Conclusions and labeling recommendations are provided later in this review.

G. Specific Search Strategies

No specific search strategies were conducted. However, the following section includes a subsection on AEs related to a safety parameter.

H. Adverse Events, Vital Sign, Laboratory and ECG Safety Parameter Results.

This subsection focuses on events that may shed further light on the observation of ADOs that are previously described in which a greater incidence of ADOs in ODT compared to tablet treated conditions was observed in the PK trials that occurred near Tmax and involved dizziness, sometimes syncope and decreased blood pressure in addition to the more common AE of nausea (±vomiting).

Upon examination of the incidence of AEs in the one pivotal study that compared the ODT to the Celexa™ formulations, Study 2730 the following common AEs (≥5% incidence in a given group) showed numerical differences between the ODT and Celexa™ treatment conditions:

- Decrease blood pressure (as described in more detail later),
- Fatigue,

- Headache,
- Decreased appetite,
- Asthenia,
- Nervousness (the incidence within a given treatment condition ranged from 0% to approximately 9%).

Table 18 in the ISS is the source of these comparisons.

Section IX of this review also provides recommendations for labeling that include a description of the above observations and the incidence in each treatment condition.

Adverse Events Related to a Safety Parameter The results and reviewer comments and conclusions described in this section are on the basis of results of summary tables in the ISS on the following: AEs related to a given clinical safety parameter and summary tables of outliers on a given laboratory or vital sign parameter (of the PK studies, combined).

In general, the results on AEs related to a clinical safety parameter and results of clinical safety parameters (vital sign, routine laboratory and ECG parameters) in the PK trials, combined, did not reveal any remarkable, new, unexpected findings except for AEs of decreased blood pressure, as described in more detail in the following paragraphs.

AEs of decreased blood pressure were reported in some subjects of which a few of them withdrew from the study due to syncope or LOC (see previous subsection on ADOs).

The incidence of AEs of decreased blood pressure was greater after ODT treatment than after Celexa™ tablet treatment and occurred in Period I in the majority of ODT treated subjects as follows. The incidence of the AE of decreased blood pressure in subjects after ODT treatment was 7.1% (11/155 subjects in the PK studies, combined) compared to 2% of subjects treated with Celexa™ (1/50 subjects). Most of these events were reported in subjects who received ODT in Period 1 in contrast to subjects receiving the ODT in Period 2 of the crossover study design.

See the subsection below regarding the incidence of subjects with vital sign values of “Potential Clinical Significance.”

Results of Vital Sign and ECG Parameters. Vital sign and ECG results of the combined studies and in each of the 4 “definitive” studies are difficult to interpret given the timing relative to treatment in which these assessments were conducted. ECG assessments were conducted at screening, 24 hours post-dose and repeated, as necessary and at post study in the 4 “Definitive” PK studies (Studies –N11F1).

ECG Results. Results of ECG assessments are difficult to interpret given that assessments were conducted at 24 hours post-dose). Nevertheless the ISS does not describe any remarkable ECG findings. Upon further inquiry the sponsor provided additional information on ECG results (in a 10/110/04 submission). *The results were generally unremarkable. Some abnormal ECG findings were reported, but are commonly observed in the general population (e.g. bradycardia,*

borderline first degree AV block, among others) and these results were observed at time-points that were generally days after drug treatment.

Vital Sign Results.

Only one study included scheduled vital sign assessments near Tmax (which was a small pilot study), while the 4 “definitive” studies generally conducted assessments at post-study. None of the studies included orthostatic measures. These studies involved multiple blood sampling for PK analyses in which subjects are generally sitting or supine and confined to the study unit.

Only 1 subject with normal vital signs at baseline had vital sign values of “Potential Clinical Importance” of decreased blood pressure post-dose (diastolic BP of 48 and 47 mm Hg at 2 hours and 8 hours post-dose, systolic BP and heart rate were within normal limits; as shown in Table 37 listing subjects with vital sign values of “Potential Clinical Importance” in the ISS). Two other subjects were identified as having low blood pressure (listed in Table 37) but also had low values at baseline.

According to Table 32 in the ISS, Study 26022 (of the ODT prototype) was the only study that included vital sign parameters near Tmax. Table 36 lists subjects with the AE of decreased blood pressure in which the results were previously described. One notable observation is that none of these subjects listed in this table were in Study 26022 (Table 36 is a summary table of vital sign-related AEs in the ISS section of the submission, found on page 57-8, Item 8H).

The following are reviewer comments on vital sign results found in the study report of Study 26022 and the following observations are based on numerical comparisons (shown in Table 14.3.3.2 found in a table located in one of the appendices of the study report for this pilot study).

Mean decreases in systolic (mild decreases), diastolic (moderate decreases) and heart rate (generally mild decreases) from baseline to post-dose time-points were observed in all 3 treatment conditions of Study 26022 (fasted and fed 40 mg ODT conditions and 40 mg Celexa™ tablet in fasted condition). The greatest mean decreases of each vital sign parameter generally occurred at the first two post-dose time-points (1.75 hours and 3.75 hours post-dose), with less of a decrease or no decrease that was generally observed at the next post-dose time-point of 7.75 hours, while little to no decreases were observed at the next and final post-dose time-point of 11.75 hours.

While decreased blood pressure and heart rate changes in Study 26022 were observed near Tmax and were likely to be at least in part, drug related, numerical comparisons between the treatment conditions (fasted or fed ODT and the tablet treatment conditions) on descriptive statistical results of vital sign parameters failed to show consistent treatment group differences.

A key caveat to the above results of Study 26022 are inconclusive with respect to PK of ODT versus Celexa™ given that Study 26022 only used a prototype ODT formulation (the study report indicates the prototype and Celexa™ were bioequivalent). The sponsor did not compare this prototype to the to-be-marketed ODT in any study. Refer to the final section of this review regarding PK-PD relationships with respect to potential safety signals described in this review.

I. Overdose Experience

A case report of an overdose of 3000 mg of citalopram HBr is reported (Kelly et al., 2003) in the submission in which the subject developed acute renal failure and adult respiratory distress syndrome (ARDS).

J. Safety Results from Other Sources

The submission includes a summary of the literature on citalopram in which the safety profile is generally similar to that described in current approved labeling with a few minor exceptions that appear to be isolated and are not clinically serious observations (transient clitoral priapism reported in one study, Berk, 1997 and “phasic craving” for carbohydrates, reported in another study, Bouwer, 1996).

Post Marketing Reports: The ODT formulation of SCT has not been marketed in any country (see Section IV.C above for details).

K. Reviewer Conclusions on Safety Results.

The ODT formulation is adequately safe from a clinical perspective and the safety profile is generally similar to that of the tablet formulation, with potential exceptions as discussed in this review.

No SAEs were reported in any of the trials. However, the following potentially unexpected observations were revealed upon review of ADOs, AEs and relevant clinical parameters. Subjects experienced decreased blood pressure and some withdrew due to events of syncope, and other potentially related events. The ADOs of syncope or LOC were transient (lasting for up to 5 seconds) and were generally associated with vasovagal-like signs and symptoms (e.g. pallor, sweating, tremor, nausea) during multiple blood sampling procedures (and sometimes after a 10 hour fast), as previously discussed. Some of the ADOs of syncope, LOC and/or nausea, vomiting were associated with decreased blood pressure, which can also occur as part of a vasovagal response.

While the role of the study drug is likely regarding these safety findings of ADOs and observed changes in blood pressure and heart rate near Tmax, the magnitude of the potential effect may be overestimated (in the absence of placebo comparison group, while considering the study population, the study conditions and study design employed, as summarized later).

The following summarizes observed safety findings in the Phase I trial in which a contributory role of the study drug is considered.

A Potentially Greater Effect of ODT Compared to Celexa™ on ADOs and Related AEs and Vital Sign Parameters. The overall incidence of ADOs (included nausea and/or vomiting and/or dizziness and/or syncope/loss of consciousness) was greater after ODT than after Celexa.™ However, the incidence of syncope and LOC was similar after ODT treatment compared to the incidence after Celexa.™

AEs of decreased blood pressure were reported with a numerically greater incidence in subjects following ODT compared to Celexa™. Mean decreases in blood pressure and heart rate were observed in the one trial that conducted vital sign measures near Tmax as part of the protocol schedule (Study 26022) that was observed in both a prototype ODT formulation (in fasted and fed conditions) and after Celexa™.

Caveats in the Interpretation of ODT versus Celexa™ Safety Findings

The relative incidence of events in ODT compared to Celexa™ treatment conditions may be confounded by the crossover study design and whether or not a given trial was balanced with respect to ODT and Celexa™ treatment conditions, that may result in relative overestimation in the incidence of events in the ODT condition compared to the Celexa™ condition. Among the 2 bioequivalent trials that used Celexa™, only one used a balance design (one Celexa™ and one ODT condition for all subjects) and used ODT, rather than the prototype ODT used in the other bioequivalent study, pilot Study 26022. This later study had 2 ODT treatment conditions and one Celexa™ treatment condition for each subject. All other trials had multiple ODT conditions.

The following describes key safety observations with respect to subjects in the definitive bioequivalent study, Study 2730, since this study was the only study comparing the two formulations and employed a balanced study design with respect to the formulations. Upon further examination of the ADOs occurring at ≤4 hours (listed in the submission for all trials), none of the ODT treated ADOs occurred in Study 2730. Yet, the sole Celexa™ treated ADO occurred in a subject in Study 2730. The incidence of AEs of dizziness, LOC were similar in ODT and Celexa™ treatment conditions in the study, while the incidence of decreased blood pressure (as an AE) in the ODT condition was almost twice that of the incidence with Celexa™ (7% and 4%, respectively in Study 2730). These observations are considered preliminary with respect to relative incident of these findings between ODT and Celexa™ treatment.¹

The following are additional common AEs (≤5% incidence in a given treatment condition) showing treatment condition differences (based on numerical comparison) in the incidence of the given AE in the definitive balanced cross-over Study 2730: fatigue, headache, decreased appetite, asthenia, and nervousness (the incidence within a given treatment condition ranged from 0% to approximately 9%). Table 18 in the ISS is the source of these comparisons.

Additional Key Caveats to Interpreting Safety Findings

Additional key caveats regarding safety findings in the PK trials are listed below, of which some caveats are discussed in more detail in paragraphs that follow (others were previously addressed):

- The dose level of the studies which was twice the recommended starting dose.

¹ When examining summary tables (Tables 17 and 18 on pages 37-39 of the ISS electronic section) on the incidence of AEs in the 2 bioequivalence studies, combined (Studies 26022 and 2730, Period 1) or in the one definitive ODT Study 2730, the incidence of dizziness is generally similar between the ODT and Celexa™ treatment conditions (18% and 16%, respectively in Study 2730 and 13% and 13% in the 2 studies, combined). LOC only occurred in 1 out of 24 Celexa™ subjects in the studies combined and in 1/32 Celexa™ subjects in Study 2730 and in none of the ODT subjects in these trials (approximately 30 subjects for each ODT dataset, described).

- Fasted versus fed conditions or other PK-related confounds. At the time of this writing, Dr. Wu cannot provided a clear explanation for observed treatment condition differences (between ODT and tablet) on the safety findings (based on communications with Dr. TC Wu of OCPB on 12/7/04 and on 12/9/04 as understood by the undersigned).
- No placebo control group in the trials.
- Vital Sign measures were only scheduled near Tmax in an ODT prototype study and not in other trials using the ODT formulation.
- That only one of two studies that included Celexa™ treatment for comparison used the proposed to-be-marketed ODT formulation (Study 2730).
- The study population and factors associated with the Phase I study conditions were likely confound the results (multiple blood sampling, sometimes fasting conditions, generally less active than outpatients, the study population, among others).
- Potential order effect: a potential order effect on the incidence of AEs of decreased blood pressure is described that suggests a potential order effects.
- Limitations in extrapolating findings from a Phase I study population to the MDD patient population.

Dr. T Wu, OCPB was consulted regarding key safety findings in the trials with respect to potential PK differences between the formulations in the trials and he was unable to find a clear explanation for a potentially greater adverse effect of ODT compared to Celexa™ near Tmax, as described in this review.

Safety conclusions relevant to currently approved versus proposed labeling and recommendations are covered in the final section of this review.

VIII. Dosing, Regimen and Administration Issues

No new changes are proposed by the sponsor pertaining to dosing and the regimen for the ODT formulation.

IX. Use in Special Populations

No new information is provided for special populations and the sponsor does not propose any labeling changes regarding treatment in special populations.

X. Conclusions and Recommendations

A. Reviewer Conclusions

From a clinical perspective, it is recommended that NDA 21-763 be granted approvable status (as long as there are no non-clinical issues that cannot be resolved) for reasons that follow.

Pending confirmation by OCPB, bioequivalence was demonstrated between the ODT and tablet formulations at the 40 mg dose-level. From a clinical perspective the ODT formulation is adequately safe for the MDD population at the recommended treatment regimen (the sponsor does not propose changing the treatment recommendations from that of approved Celexa™ tablets).

Dr. Ta-Chen Wu notes that the sponsor is requesting approval of a 20 mg ODT tablet, yet PK trials only used the 40 mg dose-level and *in vitro* dissolution studies are not adequate in his opinion to support the 20 mg ODT tablet (based on the understanding of the undersigned). From a clinical perspective it is important to have a 20 mg ODT tablet available if the NDA is approved, since 20 mg is the recommended starting dose-level. Therefore, it is recommended that OCPB issues be resolved before granting a final approval action on this NDA. Refer to Section II for more details and of possible new data that the sponsor plans to submit under the NDA (and may be submitted by the DFS date of this review, which is near or on the reviewer due date in accordance to the Division policy of internal required due dates).

From a clinical perspective, the safety results of the PK studies described in the NDA, together with safety results of the MDD trials, as described in current labeling for the tablet formulation, provide evidence that the ODT formulation is adequately safe for the generally healthy MDD population at the recommended dose in proposed labeling.

This review describes ADOs of syncope and LOC and a greater incidence of ADOs at ≤ 4 hours (of dizziness \pm nausea \pm vomiting and in a few subjects also LOC or syncope and/or decreased blood pressure) in ODT treatment conditions compared to CelexaTM treatment in the integrated safety from the 5 PK cross-over trials (of which 2 used the CelexaTM treatment). A greater incidence of decreased blood pressure reported as AEs, after ODT treatment than after CelexaTM treatment was also observed. ODT versus CelexaTM treatment differences on the incidence of common AEs such as fatigue, asthenia and others, in addition to decreased blood pressure were observed in the sole definitive bioequivalent Study 2730, as previously discussed in Section VII, K (also see labeling recommendations below with respect to these results). Finally, in the only study that conducted scheduled vital sign assessments near T_{max} (Study 20622) a mean and median decrease in blood pressure and heart rate was observed. These effects were generally similar between the prototype ODT and CelexaTM formulation treatment conditions in this study. Key caveats to interpreting these results and a more completed discussion of conclusions is provided in Section VII, K. Given the key caveats to interpreting these results, the safety findings are not considered definitive, yet a role of the study drug is considered by this reviewer as probable, primarily because of the temporal relationship of events with treatment and that some associated AEs are known to occur with citalopram and/or escitalopram (the enantiomer that was approved as LexaproTM in which decreased heart rate was also observed, among other AEs). A discussion of current labeling compared to the proposed labeling on key safety findings appears in the next subsection.

B. Reviewer Recommendations

From a clinical perspective, it is recommended that this NDA be granted an approvable action.

The following outlines issues that should be resolved, as recommended by the undersigned, before a final approval action were considered for the NDA:

- Resolve outstanding OCPB, CMC and Pharmacology Toxicology issues (to the knowledge of the undersigned, there are no major CMC or Pharmacology Toxicology issues at the time of this writing, as understood by the undersigned).

- In light of several subjects who experienced syncopal episodes and others experiencing a similar AE cluster (aside from syncope, dizziness, nausea, tremor, among others) within 4 hours post-dose, the role of the study must be considered, at least as playing a contributory role (e.g. exacerbated cardiovascular changes associated with a vasovagal response or other risk factors associated with blood sampling). These events occurred near Tmax and were associated with concomitant adverse events that are similar to those known to be associated with Celexa™ and Lexapro™ (nausea, dizziness, tremor, sweating, among others) that include subjects in Phase III trials and were not likely to be undergoing phlebotomy. Therefore, the sponsor should agree to include in their Phase III and IV trials conducted under their SCT and citalopram INDs and NDAs the following safety monitoring:
 - Clinically evaluate any subject with any of the following signs or symptoms during treatment to investigate the etiology (include diagnostic tests if a clear etiology cannot be found). Any subject with syncope or near syncope should undergo this careful evaluation. Any subject with dizziness associated with any of the following events: nausea and/or tremor and/or flushing (or related event, such as feeling cold or feeling hot). Future development plans (e.g. for a new indication, for a new formulation) should include this type of safety monitoring and plans to further elucidate a potential safety signal near Tmax. The potential for development of syncope in subjects with risk factors who receive escitalopram or citalopram treatment in any trials (Phase I-III) and in postmarketing experience should also be examined.
 - Also consider conducting the following study which could potentially provide more definitive findings that could guide methods to be employed in future Phase I-IV trials with respect to the above safety concerns. The sponsor could conduct a parallel group, placebo controlled trial, dose ranging, study (20 mg, 40mg and 60 mg) of adequate size in healthy adults (the typical Phase I study population) to determine if the safety findings of the previous ODT Phase I trials are reproducible with a placebo comparison group. Such a study should include frequent vital sign measures (to capture Tmax in a given individual) and ECG assessments. The study should use limited phlebotomy to avoid inducing vasovagal responses near Tmax. However, blood sampling for pharmacokinetic analysis should be conducted in subjects with adverse events of dizziness, and/or nausea and/or syncope (for levels of parent compound and metabolites). Consideration should be given to including telemetry, since this measure may be more sensitive in detecting heart rate changes and ruling out arrhythmia. However, the potential association of syncope and dizziness with a drug related arrhythmia in the ODT trials is considered unlikely, since the adverse dropouts and associated adverse events were more suggestive of other etiologies and confounding factors (in which subjects had vasovagal like AEs), with a potential contributory role of the study drug that requires further consideration. While decreased blood pressure and heart rate were observed, as previously described, palpitations or arrhythmias were not reported among the ADOs (refer to the safety sections of this review for details).
 - See labeling recommendations, relevant to this safety concern below.
- The sponsor is planning to submit a study report of a new Phase I ODT study, Study BO4-688PK (2914) according to a recent e-mail connection. This study used the 20 mg

ODT dose level compared to a 2XODT study. A synopsis was sent by e-mail by the sponsor on approximately mid-December of 2004 (near the internal reviewer due date for entering this review into DFS). A preliminary examination of the synopsis regarding safety observations revealed at least one subject with emesis, twice, near Tmax (at 5 hours post-dose), that may be similar to ADOs observed in the other ODT trials described in this review. This study will need to be reviewed, from a clinical perspective given the above safety concerns. The study report is intended to provide more PK support for OCPB review. (submitted upon their request). Therefore, an OCPB review is anticipated and recommended. Any issues that arise from these reviews will need to be resolved, before granting a final approval to the NDA.

- Labeling recommendations (provided from a clinical perspective) under Section C, below should be addressed.

C. Labeling With Respect to Safety Findings

Current approved Celexa™ labeling and proposed labeling in the current submission already includes dizziness and nausea as AEs among ADOs of controlled trials. In the opinion of this reviewer, these type of events (nausea and dizziness) observed in the controlled outpatient Phase III trials would likely be exacerbated by conditions of the Phase I trials (multiple blood draws, overnight fasting, likely to be less active than outpatients in Phase III trials, among other factors associated with Phase I trial conditions and the study population). Furthermore, vasovagal reactions to blood sampling is not uncommon in drug free subjects, although the Phase I trials did not include a placebo group for comparison. Decreased heart rate is also described in current labeling. The “Other Events Observed During the Premarketing Evaluation of Citalopram HBr” includes vital sign related events such as hypotension as a frequent cardiovascular event and bradycardia as an infrequent event. Syncope is listed as an infrequent event under the General category of events in this section of approved labeling. For these reasons and those previously provided, the safety findings of the ODT trials do not provide adequate evidence that is considered a remarkable change in the overall safety profile of citalopram that would be considered non-approvable issues (in the opinion of this reviewer). However, given the greater overall incidence of ADOs in the Phase I trials after ODT compared to Celexa™ treatment and other potential differences, recommendations for labeling are provided below to incorporate key findings in the ODT trials. Furthermore, the ADOs, AEs of decreased blood pressure and mean decreases in blood pressure and heart rate are observed near Tmax (see below labeling recommendations describing these results in recommended language for labeling).

With the addition of clinical information in labeling as recommended in the next bolded subsection, clinicians may be better informed so that good clinical practices may be exercised (e.g. as part of good clinical practice clinicians would monitor potentially higher risk subjects for these type of events).

Key Labeling Recommendations before Granting a Final Approval Action:

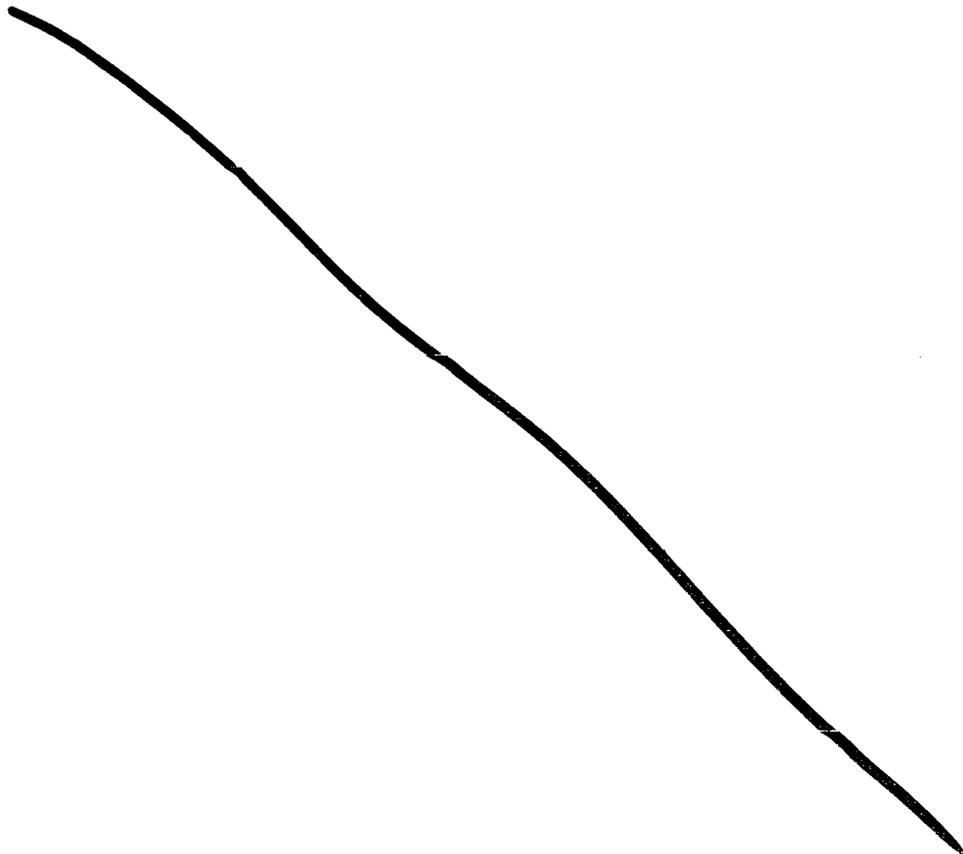
1. The “Overdosage” section should be updated to include a description of the subject described in the current submission and in this review under Section VII L in which the overdose involved 3000 mg citalopram HBr and acute renal failure and ARDS.

1 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process



3. Any section of labeling describing efficacy or safety related information should clearly specify whether or not the Celexa™ tablet was used or if the ODT formulation was used.

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODEI DNDP HFD 120

cc: IND
HFD 120/HFD 120/K Brugge/P David/P Andreason/T Laughren/T Wu/L Soldatavo/L
Fossom

¹ Data sources: Listings of AEs of decreased blood pressure and vital sign outliers in Section 10.3 starting on page 57 of the electronic ISS section. Descriptive statistical vital sign results from Study 26022 (the only study with assessments near Tmax) are in Table 14.3.3.2 in an appendix to the electronic study report.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Karen Brugge
12/21/04 06:43:07 PM
MEDICAL OFFICER

Paul Andreason
1/19/05 12:02:00 PM
MEDICAL OFFICER

I agree that the application is approvable. Please see
memo to file.