CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-365

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	21-365
Sponsor:	Forest Laboratories, Inc.
Drug	
Established Name:	Escitalopram oxalate
Chemical Name:	(+)-1-(3-dimethylaminopropyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Code Name:	Lu 26-054
Formulation:	5 mg/5 ml (240 ml) oral solution
Indication:	Major Depressive Disorder
Dates of Submission:	Received: November 6, 2001
Materials Reviewed:	Original NDA 21-365 Study SCT-PK06 Oral solution bioequivalence study comparing single oral doses (20 mg) of the oral solution (5 mg/ml) to the tablet formulation of escitalopram on PK parameters in 18 male and female healthy young adults
Clinical Reviewer:	Karen L. Brugge, M.D.
Review Completion Date:	5/9/02

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.

Background. Escitalopram (SCT) is the S-enantiomer of citalopram, a selective serotonin reuptake inhibitor (SSRI). Citalopram is currently marketed under the brand name of Celexa™ for Major Depressive disorder (MDD). MDD is the indication to which the sponsor is seeking approval of SCT in the tablet formulation under NDA 21-323, which currently has approvable status. The sponsor is now seeking approval for a new formulation (a 1mg/ml oral solution) of SCT under the current submission (NDA 21-365). The proposed claim is that the oral solution is bioequivalent to the tablet formulation based on results of a pharmacokinetic (PK) study, PK-06.

Summary of Study PK-06: A Bioequivalence Study Comparing Single 20 mg Doses of the Oral Solution to the Tablet Formulation of Escitalopram on Pharmacokinetic Parameters

This single center study involved 18 male and female young adults (all subjects completed the study) comparing single doses of 20 mg of oral solution (5 mg/ml) and tablet formulations of SCT on PK parameters using a two-way, randomized crossover design. Safety assessments were also included in the study. PK parameters examined in this study included Tmax, T1/2, Cmax, AUC, and clearance, among others. The sponsor reports no statistically significant differences between the two formulations on each PK parameter of the parent compound and of a major metabolite (S-desmethylcitalopram). No serious adverse events or adverse dropouts occurred. Safety results failed to reveal any remarkable safety findings that were not previously observed in trials involving the tablet formulation (refer to Clinical reviews of NDAs 21-323 and 21-440 for details). However, the administration of the oral solution was associated with a numerically higher incidence rate of Ss reporting either nausea or vomiting (61% and 17%, respectively) than that reported by the same Ss after receiving the tablet formulation (44% and 6%, respectively).

Overall Conclusion. From a clinical perspective, Study PK-06 provides adequate evidence supporting the sponsor's claim for bioequivalence of the oral solution formulation compared to the tablet formulation at the [redacted] (which currently has approvable status). Given this conclusion and the safety results of Study PK-06, together with safety results of the MDD trials submitted under NDA 21-323, the oral solution is adequately safe for the generally healthy MDD population at the recommended dose. Refer to this review and previous Clinical reviews of NDAs 21-323 and 21-440 for additional comments pertaining to the safety of SCT. From a clinical perspective, it is recommended that NDA 21-365 be granted an approvable status. This recommendation is contingent on the final approval of NDA 21-323.

One safety observation that is pertinent to labeling recommendations for the oral solution is regarding the incidence rates of nausea and vomiting were each numerically higher after a 20 mg dose of the oral solution than that observed following the same dose of the tablet formulation. It is recommended that this observation be described under the Adverse Reactions section of proposed labeling. It is noted that the concentration of the oral solution employed in the study was higher (5mg/ml) than that described in proposed labeling (5mg/5ml). Perhaps a lower incidence of nausea and vomiting may occur with this lower concentration of the oral solution proposed for labeling. However, without further investigation one cannot make this inference.

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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.

A. Indication and Proposed Direction of Use

Escitalopram (SCT) is the S-enantiomer of citalopram (the racemate), a selective reuptake serotonin inhibitor (SSRI). Citalopram is currently marketed under the brand name of Celexa™ for Major Depressive disorder (MDD). MDD is the indication to which the sponsor is seeking approval of SCT in the tablet formulation under NDA 21-323, which currently has approvable status. The sponsor is now seeking approval for a new formulation (a 1mg/ml oral solution) of SCT under the current submission (NDA 21-365). The proposed claim is that the oral solution is bioequivalent to the tablet formulation based on results of a pharmacokinetic (PK) study, PK-06.

The proposed recommended direction for use of the tablet formulation (as submitted under NDA 21-323) is a starting dose of 10 mg administered daily, in the morning or evening, to be given with or without food. It is also recommended (in the sponsor's submitted version of labeling) that after one week on the 10 mg daily dose that patients failing to respond may benefit from an increase in the daily dose to 20 mg.

B. State of Armamentarium for Indication

Classes of pharmacological drug products or specific drug products (generic names) currently approved for treatment of MDD include the following, of which some drug products also are available as an oral solution, as well as in capsule or tablet formulations:

- A number of SSRIs
- Tricyclics, historically referred to as Tricyclic antidepressant agents (such as imipramine and others)
- Monoamine Oxidase Inhibitors
- Serotonin and Norepinephrine reuptake inhibitors
- Serotonin 2 antagonists and serotonin reuptake inhibitors (Trazodone and Nefazadone)
- Bupropion, which appears to be a weak blocker of the neuronal uptake of serotonin and norepinephrine, as well as having some inhibitory effect on reuptake of dopamine.

C. Administrative History

As previously mentioned, NDA 21-323 has approvable status at this time (the tablet formulation of SCT for the MDD indication). A longer term efficacy claim ("relapse prevention") is proposed for the tablet formulation of SCT under NDA 21-440, which is currently under review. Also refer to the next section regarding NDAs for Celexa™.

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 bioequivalence study (Study PK-06) comparing the oral solution of SCT to the tablet formulation on PK parameters after a single 20 mg oral dose.

The Clinical Pharmacology, Biopharmaceutical Reviewer has no key issues at this time (the review is pending at this time). The sponsor is requesting the market of a 5 mg/5 ml (1 mg/ml) SCT oral solution (per proposed labeling). However, the sponsor employed a different concentration of the oral solution in Study PK-06 (5 mg/ml). Yet the total dose of 20 mg was employed in Study PK-06, coinciding with the maximum recommended dose in proposed labeling. A difference in concentration between that used in this study and that proposed in labeling is not an issue from a biopharmaceutical perspective (per communication with Dr. Mahmood Iftekhar).

The submission has chemistry information, which is under review by the Chemistry Reviewer. At this time there are no major chemistry issues (refer to the Chemistry Review, which is presently pending). There is no new preclinical information to be reviewed in NDA 21-365 (the sponsor cross-references NDA 21-323 for preclinical information, refer to the corresponding Pharmacology Toxicology review).

III. Human Pharmacokinetics and Pharmacodynamics

A. Human Pharmacokinetics

The PK results of Study PK-06 are summarized in Section VI of this review (also refer to reviews of the tablet formulation under NDA 21-323).

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
March 23, 2001	• NDA 21-365, Hard copy clinical volumes 1-13 regarding a bioequivalent study (PK-06), chemistry information and proposed labeling. Since there were no serious adverse dropouts or adverse dropouts, Case Report Tabulations or Case Report Forms were not submitted. • The sponsor cross-references Sections 5, 8, 10-12 of NDA 21-323 (SCT tablet formulation for Major depressive disorder) for other pertinent clinical and preclinical information. • 120-Day Safety Update 2/28/02 N-SU submission, which is a duplicate of the 120-Day Safety Update of NDA 21-323 (SCT tablets). This material was previously reviewed under NDA 21-323 and is not described in this current review of NDA 21-365.

B. Tables Listing the Clinical Trials

Table IV.B.1. Clinical Studies Reviewed from this Submission					
Protocol No	**Study Design**	**Treatment**	**N of Randomized Subjects**	**N (Completers) per Treatment group**	**N (ITT Safety Pop.) * per Treatment group**
SCT-PK-06 Single Dose Bioequivalence Study	Single Center, Single dose, Open Label, Randomized, Two-way Crossover Bioequivalence Study comparing oral solution to the tablet formulation of 20 mg of Escitalopram	Single dose of 20 mg of oral solution or 20 mg tablet formulation	18 (9 female, 9 male)	18	18

* ITT Safety Population: randomized subjects having at least one dose of double blind study drug.

C. Post-Marketing Experience
According to the sponsor, SCT is not being marketed. H. Lundbeck A/S in Sweden submitted an application for marketing of SCT, in which the outcome of this submission is still pending.

D. Literature Review
A literature review was not conducted since this is a bioequivalence NDA application. A literature search on this drug was conducted under NDA 21-323 (in which the sponsor makes their efficacy claim of the tablet formulation) and under NDA 21-440 (a longterm efficacy submission of the tablet formulation).

V. Clinical Review Methods
A. Materials Reviewed.
Section IV, above, describes materials utilized for this review and summarizes the clinical trial (Study PK-06) described in this submission.

B. Adequacy of Clinical Experience.
Study PK-06 is a bioequivalence study involving 18 male and female young adults comparing single doses of 20 mg of oral solution and tablet formulations of SCT using a two-way, randomized crossover design. All 18 subjects completed the trial. Clinical data described in the present submission appears to be adequate to review from a clinical perspective, together with results of clinical trials of the tablet formulation of SCT (NDAs 21-323 and 21-440) and results of clinical trials as described in labeling for Celexa® (tablet and oral solution formulations).

C. Data Quality and Completeness
Refer to the corresponding section of the Clinical Review of NDA 21-323 describing various comparisons made between listings, tables, Case Report Forms (CRFs), and/or narratives which generally appeared to show adequate accuracy, consistency and content of information. Since there were no serious adverse events, deaths or adverse dropouts in Study PK-06 there were no CRFs or narratives provided in the present submission (NDA 21-365). However, a few comparisons were made between information provided in the text of the Study report and the tables in the appendices.[1] On the basis of these observations, the quality and completeness of the data described in the submission appears to be adequate.

D. Evaluation of Financial Disclosure
The principal investigator and two other investigators are listed on Form FDA 3454 as having no disclosable financial arrangements.

[1] Each item below describes various comparisons made between the Study Report text for Study PK-06 and tables or listings in the appendices of the NDA submission:

- A comparison between the description of S003 (an outlier on blood pressure) and the line listings for this subject in the appendices (adverse event and blood pressure line listings) were consistent with the information provided in Section 8.5 in the study report.
- A comparison between that described for descriptive laboratory results in section 8.4 in the study report were generally similar to that shown in Table 4.3 in Appendix E.

VI. Integrated Review of the Bioequivalence Study Comparing Single 20 mg Doses the Oral Solution to the Tablet formulation of Escitalopram on PK Parameters

This section summarizes the study design, study population and PK results of Study PK-06. Safety results are described under Section VII.

Investigator and Study Site. The Principal Investigator and clinical site of the study:

Maria Gutierrez, MD
ICSL Clinical Studies-Fort Lauderdale-Inpatient
108 NE 1st St.
Fort Lauderdale, FL 33301

Summary of Study Design and Subjects. This is a single dose, open label, two-way crossover study. Subjects (Ss) were screened within 14 days of study entry. A total of 18 generally healthy Hispanic Ss (9 male and 9 female Ss between 18 and 35 years old) were randomized to receive a single oral dose (20 mg) of the SCT solution (5mg/ml) or the SCT tablet formulation on Day 1 of the study. On Day 15 they received a single dose of the alternative formulation. Dosing of open label SCT on Days 1 and 15 occurred in the fasted state (overnight fast) at 0800 hours.

Serial blood samples were collected at various time-points in the study for PK sampling. Blood laboratory measures and ECG assessments were conducted at baseline/screening, which occurred within 14 days prior to the first dosing (Day 1). Vital sign parameters (VSS) and adverse events assessments (Ss were asked "How do you feel?") were conducted on Days 1 and 15 at pre-dose (0 hours), 2 and 4 hours post-dose (prior to collection of the blood sample on corresponding time-points). Ss were required to be sitting for 5 minutes prior to obtaining VSS (blood pressure and pulse rate). Other potential confounding variables, such as diet, were controlled in the study. See the Study Flow Chart (Table VI.1.) in the appendix of this review (as provided by the sponsor).

Summary of PK Results and Conclusions. In summary the sponsor reports no statistically significant differences between the two formulations on each PK parameter of the parent compound and of a major metabolite (S-desmethylcitalopram). These PK parameters included Tmax, T1/2, Cmax, AUC, clearance and others. Based on these results the oral solution and tablet formulation appear to be bioequivalent at the 20 mg dose (refer to the Biopharmaceutical Review of this submission for details).

VII. Integrated Safety Information

A. Background Information

The previous section describes the study design, the safety assessments and assessment schedule time-points employed in Study PK-06. Safety results of this study are described in this section.

B. Demographic Characteristics

All Ss were Hispanic (9 female and 9 male) with demographic features summarized in the following table.

Summary of Demographic Features for 18 Subjects in Study PK-06*	
Demographic Feature	**Escitalopram Subjects (N=18)**
Mean±SD Age (years)	26.8±4.9
Age range (years)	18-35
Mean ± SD Height (cm)	168±9
Range of Height (cm)	158-185
Mean±SD Weight (kg)	68±12
Range of Weight (kg)	47-85
*This table is similar to Table 8.1 in the Study Report of the submission	

C. Extent of Exposure

All Ss completed the study and all Ss received a single dose (20 mg SCT) of each of the two formulations (the 10 mg of the 10mg/5ml oral solution and a 20 mg tablet) with each dose separated by 14 days.

D. Deaths

There were no deaths reported in Study PK-06.

E. Serious Adverse Events (SAEs)

There were no SAEs reported in Study PK-06.

F. Dropouts due to Adverse Events

No adverse dropouts were reported in Study PK-06.

G. Specific Search Strategies

No specific search strategies were conducted.

H. Adverse Events

The treatment emergent adverse event (AE) profiles of each formulation were generally similar with the most common AEs provided in the following table. The exceptions were nausea and vomiting of which each were reported in numerically higher percentages of Ss after receiving the oral solution than after administration of the tablet formulation.

Incidence (%) of Common Adverse Events (>2 subjects)* by Treatment Group in Study PK-06		
Common Adverse Event:*	**20 mg SCT** oral solution N=18**	**20 mg SCT** tablet N=18**
At least one Adverse Event	**78%**	**72%**
Nausea	61%	44%
Dizziness	22%	28%
Headache	17%	11%
Vomiting	17%	6%
Diarrhea	11%	17%
*Similar to Table 8.3 in the Study report of the submission. ** SCT=escitalopram		

I. Laboratory Findings

Laboratory measures were collected under fasting conditions at screening and at the end of the study (refer to Table VI.1, the Study Flow Chart, in the appendix). Study endpoint values were obtained within 7 days of Day 22 (Day 15 was the second single dose, also the last dose administered to Ss). The criteria employed for identifying outliers is provided in Table VII.I.1 in the appendix (as provided by the sponsor). The results of outliers and central tendency on laboratory parameters failed to reveal any clinically significant observations.

J. Vital Signs and Body Weight

Vital signs (pulse and blood pressure) were obtained at screening, and at 0, 2 and 4 hours post dose on each day of dosing (Days 1 and 15). Weight was also obtained. Incidence rates of outliers were examined (refer to Table VII.J.1 in the appendix for outlier criteria employed, as provided by the sponsor). Descriptive statistical measures were provided for screening, end of study and change from screening to the end of the study. Note that the end of study vital signs were obtained within 7 days of Day 22, in which Day 15 was when Ss received their second and last, single dose of SCT. Descriptive statistics were also provided for 2 and 4 hours post-dosing and change from 0 hours for each treatment condition.

The central tendency results of vital sign and weight parameters failed to reveal clinically significant findings except for a mean decrease in pulse rate with each formulation summarized in the table below.

Mean±SD Change (Range of Change) in Pulse Rate (bpm) from Pre-dose (0.0 hours) to Each Time Point Post Dose (Hours 2 and 4) for Each Treatment (20 mg Escitalopram given as Oral Solution or Tablet formulation) in Study PK-06		
Time Point Post-Dose	**Oral Solution N=18**	**Tablet Formulation N=18**
2 hours	-6.4±10.6 (-36 to 14)	-6.1±5.2 (-17 to 3)
4 hours	-7.9±4/9 (-17 to 2)	-7.2±7.9 (-27 to 6)
Source table is Table 3.5A in Appendix E of the Study report in the submission.		

Vital sign and weight parameter results on outliers were unremarkable. Despite the above observations on mean decrease in pulse rates, none of the Ss met outlier criteria for decreased pulse rate (≤50 bpm and a decrease of ≥ 15 bpm). None of the Ss were reported to have signs or symptoms of orthostatic hypotension. One S (#003) met outlier criteria for decreased systolic blood pressure to 90 mmHg at 2 hours post-dose on Day 1 that may have been related to drug-related nausea, as described in the following. This S had a blood pressure of 114 at screening and did not meet outlier criteria after dosing on Day 15. Upon inspection of the line listing of AEs for this S it was revealed that this S had nausea at approximately one hour post-dose on Day 1 as well as on Day 15 with a single episode of vomiting on Day 15. Nausea is one of the common AEs reported in SCT Ss and may have secondarily resulted in a slight decrease in blood pressure in S003.

K. Electrocardiographic Results

Electrocardiograms (ECGs, 12-lead) were obtained at screening and study endpoint, only (occurred within 7 days of Day 22, see Table VI.1. in the appendix, the Study Flow Chart). None of the Ss met outlier criteria for any of the ECG parameters (outlier criteria were as follows: QRS interval ≥150 msec, PR interval ≥250 msec and QTc interval >500 msec). Results

of central tendency on ECG parameters were unremarkable, as shown in the table below (note that study endpoint occurred on Day 22±7, while the last dose was scheduled on Day 15).

Mean Change (±SD) from Baseline to Study Endpoint* on ECG Parameters in All Subjects of Study PK-06	
ECG Parameter:	**All Subjects (N=18)**
Ventricular Heart Rate (bpm)	5.4±8
QRS Interval (msec)	0.7±3.8
PR Interval (msec)	1.7±9
QTc Interval (msec)	-0.6±15
*Endpoint occurred on Day 22±7days with last single dose day occurring on Day 15. Data source is Table 8.5 in the Study Report of the submission.	

A line listing of Ss by normal versus abnormal ECGs failed to show any Ss with normal ECGs at screening who had an abnormal ECG at study endpoint.

L. Overdose Experience

The sponsor does not provide any new information on overdose experience and cross-references NDA 21-323.

M. Safety Results from Other Sources

No new information is provided and NDA 21-323 is cross-referenced which described results of a literature search (refer to Clinical reviews under NDA 21-323 for details).

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

N. Conclusions on Safety Results.

Study PK-06 did not reveal any new safety findings from those previously observed in trials involving the tablet formulation (refer to Clinical reviews of NDAs 21-323 and 21-440 for details). The oral solution appears to be bioequivalent to the tablet formulation and consistent with this observation, the safety of the oral solution appeared to be comparable to that observed with the tablet formulation at the 20 mg dose level (including the safety profile of AEs).

It is noted that incidence rates of AEs were higher than that observed in controlled trials of MDD using the tablet formulation. Higher incidence rates are likely reflecting differences in study design between the MDD trials using the tablet formulation and Study PK-06. The PK study employed a study design typical for it's primary objective, which involved open label treatment, multiple blood sampling and had no placebo control group. The incidence rates of nausea and vomiting appeared to be numerically higher with the oral solution compared to the tablet formulation. These results are interpreted with caution, given the study design of Study PK-06. One S experiencing nausea (S#003) also had a decrease in blood pressure perhaps related to the nausea. In conclusion, the potential effect of oral solution compared to the tablet on the incidence of nausea and vomiting needs consideration regarding that described under the Adverse Reaction section of labeling for the oral solution formulation.

While there were no clinically significant results on laboratory and ECG parameters in Study PK-06, these clinical measures were obtained on Day 22±7 with the day of treatment on Day 15. Therefore, ECG and laboratory were not necessarily collected on the last day of treatment and could be collected as long as 2 weeks after treatment. Given the terminal half-life of SCT and its

major metabolite (27-32 hours and approximately 47 hours, respectively), the results on these clinical parameters may not be reflecting a potential effect of SCT in all Ss. Consequently, a potential SCT effect on a given parameter may be considered diluted by the use of data collected from Ss at a time-point that does not coincide with drug exposure. Hence, negative results for a drug effect on these parameters must be interpreted with caution. Despite this potential caveat, clinical results of previous trials using the tablet formulation (under NDA 21-323) add to establishing adequate safety of the oral solution since these formulations appear to be bioequivalent at the proposed recommended therapeutic dose. —

In contrast to time-points employed for the ECG and laboratory parameters, vital sign parameters were obtained at 2 and 4 hours post-dose, which approximates the observed mean Tmax of SCT and S-DCT plasma levels in these Ss (approximately 3.8 and 4.4 hours, respectively). A mean decrease of pulse rate (approximately 6 to 8 bpm) was observed with each formulation. A mean decrease in pulse rate was also observed in short term (8-week) trials in outpatients with MDD using a daily dose-range of 10 to 20 mg of SCT tablets (NDA 21-323) and in clinical trials using citalopram as described in the literature and in Celexa® labeling.

The magnitude of the mean decrease in pulse rate in study PK-06 is numerically greater than that observed in the Phase III efficacy trials of SCT or in clinical trials of citalopram. The observed mean decrease in pulse rate in SCT MDD trials was -1.9 bpm in SCT Ss, -2.4 in citalopram Ss, and –0.4 in placebo Ss (refer to the Clinical review of NDA 21-323). This is compared to a mean decrease of –6 to –8 in which results of the oral solution were similar to those of the tablet formulation in Study PK-06. A numerically greater decrease in heart rate observed in Study PK-06 may be reflecting the conditions of this PK study, in contrast to Phase III trials. Vital sign measures were conducted near Tmax in the PK study, patients were undergoing multiple blood sampling and likely to be resting and several Ss also had nausea and in some cases vomiting. The study design of Study PK-06 was that of an open label trial lacking a placebo group. Despite observations of a decrease in mean pulse rate, there were no SAEs or ADOs in Study PK-06 and none of the Ss met outlier criteria for decreased pulse rate. Consequently, these results on pulse rate are not considered clinically remarkable regarding the generally healthy non-elderly outpatient population. Previous Clinical reviews (NDA 21-323 and 21-440) of studies of SCT describe various cardiac findings including a small signal for QTc prolongation and cases of bradycardia and conduction defects, which are currently being reviewed by the Division Safety Group.

VIII. Dosing, Regimen and Administration Issues

No new changes are proposed pertaining to dosing and the regimen, since the sponsor concludes that the oral solution is bioequivalent to the tablet formulation (refer to Section IA above, for proposed treatment recommendations).

IX. Use in Special Populations

No new information is provided from Study PK-06 that pertains to special populations. The sponsor cross-references NDA 21-323 regarding a study (Study 99166) that was submitted on May 24, 2001. This study of the tablet formulation was summarized in the current NDA 21-365 submission and is reported to show a higher AUC and a higher Cmax in elderly women compared to elderly men, that was not observed in the young Ss. There was also an effect of age in which AUC values were higher in the elderly Ss compared to younger Ss. Refer to the

Biopharmaceutical review for details and recommendations (under NDA 21-323 and of the current NDA, which is pending at this time).

X. Conclusions and Recommendations

A. Conclusions

From a clinical perspective, Study PK-06 provides adequate evidence supporting the sponsor's claim for bioequivalence of the oral solution formulation compared to the tablet formulation at the 20 mg dose, which is the maximum recommended dose for MDD (the Pharmacology, Biopharmaceutical Reviewer who has no issues at this time, the review is pending at this time). Given this conclusion and the safety results of Study PK-06, together with safety results of the MDD trials submitted under NDA 21-323, the oral solution is adequately safe for the generally healthy MDD population at the recommended dose. The incidence of nausea and vomiting was numerically higher following administration of the oral solution than the incidence rates following administration of the tablet formulation. However, it is noted that the sponsor desires to market a less concentrated oral solution (1 mg/ml) than that employed in Study PK-06 (5 mg/ml) which may be associated with a smaller incidence rate of nausea and vomiting. However, without further investigation, this possibility can only be considered speculative. Refer to Clinical reviews of NDAs 21-323 and 21-440 for additional comments pertaining to the safety of SCT.

Study PK-06 revealed a mean decrease in pulse rate of approximately 6 to 8 that was observed at approximately Tmax for the parent compound and the major metabolite of SCT. A small decrease in heart rate was observed in clinical trials with the tablet formulation and was also reported with the racemate of SCT, citalopram, as described in Celexa® labeling (the section on ECG results). The Division Safety Group is currently reviewing cardiac results observed in short term and longer term MDD trials (under NDAs 21-323 and 21-440) that include a small signal for bradycardia, QTc prolongation and reports of conduction defects, (refer to previous Clinical reviews under these former NDA submissions).

B Recommendations

From a clinical perspective, it is recommended that NDA 21-365 be granted approvable status. It is recommended that issues pertaining to the cardiac results of SCT trials, including those of Study PK-06, be adequately resolved by the Safety Group prior to Approving this NDA, as was also the recommendation provided in clinical reviews of other NDAs on SCT (NDA 21-323 and NDA 21-440).

The following are some labeling recommendations pertaining specifically to the oral solution formulation, while not addressing cardiac related issues under review by the Safety Group. The sponsor indicates in proposed labeling (as provided in Section 3.1 of volume 1 of the submission on annotated labeling) that SCT is available as an oral solution (5 mg/5 ml) and that the oral solution and tablet formulations are bioequivalent. From a Clinical perspective these changes appear to be acceptable (refer to recommendations in Chemistry and Biopharmaceutical reviews of pertinent labeling sections which are pending at this time). However, one addition to the sponsor's proposed changes is recommended from a clinical perspective. It is recommended that labeling include the following subsection under the Adverse Reactions section of labeling where the incidence rates of adverse events reported in clinical

trials are described (i.e. after Table 1 and before the subsection on "Male and Female Sexual Dysfunction…"):

[ ]

Karen L. Brugge, M.D.
Medical Review Officer, DNDP
FDA CDER ODE1 DNDP HFD 120

cc: IND
HFD 120
HFD 120/
K Brugge
P David
T Laughren
J Raccoosin
D Gan

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/s/

Karen Brugge
5/9/02 10:36:59 AM
MEDICAL OFFICER

Thomas Laughren
7/21/02 01:06:05 PM
MEDICAL OFFICER
I agree that this NDA is approvable, once a final action is taken on NDA 21-323 for the — for the immediate release tablet for this drug.--TPL

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APPENDIX

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Table VI.1.

APPENDIX I: STUDY FLOW CHART

Period	Pre	Period I				Period II				Post
Study Day	Pre[1]	-1	1	2	3-8	14	15	16	17-22	22[5]
Informed Consent	X									
Medical History	X									
Physical Exam	X									X
Lab Evaluations	X									X
ECG	X									X
Pregnancy Test	X[2]	X[3]								X[3]
Admission to Clinic		X				X				
Dosing of Medication			X				X			
Vital Signs	X		X				X			X
PK Blood Samples			X	X	X		X	X	X	X
Adverse Event Assessment			X	X	X	X	X	X	X	X
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X
Discharge From Clinic				X[4]				X[4]		

1 = Must be done within 14 days prior to Day 1
2 = Serum pregnancy test
3 = Urine pregnancy test
4 = Discharge fro n clinic on Day 2 and 16 after 24 hour post-dose blood draw. Subjects seen as an outpatient on Days 3-8 and 17-22.
5 = Post-study evaluation must be done within 7 days of Day 22 or early termination.

Table VII. I.1. Criteria for Potentially Clinically Significant Laboratory Values

Laboratory Parameter	Units	PCS Criteria	
		Low Values	High Values
Hematology			
Hemoglobin	mmol/L	≤0.9 * LNL	—
Hematocrit	1.0	≤0.9 * LNL	—
Eosinophils	%	—	≥10
Neutrophils segs	%	≤15	—
Platelet Count	GI/L	≤75	≥700
WBC	GI/L	≤2.8	≥16
Chemistry			
Alkaline Phosphatase	U/L	—	≥3 * UNL
ALT (SGPT)	U/L	—	≥3 * UNL
AST (SGOT)	U/L	—	≥3 * UNL
LDH	U/L	—	≥3 * UNL
Blood Urea Nitrogen	mmol/L	—	≥10.7
Calcium	mmol/L	≤1.75	≥3.0
Cholesterol	mmol/L	—	≥7.8
Creatinine	μmol/L	—	≥175
Potassium	mmol/L	≤3	≥5.5
Sodium	mmol/L	≤125	≥155
Total Bilirubin	μmol/L	—	≥34.2
Urinalysis			
Protein		—	Increase of ≥2 or positive
Glucose		—	Increase of ≥2 or positive

LNL= Lower Normal Limit of Laboratory Reference Range
UNL= Upper Normal Limit of Laboratory Reference Range.

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Table VII.J.1. Criteria for Potentially Clinically Significant Vital Sign and Weight Parameters.

Variable	Criterion Value	Change Relative to Screening
Systolic Blood Pressure	≥ 180 mmHg	Increase of ≥ 20
	≤ 90 mmHg	Decrease of ≥ 20
Diastolic Blood Pressure	≥105 mmHg	Increase of ≥ 15
	≤ 50 mmHg	Decrease of ≥ 15
Pulse	≥ 120 bpm	Increase of ≥ 15
	≤ 50 bpm	Decrease of ≥ 15
Weight		Increase of ≥ 7%
		Decrease of ≥ 7%

A post-baseline value is regarded as a PCS value if it meets both the criterion value and the change relative to screening.

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