

Three of the 46 ADOs were due to a SAE and are described above under the SAE section. See the complete list of ADOs, as provided by the sponsor, in this appendix of this Addendum 1 Review. The ADOs were similar to those already described in the 10/19/01 review of this IND.

Selected Ss are described in the appendix, which include several Ss who were also described in the 10/19/01 review. These are events involving cardiac arrhythmias, syncope and a S with markedly elevated liver enzyme levels in which a role of SCT (some Ss also received citalopram prior to SCT) must be considered based on the information provided. These events include those also described in labeling for Celexa®. However, there is some discussion in the 10/19/01 review, regarding bradycardia and conduction defect in some Ss in the various clinical trials and related ECG and vital sign results. See the Executive Summary from the 10/19/01 review provided in the appendix of this Addendum 1 Review for a brief summary of this issue. In summary, the results of ADOs observed in Study MD-03 does not provide any new or unexpected findings from that already described in the 10/19/01 review of this NDA.

Treatment Emergent Adverse Events. A summary table was provided on page 141 in volume 1 of the amendment submission that showed the incidence rates of SCT Ss in completed depression trials, combined (MD-01, MD-02, MD-03, 99001 and 99003). Common AEs ($\geq 5\%$) in the SCT Ss for all completed depression trials are the same as those that are common in SCT Ss, as shown in Table 1 of proposed labeling, before inclusion of results of Study MD-03. The sponsor has added a few adverse events in the section of proposed labeling "Other Events Observed...". When comparing the summary table of cumulative incidence rates of AEs in SCT Ss, a number of AEs (such as bradycardia, elevated liver enzymes, among others) meeting the at least 1 in 1000 incidence criterion were excluded from the proposed labeling. It is not clear why these other AEs were excluded from the proposed labeling.

Conclusions and Recommendations.

In summary the results of serious adverse events, adverse dropouts in Study MD-03 as described above, show no new or unexpected events, not already observed and described in the NDA submission, the 120-Day Safety Update report and in the 10/19/01 Clinical Review of this NDA. More clinical information is being requested on Ss 1138 and 2299 (adverse dropouts, described in the appendix of this review) that may help to determine the etiology of the events in these Ss (abnormal ECG in S 1138 and syncope in S2299). Both events are listed under the "Other Events Observed..." section of the sponsor's proposed labeling provided in their amendment submission. The overall recommendation that this NDA be granted an approvable action, as provided in the 10/19/01 Clinical review, still remains as the recommendation from a clinical perspective for this NDA (pending confirmation of efficacy results of MD-01, MD-02, 99003 and 99001). It is also noted that examination of common AEs ($\geq 5\%$ in SCT Ss) the cumulative treatment emergent AE incidence summary table of 999 SCT exposed Ss from all completed depression trials (MD-01, MD-02, MD-03, 99001 and 99003, combined) revealed no new or unexpected common AEs.

The discussion below pertains to changes that the sponsor proposes in the Adverse Reactions section of labeling, based on the safety results of MD-03. This discussion also includes some recommendations regarding the sponsor's proposed labeling changes (refer to the 10/19/01 Clinical Review of this NDA regarding for other recommendations regarding this NDA).

The modification of the Adverse Reactions section of the sponsor's proposed labeling in this amendment submission (10/19/01 submission) shows the addition of the following AEs to AE listings under the "Other Events Observed..." section: hypertension, ECG abnormal,

flushing, varicose vein. Since this section includes Ss from MD-03, the total number of SCT exposed Ss described in this section was changed from 715 Ss to 999 Ss. This section of proposed labeling also specifies that Ss were exposed to periods of up to one year in double-blind or open-label trials during premarketing evaluation of SCT.

When comparing the summary table of cumulative incidence rates of AEs in SCT Ss (on page 141 of volume 1 of the submission, cited in the annotated proposed labeling), a number of AEs (such as bradycardia, elevated liver enzymes, among others) meeting the incidence rate criterion of at least 1 in 1000 were excluded from the proposed labeling. It is not clear why these other AEs were excluded. It is suggested that these events are included in the "Others Events Observed..." section, unless there is clear and reasonable rationale as to why the sponsor excluded these events. One event was the elevation liver enzyme levels. While only one S had this event, the elevation was markedly high (up to 3-6 fold) resulting in discontinuation of study drug. This S had normal levels preceding drug exposure and the elevated levels resolved upon cessation of study drug (see description of S2071). The narrative on this S does not describe any other information, such as alcohol abuse or underlying liver disease in this S. Therefore, it appears from the limited information on this S that this event may be drug-related. Consequently, it is recommended that while, this event appears to be an isolated event, this event (elevated liver enzymes) should be listed under the "Other Events Observed ..." section of labeling for SCT.

Karen L. Brugge, M.D.
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APPENDIX

- **A Copy of the Executive Summary section of the 10/19/01 (Completion Date) of the Clinical Review of this NDA**
- **A Listing of Serious Adverse Events in Study MD-03 (as provided by the sponsor)**
- **A Listing of Adverse Dropouts in Study MD-03 (as provided by the sponsor)**
- **A Description of Selected Adverse Dropouts in Study MD-03**

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EXECUTIVE SUMMARY OF THE CLINICAL REVIEW OF THE ORIGINAL SUBMISSION

This is the executive summary section of the Clinical Review of the original NDA submission and 120-Day Update Report. Note that references to "this review" made within the text of this summary pertain to the review (10/19/01 review completion date) of the original submission.

Background Background and Overview of Clinical Studies. 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), which is the indication to which the sponsor is seeking approval for SCT under the current NDA 21-323. The sponsor describes three positive, multicenter, placebo controlled, double-blind depression trials (SCT-MD-01, 99001 and 99003) in the submission and in labeling proposed in the 120 Day Update Report (dated 7/12/01). These studies employed a parallel group design that involved either flexible doses of 10-20 mg of SCT/day and 20-40 mg/day CT or fixed doses of 10 mg/day of SCT and in one study, an additional 20 mg/day SCT in each treatment group. A one-week single-blind placebo run-in phase was followed by an 8-week treatment phase in each study. A fourth flexible dose parallel group trial (10-20 mg/day SCT and 20-40 mg/day CT) of similar design is also described in the submission, but is not included in proposed labeling (Study MD-02).

Study Populations. A total of approximately 1300 randomized Ss were included in the three studies. The study populations were enriched in that subjects (Ss) underwent a placebo run-in phase, had to exceed cut-off scores on various standardized rating scales assessing MDD symptoms and were excluded if they were known to be resistance to treatment with SRRIs, as specified. The majority of Ss were female (approximately 67% of Ss) which is consistent with the known preponderance of women with MDD in the general population. Most Ss were Caucasian (approximately 91%) and non-elderly (mean age of approximately 40 years with approximately 94% under 65 years old). Treatment groups were generally similar on various demographic features and on efficacy measures in each of the studies. Exposure of subjects to SCT in the four studies (N=715) was approximately 51 days (58 patient years).

Primary Efficacy and Safety Results. Each of the three positive studies showed significantly greater improvement on the primary efficacy variable, the Montgomery Asberg Depression Rating Scale (MADRS) score (from baseline to treatment endpoint) in the SCT treatment group compared to placebo, at daily doses of 10 mg or 20 mg of SCT. Study MD-02 failed to show significant treatment group effects on the primary efficacy variable but SCT and CT groups showed small numerical trends in favor of efficacy, which was significant for the observed cases dataset. These findings suggest that MD-02 was a failed rather than a negative study. Significant group differences between the 10 mg/day and 20 mg/day SCT groups were not found on the primary efficacy measure in the fixed dose study MD-01. However, dose-dependent effects appeared to exist between these two groups on overall incidence of adverse events (AEs). At least trends for dose-dependent effects on some of the specific AE categories are described in the review.

The safety profile of SCT generally appears similar to that observed with CT. Vital sign and ECG data showed at least a trend for a decrease in mean heart rate and prolongation of the QT or QTc interval in the SCT group compared to placebo that also appeared to exist with CT. However, the magnitude of these trends was small, such that they do not appear to be clinically significant to the general population. In contrast to the general population, the cardiac results may be clinically relevant for patients at risk of bradycardia, conditions of conduction defect or

arrhythmia, including patients taking medications that decrease heart rate or prolong the QT interval. Other ECG changes, noted in the review, appear to be consistent with this conclusion. Other potential safety issues pertaining to SSRIs, as a class, are also discussed in the review. One issue is a possible association of abnormal bleeding or platelet function with SSRI treatment (as suggested by a recent BMJ 1999;319:1106-9 publication of a possible association with upper gastrointestinal bleeding). Another issue pertaining to SSRIs as a class, is the reported association of AEs with cessation of SSRI treatment (based on reports in the literature). These safety issues and others, along with some recommendations are discussed in the review.

Overall Conclusion. In conclusion, three (MD-01, 99001 and 99003) out of the four adequately controlled 8-week trials were positive for demonstrating efficacy of SCT in treating outpatients with MDD. For unclear reasons Study MD-02 failed to show significant treatment group effects, but the study did not appear to be a negative study. The clinical trials described by the sponsor demonstrate a benefit to risk ratio in favor of the use of SCT in treating patients with MDD. When considering the risk to benefit ratio of drugs for treating MDD, it is important to note that MDD can be life threatening and is a debilitating chronic disorder typically with a course of recurrent acute episodes over many years in a patient's life. From a Clinical perspective and pending confirmation of the efficacy results by Biometrics, it is recommended that this NDA be given an approvable status. Refer to the Clinical Review, for a complete and more detailed review of the clinical aspects of SCT, as revealed by studies described in this NDA and for some recommendations from a clinical perspective.

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Panel 15. List of Patients with Serious Adverse Events

Treatment/ Patient Number	Age (yrs)	Sex	SAE Start Day ^a	Preferred Term
OPEN-LABEL PHASE: ESCITALOPRAM TREATMENT				
1125	60	F	126	Breast Neoplasm
1306	26	F	15 15	Migraine* Paresthesia*
2172	33	F	12 15 15 16	Alcohol Abuse Depression* Suicide Attempt* Anxiety
2325	69	F	24	Bladder Carcinoma*
2374	53	M	46 46 46	Gastric Ulcer Syncope Inflicted Injury
DOUBLE-BLIND PHASE: PLACEBO TREATMENT				
2229	22	M	232	Pharyngitis ‡
DOUBLE-BLIND PHASE: ESCITALOPRAM TREATMENT				
1234	44	F	190 190	Abdominal Pain Appendicitis
2101	24	M	228	Tonsillitis
2307	44	F	70	Uterine Hemorrhage

a: SAE Start Day = SAE Start Date – Date of First Dose of Study Medication in Respective Phase + 1.

*Study drug discontinued because of this event.

Cross-reference: Table 7.1. Patient 1125 is not included in Table 7.1, as the SAE was reported approximately 2 months after the last dose of study medication, and is not included in the clinical database.

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Panel 16. List of Patients who Discontinued due to Adverse Events

<i>Treatment/ Patient Number</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>AE Start Day^a</i>	<i>AE (Preferred Term)</i>
OPEN-LABEL PHASE: ESCITALOPRAM TREATMENT				
1018	44	F	-28	Libido Decreased
1065			2	Headache
			28	Chest Tightness
			28	Agitation
			28	Insomnia
1094	40	F	-8	Fatigue
			7	Somnolence
			10	Weight Increase
			17	Restlessness Aggravated ²
			45	Palpitation
			45	Arthralgia
1106	52	F	1	Insomnia
			2	Decreased Appetite
			2	Urinary Frequency
			3	Palpitation
			4	Vasodilation
			4	Jitteriness
1108	38	F	10	Chest Pain
1122	57	M	10	Increased Sweating
			10	Faintness
			10	Paresthesia
			10	Anxiety
1138	45	M	42	ECG Abnormal
1140	51	M	14	Sleep Disorder

Panel 16.

List of Patients who Discontinued due to Adverse Events

<i>Treatment/ Patient Number</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>AE Start Day^o</i>	<i>AE (Preferred Term)</i>
1141	50	F	-2	Anorgasmia
1303	23	F	-63	Weight Increase
1306	26	F	15	Migraine*
			15	Paresthesia*
1311	57	M	43	Atrial Arrhythmia
1391	58	F	31	Fatigue
1408	45	F	10	Mitral Valve Prolapse
			11	Anxiety
			11	Insomnia
2029	41	F	-30	Weight Increase
2046	42	M	2	Palpitation
			2	Anxiety
			2	Bruxism
			2	Insomnia
			4	Tremulousness Nervous
2071	40	M	51	Hepatic Enzymes Increased
2083	35	F	41	Hypertension
2116	62	F	29	Diarrhea
2133	56	F	1	Weight Increase
2142	47	M	15	Rash
2172	33	F	15	Depression*
			15	Suicide Attempt*
2176	25	F	32	Nausea
2181	42	F	30	Somnolence

Panel 16. List of Patients who Discontinued due to Adverse Events

<i>Treatment/ Patient Number</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>AE Start Day^a</i>	<i>AE (Preferred Term)</i>
2184	45	M	1	Asthenia
			1	Headache
			1	Shaking
			1	Constipation
			1	Nausea
			1	Insomnia
			1	Visual Disturbance
2187	33	M	2	Headache
			2	Pain Neck / Shoulder
			2	Lethargy
			3	Chills
			3	Nausea
			4	Chest Pain
			6	Vomiting
2198	51	F	1	Fatigue
			1	Headache
			1	Nausea
			1	Jitteriness
2201	51	M	22	Somnolence
2254	48	F	-2	Nodal Arrhythmia
2299	44	M	41	Syncope
2306	24	F	4	Dizziness
			4	Somnolence
2345	24	F	1	Bradycardia
2374	53	M	30	Aggravated Depression

Panel 16. List of Patients who Discontinued due to Adverse Events

<i>Treatment/ Patient Number</i>	<i>Age (yrs)</i>	<i>Sex</i>	<i>AE Start Day^a</i>	<i>AE (Preferred Term)</i>
DOUBLE-BLIND PHASE: PLACEBO TREATMENT				
1103	47	M	15	Anxiety
			15	Irritability
1233	62	F	-27	Headache
1559	34	F	2	Increased Appetite
			3	Fatigue
			3	Insomnia
			3	Irritability
2157	33	F	2	Dizziness
2217	38	M	-6	Light-Headed Feeling [‡]
			14	Tinnitus
2325	69	F	-35	Bladder Carcinoma*
DOUBLE-BLIND PHASE: ESCITALOPRAM TREATMENT				
1334	45	F	68	Edema
			68	Weight Increase
1542	57	F	19	Palpitation
			19	Abnormal Crying
			19	Insomnia
2005	44	F	-126	Weight Increase
			-119	Libido Decreased
2136	29	M	2	Abdominal Pain
2249	54	F	174	Dizziness
			174	Scotoma
2356	73	M	144	Libido Decreased
2425	40	F	52	Apathy

^aAE Start Day = AE Start Date – Date of First Dose of Study Medication in Respective Phase + 1.

* The event was classified an SAE.

Cross-reference: Tables 7.3A and 7.3B.

Selected ADOs.

S1138 discontinued open label SCT treatment (had received 58 days of citalopram in the lead-in study and 57 days of open label SCT) **due to an abnormal ECG** on 2/29/00 (the day the drug was discontinued) which was first detected on 2/14/00. ECG results of this 45 y.o. male showed **“abnormal left axis deviation and left anterior fascicular block.”** This result was also found on a repeat ECG at the terminal visit on 3/4/00 and was interpreted by the physician as being due to “high lateral or inferior myocardial or pericardial damage.” This information, as provided in the narrative is insufficient to determine if whether or not this event was drug-related. The gender and possibly the age of the S are associated with an increase risk for cardiac disease. The S was reported as having no concomitant medications, so otherwise he appeared to be in good health. There were no other signs or symptoms described in the narrative. The sponsor has added “abnormal ECG” as an infrequent event under the “Other Events Observed During the Premarketing Evaluation...” section of proposed labeling. Further information regarding this S is also being requested from the sponsor.

S 1311 discontinued open label SCT treatment (55 days on 10 mg/day SCT in the lead-in study, which was continued, as open label drug, for 44 days) **due to atrial arrhythmia revealed on ECG** (“multiple atrial premature complexes”) obtained on 6/26/00. His ECG on 5/15/00 was normal, when he started the open-label phase of MD-03 (note he had received 55 days of double-blind SCT in the lead-in study and treatment on the same dose was continued as open label drug without interruption between studies). His ECG was also normal in a follow-up ECG after cessation of treatment on 7/10/00 (his abnormal ECG was on 6/26/00 with the stop date of 6/27/00 of the study drug). It is not clear if whether or not this event was drug related since the abnormal ECG appeared to be intermittent in a 57 year old male (risk factors for cardiac disease) and the S was not reported in the narrative as having associated symptoms. Nevertheless, abnormal ECG is listed under the “Other Events...” section of proposed labeling.

S 2254 discontinued open label SCT treatment (69 days on 10 mg/day double-blind SCT in the lead-in study, and continued on open label SCT for two days) **due to a “moderate junctional escape rhythm”** on ECG when the S began the open-label treatment phase of MD-03. A follow-up ECG 2 days later (also 2 days post cessation of the study drug) was normal. This patient was reported as having an ongoing bradycardia. This 48 year old female S is also described in the 10/19/01 review of the original submission. The temporal relationship of ECG abnormalities with resolution of the arrhythmia suggests a possible role of SCT treatment. However, this subject was reported to have bradycardia at baseline, whereby she appeared to be at risk of a junctional nodal arrhythmia. The issue of bradycardia and conduction defect in Ss in the various clinical trials is discussed in the 10/19/01 review and briefly summarized in the Executive Summary of the 10/19/01 review which is also provided in the appendix of this Addendum 1 Review.

S 2345 discontinued open label SCT due to bradycardia. This 24 year old female had a ventricular rate of 38 bpm on 4/27/00 when she entered the open label phase of MD-03 (had completed 52 days of double blind SCT). A repeat ECG on 5/15/00 after 18 days of open label SCT showed a rate of 47 bpm. Treatment was discontinued due to sinus bradycardia. It is not clear if this event is drug-related. However, bradycardia in a young healthy female is not uncommon and there were no associated symptoms reported in the narrative.

S 2299 discontinued open label SCT due to syncope. According to the narrative, this S was a 44 year old male who received 26 days double blind citalopram followed by 15 days of open label SCT. On Day 15 of open label treatment he experienced syncope resulting in cessation of

treatment. The syncope resolved on the same day that it occurred. It is not clear if this drug related given the information provided in the narrative. This S was taking ibuprofen and naproxen at various times during the study for sinus headache or migraine. Syncope is listed in the "Other Events..." section of proposed labeling.

S2071 is a 40 year old male with **elevated liver enzyme levels (up to about a 3-6 fold increase from baseline)** who had normal levels at baseline. This S was also described in the 10/19/01 review of this NDA but is also described in the following. These abnormal results led to cessation of treatment. Upon treatment cessation, this S had received 51 days of citalopram followed by 58 days of open label SCT treatment. Within 4 days after treatment was discontinued, the elevated levels returned to baseline levels (within normal limits). The elevation in enzyme levels from baseline to Day 51 of open label SCT (after completing 51 days of citalopram in a previous trial) were as follows:

- SGOT increased from 23 IU/l at baseline to 74 IU/l.
- SGPT increased from 26 to 149 IU/l.
- LDH increased from 163 to 492 IU/l.

Given the temporal relationship of elevated liver enzymes with treatment, as above and in the absence of any other information, it appears that this event could be drug-related. However, this event is listed in the "Other Events Observed..." section of Celexa®.

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**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
11/13/01 12:12:45 PM
MEDICAL OFFICER

Thomas Laughren
12/27/01 07:16:51 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo
to file for more detailed comments.--TPL

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**REVIEW AND EVALUATION OF CLINICAL DATA
RESPONSE TO THE ACTION LETTER**

NDA: 21-323

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: 10 mg and 20 mg encapsulated tablets (also 20 and 40 mg citalopram encapsulated tablets and placebo were employed)

Indication: Major Depressive Disorder

Dates of Submission: Correspondence date: 2/20/02
Received: 2/21/02

Materials Reviewed:

- Clinical sections of a response (N-BZ submission) to the 1/23/02 Approvable Action Letter.
- A 3/26/02 sent by e-mail via Project Manager Paul David

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

Review Completion Date: 4/2/02

I. Background

This review is to assist the Division Team Leader and Director in the regulatory processing of this NDA. The original NDA dated March 23, 2001 was for the approval of Escitalopram (SCT) in the treatment of Major Depressive disorder based on results of 8-week placebo controlled, multi-center, double-blind, parallel group trials of adult outpatients with Major Depressive disorder (MDD). The NDA was granted approvable status (see the 1/23/02 Action Letter). The present submission is a response to the 1/23/02 Action Letter. This review includes additional information provided by the sponsor on 2/20/02 upon our request.

II. Sponsor's Responses Regarding Clinical Issues

A. Safety Update

98 serious adverse events (SAEs) were reported during the period between 2/2/01 and 12/1/01. Ten of the 98 SAEs were deaths. The information regarding these SAEs consisted of line listings (arranged by study site) and narratives only. A clustering of SAEs appeared to exist in one particular study, Study 99258, in which 31 SAEs were reported. Upon our request, the sponsor provided a summary table of active studies

between the 2/2/01 to 12/1/01 period (see Table 1 in the appendix, as provided by the sponsor), along with a brief description of each study. Based on this information, it was discovered that Study 99258 was a one-year extension study in a geriatric patient population receiving open label SCT. The study is ongoing. Due to the clustering of SAEs in this study, that the population is a high-risk population that may be more sensitive to drug effects (see the next paragraph), a subsection below focuses on SAEs reported in this study.

Currently, potential cardiac safety issues pertaining to SCT treatment are under review by the Division Safety Group. Similar to that of the racemate of SCT, Celexa® SCT treatment is associated with mild bradycardia. Clinical trials of SCT also revealed a possible small mean prolongation of the QT interval and some Ss showed cardiac conduction defects on ECG (refer to NDA 21-323 and NDA 21-440 reviews). Fatalities, QT prolongation and other cardiac conduction defects are reported in cases of citalopram overdose. Given these observations, some subsections on SAEs below focus on events that were or that potentially could be cardiac-related.

Another clustering of SAEs appeared to exist, in that a number of SAEs were identified as "Inflicted Injuries" such as fractures and others. Many of these SAEs were in elderly Ss, particularly Ss from Study 99258. Inflicted injuries among elderly patients are more often associated with falls, as falls, as well as fractures are more common among the elderly. Injuries due to falls can result in debilitating, serious and life threatening events, such as fracture of the neck of the femur and subdural hematoma (both outcomes are associated with mortality). In turn, falls may be due to cardiac related events or other serious life threatening events (S5139 had the SAE of "Inflicted Injury" and upon examination of the narrative it is revealed that he "collapsed and was unresponsive for two minutes." Furthermore, falls can have serious and life-threatening outcomes (one S died; S5336 who had pulmonary embolism following a fracture "in the leg."). Finally, this topic is among the major public health concerns, given that the geriatric population is a growing population with significant health care needs. Consequently, subsections below focus on these potential safety issues and attempt to examine a potential relationship with the study drug.

Deaths: A total of 10 SAEs were associated with death. 7 out of the 10 deaths occurred in SCT treated subjects (Ss). Each death is listed below (Preferred/Investigator Terms provided) in which events described in these Ss were generally, likely to be due to underlying or pre-existing medical conditions, underlying psychopathology or lack of efficacy, as described in more detail below.

Listing of Seven SCT Ss who died:

S 5873: Brain neoplasm malignant/malignant oligodendroglioma

S 5078: Suicide Attempt

S 1499: Alcohol Abuse/Alcohol Intoxication

S5889: Arteritis/Arteriosclerosis/Pulmonary Edema

S5574: Bronchitis/Acute Bronchitis and Cardiac Failure/Heart Failure and Respiratory Insufficiency

S5369: Cerebrovascular disorder (Fatal)

S5336: Pulmonary Embolism (Fatal) and Inflicted Injury/Leg fracture

Listing of Deaths in Other Ss:

S5432: on placebo (a drowning)

S5351 on fluoxetine

S6420: on blinded drug (suicide by gunshot). This S is described in Attachment 1 of this review

The following is a discussion of the seven SCT deaths.

Two deaths (S5889 and S5574) involved the cardiovascular system (of which one also involved the pulmonary system), one event (S5369) involved the cerebrovascular system, and one event (S5336) involved pulmonary embolism after a fracture in the leg. These events occurred in elderly Ss with multiple medical conditions, or had a history of the given condition, and/or had several risk factors and/or were on concomitant medications. Consequently, these events were likely due to underlying or pre-existing medical conditions or risk factors. However, a potential contributory role of SCT treatment cannot be completely eliminated, as is the case for most complex and multi-factorial scenarios, particularly when examined retrospectively. These four deaths are described in more detail in Attachment 1 of this review.

One death involved brain neoplasia in an elderly woman (S5873). Given that treatment was acute, the age of this S, together with that already known about SSRIs (including Celexa®), this event was not likely to be drug related (refer to Attachment 1 for details on this S). Two deaths (S5078 and S1499) appeared to be related to underlying psychopathology and/or lack of efficacy (one event involved alcohol intoxication and one event was a suicide). S5078 who had underlying psychopathology and a positive family history that included risk factors for suicide, 15 days after he had completed an open label SCT trial. S1499 had an autopsy report showing aspiration of vomitus as the cause of death and alcohol intoxication as a contributory factor. However, this S also experienced severe chest pain just preceding his death, of which the diagnosis and etiology of this chest pain is unclear (refer to Attachment 1).

2. Serious Adverse Events Not Resulting in Death

The following enumerates SAEs (not including deaths) by study drug:

SCT: 47 SAEs

Blinded: 26 SAEs

Placebo: 3 SAEs

Citalopram: 4 SAEs

Other Selective Serotonin Reuptake Inhibitors (SSRIs): 8 SAEs

a. 31 SAEs in SCT Ss in a Geriatric Open-Label SCT, One Year, Extension Study: Study 990258.

A summary table of active studies with an enumeration of SAEs between 2/2/01 and 12/1/01 (refer to Table 1 in the appendix) shows a clustering of SAEs in Ss in Study 990258 (31 Ss with SAEs of which 4 Ss died). This study is an ongoing one year open label SCT geriatric study and is an extension study of Study 99024. Study 99024 was a study (now completed) of geriatric patients with "depression" (173 SCT Ss, 180 placebo Ss and 164 active controls). A subgroup of Ss from Study 99024 were enrolled and

treated in Study 990258 (N=225), all of which were assigned to SCT treatment. These SAEs and deaths involved events that are generally expected in the geriatric population. Furthermore, the chances of observing SAEs are greater in a longer term one year trial in contrast to shorter term trials, during which Ss are more closely monitored than individuals in the general population. Finally, this study was not placebo controlled, such that results on the incidence of SAEs (overall or within a given category) are difficult to interpret. Nevertheless, a possible role of SCT or contributory role may be considered for at least some of these SAEs, as described in later sections of this review. Listings of the deaths (see previous section for more details) and SAEs reported in Study 990258 is provided below (refer to later sections of this review for more details on SAEs).

SAEs/deaths in Study 990258.

Deaths in Study 990258: These Ss are described previously in the section of deaths (also in Attachment 1).

S5336: Pulmonary embolism inflicted injury/leg fracture

S5574: Bronchitis/Acute Bronchitis, Cardiac Failure/heart failure/Respiratory Insufficiency

S5369: Cerebrovascular disorder (Fatal)

S5889: Arteritis/arteriosclerosis, Pulmonary Edema

Ss with SAEs in Study 990258:

- SAEs with Terms that involve the cardiovascular, cerebrovascular, pulmonary systems or appeared to involve these systems are listed below. The first four Ss are described in subsequent sections of this review (a section that focuses on cerebrovascular, cardiovascular conditions). S5568 is described under a subsection on SAEs of syncope and hypotension and S5380 is included in a listing under "Additional SAEs in SCT Ss," later in this review.

S5398: Transient Ischemic Attack

S5469: Embolism Pulmonary/ Gastric Ulcer

S5608: Myocardial Infarction/pulmonary edema

S5852 Angina Pectoris

S5380: Pneumonia/Bronchopneumonia NOS

S5568: Syncope/Collapse

- SAEs of Inflicted Injuries. Falls and fractures are common in the geriatric population. However, a potential role of SCT cannot be completely ruled out, as described in a subsection on this topic, below (also where the Ss are described in more detail).

S5139: Inflicted Injury/Femoral Neck fractures

S5171: Inflicted Injury

S5381: Inflicted Injury/femoral neck fracture

S5811: Inflicted Injury

S5603: Inflicted Injury/foot fracture

S5604: Pain in Limb/Pain in arm

- Additional SAEs in Study 990258: The following are additional SAEs that did not

appear to reveal any new or unexpected findings for the class of SSRIs or SCT or were SAEs that were not likely to be drug-related. Some of these SAEs appeared to be related to underlying pathology (had a history of or current conditions) or occurred in patients with risk factors (such as elderly Ss or Ss with a mood disorder).

S5617: Cholecystitis

S5683: Diarrhea

S5058: Arthrosis

S5526: Arthrosis/knee arthroplasty

S5601: Arthrosis/localized osteoarthritis

S5260: Urinary Tract Infection/Pyelonephritis

S5623: Extrapyrarnidal Disorder

S5399: Depression Aggravated

S5566: Depression Aggravated

S5626: Depression Aggravated

S5629: Depression Aggravated

S5697: Emotional Problems

S5430: Hypomania

S5467: Uterine neoplasm

S5788: Colon Carcinoma

b. SAEs in Various Studies (see Table 1 in the appendix). Subsequent sections are regarding Ss with SAEs which are not categorized by the study from which they were reported (including Ss from Study 990258). Refer to Table 1 (in the appendix) for enumeration of SAEs by each study (as provided by the sponsor). Several caveats regarding the interpretation of these data exist. First, not all studies were placebo controlled. Secondly, some studies were ongoing, while others were completed and the SAEs reported were between a discrete window of time. Nine out of 21 studies were completed between the observation/reporting period. Among these completed studies, 0 to 10 Ss had SAEs within this time-window (2/2/01-12/1/01), as shown in Table 1 (the maximum number of 10 Ss occurred in a short-term geriatric trial). Finally, several studies were not placebo controlled or involved phases without a placebo group. Hence, the overall incidence rates of SAEs or incidence rates within a given SAE category, which were not provided by the sponsor, are difficult to interpret. However, an effort was made to enumerate SAEs by organ system categories that appeared to show a clustering of SAEs. Also refer to the previous discussion regarding specific categories of SAEs in introductory paragraphs of this Section (under Section II.A.).

SAEs with Preferred Terms Involving the Cardiovascular or Cerebrovascular Systems in SCT Ss and Ss on Blinded Study drug. 5 SCT Ss and 4 Ss on Blinded study drug had SAEs (by Preferred Terms) involving these systems as listed below (the preferred terms are provided):

SCT Ss. The Ss listed below were elderly, had pre-existing medical conditions or a history of multiple related conditions, and several were on multiple medications. While a potential contributory role of SCT cannot be completely disregarded, these SAEs were likely related to pre-existing conditions. Furthermore, several Ss (S3112 and S5852) were able to continue SCT treatment after they recovered and one S experienced their

SAE 12 days after completing SCT treatment. Their narratives are provided in Attachment 2 of this review.

S3112: Asthma, Chronic Obstructive Airways disease, Cardiac Failure, Hypertension

S5398: Transient Ischemic Attack

S5852: Angina Pectoris

S1567: Atrial Fibrillation

S5608: Myocardial Infarction/Pulmonary Edema

Ss on Blinded Drug with SAEs involving the cardiovascular or cerebrovascular systems: The SAE in S3353 (cardiac failure) may have been drug-related, while the SAEs in other Ss did not appear to be likely due to SCT treatment. However, a possible contributory role of SCT may be considered at least for some cases, as below.

S3353: Cardiac Failure: This was an elderly women with history of mitral valve replacement in 1970, was taking warfarin and had an abnormal ECG at screening. Given this history and an abnormal baseline ECG, this SAE was not likely due to study drug. However, consideration is given to a potential contributory role of SCT treatment to this event, as described in Attachment 2 of this review.

S3244: Cerebrovascular disorder: It does not appear that this SAE was likely to be due to study drug (refer to Attachment 2 for details).

S6083: Myocardial ischemia, Chest tightness of, Dyspnea, Paresthesia. For reasons described in Attachment 2 where this S is described, this SAE was not likely due to study drug.

S6240: Myocardial Infarction. This SAE was also not likely due to study drug for reasons described in Attachment 2 where this event is described. However, a possible contributory role of the study drug can not be completely eliminated.

SAEs of Inflicted Injury due to Falls and Potentially Related SAEs. A number of SAEs were events in SCT Ss that were given the Preferred Term of "Inflicted Injury." These SAEs are enumerated below. Some of these SAEs were due to falls.

- 9 SCT Ss (S5336, S5139, S5381, S5603, S5811, S1465, S8203, S5252, S1360)
- 3 Ss on Blinded drug (S3164, S8075, and S2158)
- 2 citalopram Ss
- 1 placebo S (the S1330, who was assaulted)

SCT Ss with SAEs of Inflicted Injury. The following describes selected SAEs of "Inflicted Injury" in SCT Ss that were associated with falls or were fractures with no description of events leading to the fracture. Refer to Attachment 2 for a detailed description of these SAEs except for S5139, who is described below. These SAEs involved primarily elderly Ss, a population in which falls and fractures are known to be more common. The outcome of falls in the elderly can be serious, debilitating and

sometimes fatal (such as with fracture of the femur and subdural hematoma). In addition, events that lead to falls (e.g. syncope secondary to an arrhythmia) can also be serious and potentially life-threatening. One elderly S (S5139) was described as collapsing and being “unresponsive” for 10 minutes and suffered a fractured neck of the femur, as described below. This S appeared to be in good health prior to his SAE.

Two elderly Ss who fell (S5139, the S previously mentioned above, and S 5381) appeared to be in good health (no concomitant medications or medical illnesses). Another S (S5603) also appeared healthy who had an injury, possibly due to a fall (events leading to the injury were not described). A possible role or contributory role of the study drug regarding events that lead to these injuries or falls needs consideration. However, each of these 3 Ss were taking SCT for at least 6 to 7 months before having their injuries, suggesting that these events were not likely to be drug related. A fourth elderly S (S5811) fell after one week of SCT treatment but continued treatment after the event with no recurrence described in the narrative. Given this observation, it appears that the fall in S5811 was not likely to be drug related.

One elderly S (S5336) had multiple medical conditions and was taking multiple medications, such that her injury was not likely related to SCT treatment. Finally, one nonelderly S (S1360) who had an injury, described in Attachment 2, was reported by a friend as having a “change” in “character” following an increase in her daily dose of SCT (from 10 mg to 20 mg). She later suffered an injury and was found to be intoxicated with alcohol.

Description of S5139: This is an 89 year old (y.o.) male who “**collapsed and was unresponsive for 10 minutes**” after 270 days of 10 mg daily SCT treatment. He experienced fracture of the neck of the femur surgically treated. This S had no concomitant medications and no past medical history was described. No other information is provided other than being discharged after several weeks. Given the lack of any other information and in the absence of any medical conditions or concomitant medications (additional information on this S is being requested). Nevertheless, this was an elderly S, a population in which such events are not uncommon. Furthermore, this S had already received 270 days of SCT treatment and not events prior to this date were described in the narrative. Consequently, this SAE was not likely to be drug-related.

Other SAEs of Inflicted Injury in SCT Ss. Other SAEs involving injuries that are not previously described are summarized in this paragraph. Three Ss (S1465, S8203 and S5252) had injuries due to accidents that did not involve falls. S5252 was attacked by a dog. S1465 had injury (gas intoxication) related to a gas explosion at work. The third S (S8203) was a nonelderly female who did not have a fall, but appeared to have an accident in which a possible contributory role of SCT might be considered given the unusual nature of this event (as it appears to this reviewer). She “accidentally” shot herself with a nail gun in what appear to be peculiar locations, the neck (two nails) and abdomen. The nail in the abdomen resulted in an outcome associated with a high mortality rate (perforated peritoneum which required surgery). This S is described in more detail in Attachment 2. Two other Ss (S5171 and S5604) had SAEs involving a fall or a “previous fracture”. Since these events were not likely to be drug-related, they are described in Attachment 2.

SCT Ss with SAEs of Syncope or Hypotension. Syncopal and hypotensive episodes may result in falls and/or injury and S5139 who fell was described as “collapsing” and being “unresponsive” with no explanation provided (previously described in more detail). Also refer to the introductory paragraph in this section (under Section II.A) regarding potential cardiac related events in SCT trials. Therefore, SAEs of syncope (S5568) and hypotension (S8142) are noted in this paragraph and are described in Attachment 2. While, these two SAEs did not appear to be drug-related, a potential contributory role of SCT cannot be ruled out.

3 Ss with SAEs of “Inflicted Injury” on Blinded Study Drug. The SAE in 1 of these 3 Ss did not appear to be drug-related (S8075, a nonelderly S in a car accident not considered her fault). A fourth S (S6144) is also described below, who was reported as having the SAE of a “burn” (the Preferred Term) instead of inflicted injury. The SAEs in Ss 2158, 3164 and 6144 may have been drug-related, as follows:

S2158 was a 52 y.o. female with a medical history of low blood pressure and on no concomitant medications who fell after 24 days of blinded treatment. Her fall resulted in fractured ribs and a pneumothorax, requiring hospitalization. She recovered. One cannot rule-out that this event was drug-related.

S3164 was elderly who had a climbing accident after about two weeks of blinded study drug that resulted in a head injury. This S was hospitalized for two days during which study drug was discontinued. The S recovered and continued the study. It appears that since the study drug was continued without subsequent sequelae or a recurrence, that this was likely not to be drug related.

S6144: This was a young adult who had a “burn” (the Preferred Term) due to falling against the stove. The reason for her fall was not clear.

2 Citalopram Ss had SAEs of “Inflicted Injury.” Since citalopram is the racemate of SCT, these SAEs are described. One event S4160 was not likely related to citalopram, as the S slipped and fell on ice and is therefore not described in detail. The other SAE in which a contributory role of study citalopram cannot be eliminated, is described below:

S 4337: A 31 y.o. male who was hospitalized for a fracture in the leg and was had no medical conditions or on concomitant medication. He had received approximately 72 days of citalopram treatment and was continued for another 7 days of treatment after his hospitalization. This event is likely not to be drug-related, although a possible role of citalopram treatment cannot be completely ruled out.

Additional SAEs in SCT Ss. The following is a listing of other SAEs reported in SCT Ss, not already described in this section. Most of these SAEs were events that appeared to be due to underlying or pre-existing medical conditions, underlying psychopathology, the presence of risk factors, or were events already reported with SCT, Celexa® and/or

other SSRIs and included the following (each was reported in one S, unless otherwise indicated). However, a potential role of SCT cannot be completely ruled out.

- Carpal tunnel syndrome
- Back pain, pain in limb
- Eczema
- Neuropsychiatric conditions: Depression aggravated (7), debility/worsening of social situation, suicidal ideation (2, of which one also had “depression aggravated”, counted above), hypomania, extrapyramidal disorder, emotional problems, acute psychosis
- Gastrointestinal disorders/conditions: hernia, cholecystitis (2), diarrhea, colon carcinoma, gastric tract bleed NOS/anemia (S5648, occurred during screening and after being treated the S continued and completed the study).
- Gynecological disorders: Uterine fibroid, endometrial cancer, breast neoplasia
- Musculoskeletal system: arthrosis (3)
- Pyelonephritis
- Pneumonia
- Injury

The S with breast neoplasia (S5128) was a 39 y.o. female with a 5 year history of an “unchanged left breast lump”. After receiving 84 days of SCT she noticed enlargement of her lump and underwent biopsy. She was diagnosed with infiltrating carcinoma and SCT treatment was discontinued. It appears this event was due to underlying pathology, yet a potential contributory role of SCT cannot be eliminated. Furthermore, SCT or related drugs, are not known to be associated with this type of an event.

In addition to the above, the following involved gastric ulcer and gastrointestinal bleeding (Preferred Terms):

S5469: Pulmonary Embolism/Gastric Ulcer. This S is described in Attachment 2. Gastritis is not uncommon AE in patients treated with SSRIs, such that a possible role of SCT is considered. It is not clear if this S had pulmonary embolism. She is reported as having hemoptysis of which the etiology is not clear (perhaps could be secondary to pulmonary embolism, upper gastrointestinal bleed, or other etiologies). This S had risk factors for pulmonary embolism.

S5678: Gastrointestinal tract bleed, NOS/Anemia. This SAE is not likely to be drug-related given that the event occurred before the screening phase of the study and after receiving treatment she continued and completed the study.

SAEs in Ss on Blinded Study Drug (not previously described). The following is a listing of SAEs in Ss on blinded drug (number of Ss also provided). Most of these SAEs were not unexpected or were likely due to a pre-existing condition, lack of efficacy, or the S had risk factors (although a potential contributory role of study drug cannot be ruled out in some of these cases). This listing does not include Ss already described (see Attachment 2 for a description of some of the SAEs listed here): pancreatitis (1; had history of pancreatitis), cholecystitis (1), gastritis (1), gastroenteritis/hives (1), non-accidental overdose/suicide attempt (1), suicide attempt (1), endocarditis (1; recovered

with intravenous antibiotics), tonsillitis (2), anxiety, facial palsy/Palsy Bells (1), arthritis/arthritis infection (1), headache (1), hypertension (1).

3. Regulatory Status Update

SCT was approved in two non-US countries: Sweden (12/7/01) and Switzerland (12/21/01) for "depression and maintenance therapy against relapses." Additional

4. Worldwide Literature Update

The sponsor describes a literature search on citalopram covering the period since their last SCT submission (NDA 21-440) to the present (from 11/30/01 to 2/5/02) using 4 databases (BIOSIS, EMBASE, MEDLINE and International Pharmaceutical Abstracts). Three new clinical trials in MDD and other indications were revealed from this search. Based on publications revealed from this search the sponsor concludes that no new safety observations, not already described in labeling, were reported. Two overdoses of citalopram are mentioned. One overdose (drug plasma levels: citalopram=3402 ng/ml, alprazolam =190 mg/ml) resulted in death and the other overdose resulted in hospitalization due to abnormal ECGs (a patient who had a seizure and right bundle branch associated with citalopram and fluoxetine ingestion).

A literature search on SCT covering the period from the last SCT submission and present, as above (11/30/01 to 1/31/02) was also conducted using the same four databases, along with two additional databases (Dewent Drug File and SciSearch). Five new articles were revealed, but none of them were of clinical drug trials. No new information on safety was described from this updated search.

B. Proposed Labeling.

The following describes key clinical labeling issues of the clinical sections of labeling to which the sponsor provides annotated explanations for their proposed changes (refer to the Biopharmaceutical, Chemistry and Pharmacology/Toxicology Reviews regarding the sponsor changes in Biopharmaceutical and CMC aspects of labeling).

Key issues regarding Clinical Efficacy Trials:

1. The sponsor proposes

The sponsor indicates that other approved drugs describe results of secondary efficacy measures and believes that exclusion of these HAMD results would "undermine interpretability" of the efficacy results of SCT, as the HAMD is a depression scale that is "most familiar" to US clinicians.

2. The sponsor proposes _____
 their data on subjects with a baseline HAMD score of at least 25 units.
3. The sponsor states that the third longer term citalopram study that is described in sections of labeling employed a 76 week double-blind treatment phase (535 days) rather than 72 weeks. Therefore, they propose to _____
4. The sponsor proposes _____
 distinctions between _____
 pertain to _____ as described in item 1 of the next subsection below. The sponsor's intention is to "conform to the study protocol and with current usage in academic psychiatry."
 These changes involve making treatment as they reportedly

Key Issues on Indications and Usage and Dosage and Administration:

1. The sponsor makes a distinction between "standard continuation treatment following an acute response and long-term maintenance treatment" in language proposed in labeling sections that pertain to efficacy claims and treatment recommendations in labeling (in addition to sections regarding study design). Also proposed are the distinctions between _____

 The proposed labeling changes are reported to "conform with current terminology in academic psychiatry." The sponsor proposes to _____
 and _____ The modified sections include those describing the study design of longer-term trials, efficacy claims and treatment recommendations based on these efficacy claims.
2. Also see item 2 in the previous subsection, regarding the proposed inclusion of additional benefit with 20 mg of daily SCT in "severe" patients.

Key Issues on Contraindications:

1. The sponsor proposes to _____

 section. The wording is also changed from being a _____
 _____ against co-administration. The sponsor provides the following rationale for these changes. Safety concerns regarding concomitant use of SCT with citalopram is "substantially less significant" than with monoamine oxidase inhibitors. The sponsor describes the safe treatment with SCT within 24 hours of exposure to 40 mg and 60 mg of CT in Studies SCT-MD-03 and SCT-MD-11. The administration of 80 mg of daily citalopram in patients in Study 85A submitted in NDA 20-822 was also reported to be safe. This dose is reported to be equivalent to 20 mg/day of SCT, 40 mg/day CT and 20 mg/day of R-citalopram.

Key Issues on Pregnancy under Precautions:

1. The sponsor proposes to _____ patients receiving citalopram. Proposed labeling includes statements that citalopram did “ _____”

Key Issues on Adverse Reactions:

1. The sponsor proposes to _____ section of labeling. The sponsor explains that these subjects were those that received placebo or citalopram in lead-in studies before receiving open-label SCT (new exposed to SCT) in Study SCT-MD03, a longer term SCT study in MDD patients.
2. The sponsor describes methods for rounding off percentages which in turn explains why some AEs are included or excluded in specified sections in labeling. The listing of AEs resulting in treatment cessation that were reported in at least 5% of SCT Ss, at a rate of at least twice that of placebo (in the paragraph that precedes Table 1), appears inconsistent with incidence rates shown in the Table 1. The methods for rounding off percentages, as described by the sponsor also appear to be inconsistent with that employed in other sections of proposed labeling.

An example of an inconsistency between Table and a listing of AEs that appear in the preceding paragraph is described in the following. The sponsor indicates that an incidence of 3.5% was rounded up to 4%, while an incidence of 7.4% was rounded down. Since nausea was 7.4% in placebo subjects it was rounded down to 7%, such that the incidence in SCT Ss (14.7% which was rounded up to 15%). Therefore, the actual incidence of nausea in SCT Ss was not actually twice that of placebo and was not listed as such in the paragraph preceding Table 1 (when using incidence rates before they are rounded off). However, when examining the rounded off incidence rates shown in Table 1, nausea appears to occur in at least twice that of placebo.

A different method from that described above, for rounding off incidence rates appeared to be employed by the sponsor in another section of labeling. The overall incidence of AEs in the 10 mg SCT Ss is shown as 66% in the Dose Dependency subsection of labeling. Yet the incidence rate before rounding it off to 66% was 66.5% (as described in the ISS of the original NDA submission and included in Attachment 16 in this response submission). Given the previous examples it appears that 66.5% would then be rounded up to 67% when using the sponsor's methods, rather than rounding it down to 66%, as shown in the sponsor's proposed labeling (changed from 67% in our version of labeling). Therefore, the methods for rounding off incidence rates of AEs appear to be inconsistent.

3. The sponsor was asked the following “*Please provide information on the comparison of the 20 mg groups vs placebo*” in the section regarding incidence of AEs resulting in termination of treatment. The following statement was inserted in proposed labeling in response to this request: “*The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day of Name of Product™ was 10%.*”

4. The sponsor proposes to _____

III. Conclusions and Recommendations

This updated safety report provides results that do not change overall conclusions regarding the safety of escitalopram, as described in previous reviews under this NDA and under NDA 21-440. Escitalopram (at the recommended dose) appears to be adequately safe in the study population examined in clinical trials supporting the efficacy claim for MDD. Potential cardiac issues remain that are currently under review by the Division Safety Group (refer to previous Clinical Reviews of SCT submission under NDAs 21-323 and 21-440, regarding potential cardiac issues).

The following are some key recommendations regarding labeling (items and sections below correspond to the above items and sections listed in the Labeling section of this review). In addition to the following recommendations, it is also recommended that the "Other Events Observed During the Premarketing Evaluation ..." section is updated to reflect all new adverse events described in the updated safety section of this submission.

Key issues regarding Clinical Efficacy Trials:

1. The sponsor proposes to _____
_____ the Division's current view on describing results of secondary efficacy variables is that the sponsor must declare secondary variables they ultimately wish to include in labeling as key secondary variables, *a priori*, like that of primary variables. Secondly, the sponsor must correct for multiple comparisons. Thirdly, given that key secondary results are positive (which is contingent on showing positive results on primary variables), these positive results must be replicated in a second independent, adequately controlled study. The sponsor did not follow and meet all of these criteria. Therefore, it is recommended that secondary results are not included in proposed labeling. The primary measure, the MADRS is described in labeling and is considered by the Division as an acceptable primary variable in trials in the US. This reviewer does not agree with the sponsor that a description of only the MADRS results, in the absence of HAMD results, "undermines the interpretability" of the efficacy results of SCT trials. Furthermore, this reviewer does not agree with the sponsor's comments on how these results may be viewed by US physicians.
2. The sponsor's proposed labeling describes an " _____"
_____ This proposal is based on a analysis of the sponsor's data (this item also pertains to item 2 under Indications and Usage and the Dosage and Administration section). The analysis of these data is retrospective and was not an *a priori* primary or key secondary objective in the study. Furthermore, the sponsor's results were not replicated in two independent prospective adequately controlled trials. Additionally, the sponsor does not justify the validity of stratifying subjects, as proposed. The scientific or diagnostic basis for such a stratification of patients within a diagnostic category was not provided and is not

evident. Therefore, this stratification and retrospective analyses appear arbitrary. Other issues not addressed here also exist regarding the proposed description of this subcategory of patients.

3. The sponsor states that the third longer-term citalopram study in labeling, employed a double-blind treatment phase of 76 weeks (535 days) rather than 72 weeks. However, based on the study design described in the original review (Dr. Sue Molchan's review of a 2/28/00 48.1 SE1-009 submission) and memos (from the Team Leader), this study employed a 72 week double-blind treatment phase. The sponsor provided exposure tables of citalopram and placebo Ss for this study (provided in Attachment 7 of the response submission). These tables are similar to those in Dr. Molchan's review that show that 46% of citalopram Ss and 28% of placebo Ss were exposed to 365-544 days of treatment. The tables that the sponsor provides are results of study drug exposure and do not reflect the actual study design (i.e. the duration of the double-blind phase of the study). The tables show study drug exposure of Ss across windows of time, in which the maximum time window of exposure was 365 to 544 days in which a subgroup of Ss were exposed to study drug within this window of time. Changing the description of the study design employed (in this case the duration of double blind treatment) and to base this change on exposure results of a subset of the study population (the subset that had exposures between 365-544) can result in misinterpretations of efficacy results. Furthermore, in the opinion of this reviewer, these tables do not provide a justification for changing the description of the study design and making efficacy claims, accordingly.
4. The sponsor proposes _____

_____ The sponsor's intention is to "conform to the study protocol and with current usage in academic psychiatry." These proposed modifications are not considered by this reviewer to be acceptable for a number of reasons provided in previous reviews (refer to reviews of this NDA 21-323 and NDA 21-440). It is recommended that labeling does not reflect these distinctions, so as to avoid making assumptions on the interpretation of efficacy results of longer-term trials. The longer-term trials (such as SCT-MD-03) were not designed to meet these specific objectives (such as demonstrating prevention of relapse and making a distinction from a recurrence of a depressive episode). It is the opinion of this reviewer that the potential for making misleading interpretations of efficacy results of these longer term trials, can be minimized, by avoiding language that makes specific distinctions such as that proposed by the sponsor.

Key Issues on Indications and Usage and Dosage and Administration:
Items 1 and 2:

These items are already addressed (refer to Items 1 and 4 in the previous section, above).

Key Issues on Contraindications:

1. The sponsor proposes to _____

The sponsor's proposed changes appear to be reasonable. However, potential cardiac issues with SCT treatment are currently under review by the Division Safety Group. Therefore, this modification is subject to change, pending results of the Safety Group review and their recommendations.

Key Issues on Pregnancy under Precautions:

1. The sponsor proposes to _____

_____ This was a survey study and was not a placebo controlled, double-blind, randomized, prospective study. It is also not clear from a single study if results are reproducible. Therefore, this survey study does not provide adequate evidence for conclusions being made in proposed labeling. Additionally the insertion of these results introduces the potential for providing some false hope or expectations regarding the safety of SCT treatment in pregnant patients.

Key Issues on Adverse Reactions:

1. The sponsor proposes to _____

_____ Since this section pertains to the 715 subjects in controlled trials exposed to double-blind treatment, the additional 284 subjects are not considered to be pertinent to this section. However, they are pertinent to the section of "Other Events Observed During the Premarketing Evaluation of..." where they are included in the total of 999 subjects described in this section of labeling.

2. The sponsor proposes _____

_____ The methods that the sponsor describes appear to be inconsistent across sections of labeling under "Adverse Reactions." Also listings or descriptions of adverse events based on actual incidence rates (before rounding off the percentages) rather than based on percentages shown in Table 1 (after rounding off the percentages), creates internal inconsistencies and appears confusing. Therefore, it is recommended that there is internal consistency within labeling regarding descriptions and tables on incidence rates of events.

3. The sponsor was asked to provide information comparing the 20 mg groups versus placebo on AEs resulting in discontinuation of study drug in fixed dose trials. The statement they proposed to be inserted in labeling does not show a comparison to the rate in placebo subjects in this fixed dose trial. However, the following statements do reflect results of placebo compared to SCT groups and are recommended as being included in this section of labeling: *One fixed study showed the following incidence rates of 3% in the placebo group, 4% in the 10 mg/day Name of Product group™ and 10% in the 20 mg/day Name of Product Group. In another fixed dose trial employing only the lower dose of Name of Product,™ the 10 mg/day group showed a rate of 4.2% compared to 1.1% in the placebo group.*

4. The sponsor proposes to _____

by deleting this section, labeling will no longer include a description of reported serious and in some cases potentially life threatening conditions, such as neuroleptic malignant syndrome, thrombocytopenia, and others. Also, the removal of this section would result in the lack of any description of potential syndromes reported with SSRIs. Therefore, it is recommended that this section remain.

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

**APPEARS THIS WAY
ON ORIGINAL**

**APPENDIX
ATTACHMENTS 1 AND 2**

**APPEARS THIS WAY
ON ORIGINAL**

**Table 1 Number of Subjects by Treatment Group (as provided by the sponsor)
Active Studies – February 2, 2001 to December 1, 2001
Cutoff date: December 1, 2001**

Study Groups	Treatment Group				Total*	Status@	Patients with SAEs#
	Escitalopram	Citalopram	Other Active Control	Placebo			
Non-US Studies							
99002 ⁽¹⁾	590	0	0	0	590	Completed	7
99012 Social Phobia	181	0	0	177	358	Completed	1
99022 Cit Comp	175	182	0	0	357	Completed	0
99024 Geriatric	173	0	164	180	517	Completed	10
99067 Venlafaxine	147	0	146	0	293	Ongoing	8
99258 ⁽²⁾	225	0	0	0	225	Ongoing	31
99269 SAD Relapse ⁽³⁾	517	0	0	173	517	Ongoing	7
99270 SAD Fixed Dose	341	0	114	114	569	Ongoing	10
99505 Paroxetine	109	0	109	0	218	Ongoing	4
99610 Bioequivalence	16	0	0	0	0	Completed	0
US Studies							
SCT-MD-03 ⁽⁴⁾ Relapse	504	0	0	93	504	Completed	0
SCT-MD-04 Panic	128	119	0	119	366	Completed	3
SCT-MD-05 GAD	126	0	0	128	254	Completed	0
SCT-MD-06 GAD 2	137	0	0	136	273	Ongoing	0
SCT-MD-07 GAD 3	160	0	0	159	319	Ongoing	1
SCT-MD-08 ⁽⁵⁾ Esc 30 mg	21	0	0	0	21	Ongoing	0
SCT-MD-09 Sleep Disorder	15	0	15	0	30	Ongoing	0
SCT-MD-10 Psychomotor ⁽⁶⁾	17	0	0	17	17	Ongoing	0
SCT-MD-11 Recurrence ⁽⁷⁾	425	131	385	97	516	Ongoing	10
SCT-MD-16 Fluoxetine	98	0	99	0	197	Completed	2
SCT-MD-17 ⁽⁸⁾	408	0	0	0	408	Ongoing	3

* Patients are counted once and only once in the total.

@ Completed: completed treatment as of December 1, 2001.

Number of patients with serious adverse events reported during the period February 2, 2001 to December 1, 2001.

1. Extension of 99001 and 99003.
2. Extension of 99024.
3. A total of 517 patients were enrolled and received escitalopram in the open-label phase. One half (173) of the total 346 randomized in the double-blind phase is estimated to have received placebo.
4. Extension of SCT-MD-01 and SCT-MD-02. A total of 504 patients were enrolled and received escitalopram. A total of 93 of the 274 patients randomized in the double-blind phase received placebo.
5. A total of 21 patients (nonresponders from SCT-MD-11B) were enrolled and received 30 mg of escitalopram.
6. Crossover study in healthy volunteers.
7. Consists of 4 studies: 11A, 11B, 11C, and 11D. A total of 516 were enrolled in study 11A and received one of the four active controls: citalopram, paroxetine, sertraline, and fluoxetine. A total of 425 of the 516 patients received escitalopram: 139 patients in study 11B (nonresponders from study 11A), 46 patients in study 11C (AE discontinuations from study 11A), and 329 patients in open-label phase of study 11D (responders from studies 11A, 11B, or 11C) less 89 patients in study 11D who previously participated and received escitalopram in either study 11B or study 11C. One half (97) of the total 194 randomized in the double-blind phase is estimated to have received placebo.
8. Extension of studies SCT-MD-05, SCT-MD-06, and SCT-MD-07.

Attachment 1. Descriptions of Selected Deaths in Subjects treated with Escitalopram or Blinded Study Drug (subject numbers and Preferred Terms are provided, refer to Section II.A.1 of the Review).

S6420 on blinded study drug: **Suicide attempt**. This 34 y.o. male started blinded study drug on 5/11/01 and on 6/26/01 was found dead (gunshot wound in abdomen and thorax). Last seen alive on 6/14 and estimated day of death was 6/16 per autopsy report. 0.8 promille ethyl alcohol was found in the blood. It is likely that this was due to underlying psychopathology.

S5369: **Cerebrovascular disorder (CVA)**. This was an elderly patient with multiple illnesses and risk factors for this event, such that it was not likely to be drug-related. This 91 year old (y.o.) female (F), residing in a senior residential facility, who had a past medical history (PMH) of chronic pulmonary disorder (COPD), hypertension (HTn) on Flixotide for COPD. After 228 days on SCT treatment she had an episode of neurofocal deficits consistent with CVA (left hemiplegia, left facial paralysis and aphasia), was not hospitalized (remained in the senior residential facility) and died on the following day. No autopsy was performed.

S5574: **Bronchitis/Cardiac Failure/Respiratory Insufficiency**. This was an elderly woman with multiple medical conditions and on multiple medications appeared to suffer a series of medical illnesses culminating in her death that appeared to start with an infection (her diabetes mellitus being a risk factor). Her pulmonary infection (bronchitis), in turn, appeared to lead to more serious events resulting in her death, as follows. This 76 y.o. F had a PMH of HTn, aortic sclerosis, emphysema and diabetes mellitus, who was on multiple medications (Adebit, Glibencamid, Metoprolol tartrate, and Enalapril maleate) who died on June 2, 2001. An autopsy was conducted and the diagnosis was "cardio-respiratory insufficiency with acute purulent bronchitis leading to heart failure." This S was on SCT treatment from 4/19/01 to June 2001.

S5889: **Arteritis/Arteriosclerosis/Pulmonary Edema**. This was a 78 y.o. male (M) with multiple medical conditions (history of arteritis, angioplasty, myocardial infarction with coronary artery bypass X 3) on multiple medications (Nitroderm, Amlodipine, Celiprolol, Clopidogrel, Prednisolon) who experienced a series of medical events (arteritis, thrombosis resulting in a leg amputation) requiring hospitalization for treatment. A partial occlusion of a carotid artery was revealed (70% stenosis) and he was rehospitalized for surgical treatment. A few days later he developed acute pulmonary edema with cardiorespiratory arrest (CRA) and received emergency treatment and transferred to the intensive care unit where he later had a second episode of CRA and died "from acute pulmonary edema." This S was on SCT treatment for 173 days, which he was receiving until the day of his first episode of CRA.

S5336: **Inflicted Injury/Embolism Pulmonary**. This 75 y.o. F had multiple medical conditions (ischemic heart disease, HTn, pyelonephritis, obesity) on multiple medications (diltiazem for HTn, salicylic acid for thrombosis prophylaxis) who "broke her leg" after approximately 5 months of SCT treatment and was hospitalized and died approximately

10 days later. The “probable cause of death was pulmonary emboli.” This patient received SCT for a total of 165 days (stop date was on the day she died). It appears given her age, gender, obesity, immobilization (due to her injury and hospitalization) and possibly other risk factors that she developed thrombosis and emboli resulting in her death. It appears that her death was not drug-related. However, it is not clear if her injury occurred secondary to a drug-related event, since the narrative does not provide information on events that culminated in her injury. Nevertheless, given her age, obesity and other potential factors (probably had osteoporosis associated with her age and postmenopausal status), she appeared to be at risk for her injury.

S5873: brain neoplasia. The S was a 68 year old female and presented with aphasia-like and intermitted abnormal arm movements after approximately 20 days of SCT treatment. Subsequently she was informed of having a brain tumor and secondary partial seizures and SCT treatment was discontinued two days later (a total of 28 days of SCT treatment). Approximately 4 days later a CT scan revealed a brain tumor (left hemisphere with temporal involvement) and diffuse hemorrhagic lesions in the cerebellum. The S was hospitalized and a biopsy revealed a “high-grade oligodendroglioma” and she received chemotherapy and radiation treatment. She died approximately 9 months after the initial diagnosis. Given that treatment was acute and what is know of SSRIs (including Celexa®) and the patient’s age, it is not likely that this event was drug related. The diffuse hemorrhage, together with the tumor enlarging were likely the reason her neurological symptoms appeared and were not drug-related.

S1499: Alcohol Abuse. This was a 49 y.o. male taking open label SCT for about one month (no medical history or concomitant medications) who died after ingesting “herbal alcohol,” a product called “Vital Force.” The blood alcohol concentration was “2.9 o/oo.” The S’s wife stated he had severe chest pain lasting 2 minutes before collapsing, followed by vomiting, aspiration and death. Cause of death per autopsy report was aspiration of vomitus, and alcohol intoxication, as a contributory factor. It is not clear from the narrative if the autopsy report provided any description pertaining to cardiac disease or evidence of myocardial infarction, as suggested by the severe chest pain that this patient experienced. Ingestion of alcohol does appear to be a contributory factor, but would not alone, account for the episode of severe chest pain. It does not appear that this event was likely to be drug-related. However, given that there is no other information, one possible consideration is a contributory role of SCT treatment with events leading to death (i.e. interaction with alcohol and/or interaction with underlying, undiagnosed cardiac disease or some other role).

Attachment 2.

A Description of Selected SAEs Cardiovascular or Cerebrovascular System Related SAEs in SCT Subjects (as described in the review).

S3112: Asthma/Chronic Obstructive Airways disease/Cardiac Failure/Hypertension
(below are sections of the narrative)

Relevant concomitant medications:

Aprovel (irbesartan) since 27-Oct-1997. Indication: Hypertension. Cardizem since 27-Aug-1998. Indication: Hypertension. ASA since 31-Aug-1994. Indication: Arteriosclerosis Fluticasone since 28-May-2000. Indication: Asthma Oxis (formoterol) since 1999. Indication: Asthma
NARRATIVE
This report concerns a 65-year-old female with a medical history of asthma since 1950, hypertension since 1993 and angina pectoris since 1998. She received escitalopram beginning on 30-May-2000. The patient completed the study and received the last dose of study medication on 8-Jun-2001. On 9-Feb-2001, the patient was hospitalised suffering from flu with fever. Her asthma worsened and she had respiratory difficulties. Study drug continued unchanged. The event was considered resolved on 16-Feb-2001. On 16-Jun-2001, the patient was hospitalised due to cardiac insufficiency. Hypertension was also reported. The patient had asthma for several years; the symptoms worsened and she had dyspnoe, crepitations, and oedema. X-ray showed pulmonary oedema, and spirometry showed obstructive lung disease. The patient recovered on 23-Jun-2001. Prior to inclusion in Study 99002, the patient received escitalopram in Study 99003 (30-Mar-2000 – 29-May-2000).

S5398: Transient Ischemic Attack (below are sections of the narrative)

RELEVANT CONCOMITANT MEDICATION(S)
Marcoumar 18-May-1985 for atrial fibrillation. Ongoing. Tenormin 18-May-1985 for hypertension. Ongoing.
NARRATIVE
This report concerns a 72-year-old male patient, with a medical history of hypertension and atrial fibrillation, who received escitalopram beginning on 16-Nov-2000. On 12-Mar-2001, the patient became confused and forgetful. On 17-Mar-2001, he had a TIA and was hospitalized. The patient was given galantamine hydrobromide for the forgetfulness from 29-Mar-2001 to 23-May-2001. The patient was reported as recovered. Prior to inclusion in Study 99258, the patient participated in Study 99024 (7-Sep-2000 – 8-Nov-2000) and received escitalopram 10 mg.

Continued on the next page.

S5852: Angina Pectoris (below are sections of the narrative)

RELEVANT CONCOMITANT MEDICATION(S)
Metoprolol for hypertonia 19-Oct-2000 and ongoing Enalapril for hypertonia 19-Oct-2000 and ongoing Trimetazidine for ischaemic heart disease since 11-Jan-2001 Glyceryl trinitrate transdermal for ischaemic heart disease since 19-Oct-2000 Glyceryl trinitrate sublingual for angina pectoris since 21-May-2001 ASA for arteriosclerosis since 19-Oct-2000 Pentoxifylline for arteriosclerosis (therapy dates unknown) Piracetam for arteriosclerosis since 11-Jan-2001
NARRATIVE
This report concerns a 75-year-old-male patient, with a history of cardiovascular disease, who received escitalopram beginning on 08-May-2001. On 12-Jun-2001, the patient was hospitalised due to angina pectoris following a month of cardiac symptoms. The patient recovered and continued in the study. Prior to enrollment in Study 99258, the patient participated in Study 99024 (3-Mar-2001 – 7-May-2001) and received placebo.

S1567: Atrial Fibrillation (below are sections of the narrative)

RELEVANT CONCOMITANT MEDICATION(S)
None
NARRATIVE
This report concerns a 63-year-old male, with a medical history of myocardial infarction in 1996, who received escitalopram in the open-label phase of the study from 23-May-2001 until 06-Jun-2001. The patient stopped study drug due to sexual dysfunction. Twelve days after the last dose of study drug, on 18-Jun-2001, an ECG showed atrial fibrillation and probably an old inferior infarct. A screening ECG on 15-May-2001 had shown sinus bradycardia, left axis deviation, but could not rule out old inferior myocardial infarction. On 28-Jun-2001, the patient commenced treatment with warfarin 5 mg/day p.o. and recovered on 31-Jul-2001.

S5608: Myocardial Infarction/Pulmonary Edema. This was a 70 y.o. female with history of HTn, diabetes mellitus type 2, status/post varicose vein surgery and complicated bilateral sural phlebitis and pulmonary embolism, dyslipidemia and obesity. After approximately 5 months of SCT treatment she woke up with signs and symptoms of myocardial infarction (MI) or ischemia with pulmonary edema (retrosternal pain radiating to the arms, thoracic oppression dyspnea and orthopnea). She was hospitalized and diagnosed with MI and pulmonary edema and underwent angioplasty with a stent. After her recovery and discharged she continued on SCT treatment for approximately one more month (received a total of 218 days of SCT) but withdrew from the study due to "feeling better."

Cardiovascular or Cerebrovascular System Related SAEs in Subjects on Blinded Drug (as described in the review).

S3353: **Cardiac Failure:** This was an elderly woman. This was a 74 y.o. woman with history of mitral valve replacement in 1970 and was taking warfarin who received blinded drug from 9/18/01-10/3/01. She had incomplete left bundle branch block in September 2001 (the exact day was not given). The sponsor provided clarification regarding the date of this ECG, upon request. The exact date of the ECG was 9/11/01 during screening. The sponsor also described additional observations regarding this ECG, as follows, which were considered to be minor and of "equivocal significance:" "broad p waves, prolonged QRS duration, ST wave changes in the lateral leads." On 10/3/01 the S had left ventricular failure with supraventricular tachycardia/atrial flutter and was successfully electroconverted and hospitalized. The echocardiogram (echo) showed that the mitral valve was "well-seated with no regurgitation" and revealed a large anteroseptal area of hypokinesia. A repeat echo showed normal wall motion and ejection fraction of 56% (left atrial diameter of 4.4 cm). This S had several risk factors (her age, pre-existing mitral valve abnormality, abnormal ECG at baseline) for this event. The narrative does not describe any work-up for myocardial ischemia or infarct (such as no cardiac enzyme levels, no mention of ST elevation or depression on ECGs, or other diagnostic test results). Given the normalization of abnormal findings on echo, in the absence of echo results of mitral regurgitation, one cannot rule out the possibility that this SAE was drug-related. The abnormal baseline ECG suggests the presence of an underlying condition that may have lead to cardiac failure, yet a potential contributory role of SCT may be considered. Clinical trials of SCT show evidence for a mean decrease in heart rate (not considered clinically significant in the study populations examined) and possibly a signal for a small prolongation of the QT interval. Some SCT Ss in these trials also had ECGs showing similar types of arrhythmia. The cardiac safety of SCT is currently under review by the Division Safety Group.

S3244: **Cerebrovascular disorder:** This S had multiple risk factors for this event (53 years old and a medical history of hypertension and goiter, and was taking metoprolol and L-thyroxin). Furthermore, she was taking placebo for 5 days (after completing 8 weeks of blinded study drug) before the event was reported. Consequently, this SAE was not likely due to study drug.

S6083: **Myocardial ischemia, Chest tightness of, Dyspnea, Paresthesia.** This S was a 56 y.o. male smoker with history of hypercholesterolemia (taking Pravastatin). He had nausea and anxiety on 8/10/01 after one dose of blinded study drug (a trial on patients with social anxiety disorder). The next day he had vomiting and disorientation and one day later (8/12/01) he was treated with diazepam for anxiety. The investigator did not consider these events as serious, but study drug was discontinued. The next day (8/13/01) the S awoke with shortness of breath, chest heaviness, and parasthesia of his fingers and a "cardiac event was suspected." The narrative does not describe any diagnostic work-up. However, his physician saw the S on 8/13 and "nothing abnormal was found." An ECG at the early termination study visit (date not given) was normal. It appears that this S had episodes of panic attacks due to underlying psychopathology

coupled with potential anticipatory anxiety regarding initiation of blinded study drug. Nevertheless, one cannot rule-out myocardial ischemia, or some other etiology (no diagnostic work-up is described). If this was a cardiac event, this S had risk factors for cardiovascular disease. In conclusion, it appears unlikely that the SAE on 8/13 was drug-related, particularly since the SAE occurred 3 days after only one dose of blinded drug. However, nausea is one of the more common AEs associated with SSRI treatment, such that one might consider a potential role of study drug, in the case that the nausea was not associated with his anxiety.

S6240: Myocardial Infarction. This S was a 49 y.o. male with no “relevant” medical history who an acute myocardial infarction without any “warning symptoms before the attack”, which occurred after 4 months on blinded study drug. The S was hospitalized and high cholesterol levels were revealed. He recovered and continued on study drug. Given that this was not a young adult and the presence of known risk factors for cardiovascular disease (gender and high cholesterol levels) and that he continued on study drug without recurrence, it appears that this SAE was not likely to be drug-related. However, without additional information one cannot rule out a possible contributory role of the study drug.

Selected SAEs Related to Injuries/Possible Falls and Other SAEs (as described in the review).

S5381: This 80 y.o. female “fell” after receiving approximately 7 months of daily treatment with 10 mg of SCT. She sustained a fractured neck of the femur requiring hospitalization and surgical treatment. She was not on concomitant medications and no past medical history was described. She had previously completed a study in which she received 20 mg fluoxetine treatment (approximately 8 weeks). While the S was elderly, there is no other information to explain the reason for the fall. Therefore, one cannot rule-out that her fall was due to a drug-related event. However, a treatment period of 7 months would suggest that the event was not likely to be drug-related.

S5603: This 67 y.o. female had a **calcaneus fracture** after approximately 6 months of 10 mg SCT treatment that required surgery. The S had no concomitant medications or medical conditions described in the narrative. It is not clear how this S sustained his fracture and whether or not this was drug-related. However, the S recovered and continued the study and had previously completed a study in which she received approximately 8 weeks of 10 mg of SCT treatment.

S5336: This 75 y.o. female had a “**fracture in the leg**” that was followed by a series of medical complications including “pulmonary embolism,” culminating in her death. The cause of her fracture or events leading to this injury were not included in her narrative. However, she had multiple medical conditions (obesity, ischemic heart diseases, hypertension, and pyelonephritis) and was taking diltiazem and acetylsalicylic acid. Hence, she had several risk factors, in addition to her age, for accidents such as falling. However, a potential contributory role of SCT cannot be ruled out (she received 165 days

of treatment). This S who eventually died, is described in more detail in the Attachment 1 and in the previous section on deaths.

S5811: This was a 74 y.o. female who had a history of several fractures who fell and sustained a **fracture in her wrist** after approximately one week of 10 mg SCT treatment (hospitalized). She recovered and continued in the study. Given this S's age and history of fractures, it appears the this SAE was not drug-related, although a potential contributory role cannot be ruled out.

S1360: This 25 y.o. female S had a blood alcohol level of 2.1% on the day of her **fall from climbing scaffolding to a 6th floor balcony of her friend's flat** (53 days on SCT treatment). Given this blood alcohol level this event does not appear drug-related. However the narrative describes a "changed" in "the patient's character," as reported by her friend after an increase in her dose from 10 to 20 mg daily. It appears this S may abuse alcohol and is likely to have psychopathology (given that this is a clinical trial). Alcohol use and potentially pre-existing psychopathology, can together or independently result in changes in behavior, personality and judgement. However, a potential role of study drug in the reported personality change, might be considered, in the absence of additional information (the narrative does not describe any use of concomitant medications or illicit substances and does not provide any past medical or psychiatric history, or history of alcohol abuse). Ss who have substance or alcohol abuse or dependence disorders, typically report their condition (are in denial).

S5604: This SCT S had "**pain in a limb**" as the SAE, associated with a previous fracture in the arm. It is not clear when the S had the fracture, why and the date of the fracture was not given (perhaps it occurred prior to SCT treatment). However, this S recovered and was continued in the study. She had also completed a study of approximately 8 weeks of 20 mg of fluoxetine treatment. Therefore, it appears that the event was probably not drug-related.

S5171: This was a 78 y.o. female with history of vertigo being treated with prochlorperazine. Eight days after completing the study (343 days of SCT treatment) she "**tripped and fell**" and developed a septal hematoma requiring hospitalization and treatment. It appears that this event was secondary to vertigo and it occurred over a week after treatment cessation

S8203: A 32 y.o. female who accidentally **shot herself with a nail gun** (two nails in the neck and one in the abdomen). As a result of the nail in the abdomen she perforated her peritoneum requiring hospitalization and surgery. She had received 13 days of SCT treatment and had previously completed a study of 56 days on citalopram prior to this event. The reason for the location of where this S accidentally shot herself with the nail gun and why this occurred in multiple places (neck and abdomen) was not provided in the narrative. One possibility is that this was not an accident, but that the events were of self-mutilation or as suicidal gestures, secondary to underlying psychopathology, yet the S did not report the event as such. The S's judgement may have been impaired, which

may be associated with underlying pathology. However, with lack of sufficient information, a potential role of SCT treatment cannot be ruled out.

S5568: This is an 82 y.o. female how had the SAE of **syncope** (preferred term) after approximately 3 and half months of receiving 10 mg SCT daily. She had a history of hypertension and ischemic heart disease and was on multiple medications (Isosorbide mononitrate, Enalapril, and Trandolapril). She collapsed and vomited and was hospitalized. Her blood pressure was 180/100 mmHg. She recovered and was discharged within approximately one week. She was continued in the study. This S had previously completed a study of approximately 8 weeks of 20 mg fluoxetine treatment. Given this S's age, medical history and concomitant medications, and that she continued in the study without apparent sequelae or recurrence, this event is likely not related to SCT. However, a potential contributory role of SCT cannot be ruled out.

S8142: This was a 62 y.o. male with history of herniated disc who underwent microscopic infusion for herniated disc as an outpatient after about one month of treatment with blinded study drug. However, the S had **hypotension**, while receiving narcotic analgesia, such that he was hospitalized overnight. After discharge he was continued on blinded study drug. It is likely that this event was not study drug-related and due solely to an adverse effect of the narcotic agent. However, a potential drug-drug interaction effect cannot be ruled out.

Other Selected SAEs in SCT Ss (as described in the review)

S5469: **Pulmonary Embolism/Gastric Ulcer.** This was a 73 y.o. female with history of hypertension, ischemic heart disease, and cerebral ischemia and was on multiple medications (nitroderm, renitec, pentoxifylline). She had hemoptysis (exact date not provided) and her dentist and laryngologist found no abnormalities. After approximately 2 months of SCT treatment a gastric ulcer was diagnosed and ranitidine treatment was initiated. She was hospitalized for a total of approximately 10 days. After about 5 days of this hospitalization, Acenocoumarol treatment was started "to prevent pulmonary embolism" and "ranitidine was re-initiated" upon discharge. It is not clear in the narrative, if this S actually suffered a pulmonary embolism, but appeared to be at risk for one (age, history, decreased activity secondary to hospitalization). The cause of her hemoptysis is also unclear, perhaps it was pulmonary embolism or it was related to her gastric ulcer. However, one must also consider other causes, such as tuberculosis, among others (the narrative does not describe a diagnostic work-up of the hemoptysis other than that described above). Given the lack of information these events may have been drug-related. However, she appeared to have risk factors for these conditions. Concomitant treatment with petoxifylline was a likely contributory factor regarding her episode of hemoptysis. Gastritis is not an uncommon AE with SSRIs. A role or contributory role of SCT treatment and a possible upper gastrointestinal bleed (yet it is not clear if this is what she had) may also be considered.

Selected SAEs in Ss on Blinded Study drug (as described in the review):

S 6645: Facial Palsy/Paresthesia. A 41 y.o. who appeared to have classic signs and symptoms of Bell's Palsy within 6 hours after their second daily dose of study drug, which was discontinued due to this event. The S was treated with Prednisolone.

S 2000: Headache. This 66 y.o. S was hospitalized due to having a headache. Study drug was discontinued. The S was taking multiple medications and had a history of hypertension, coronary insufficiency and cervical arthrosis. He recovered and was discharged from the hospital.

S2257: Cholecystectomy. This 26 y.o female had a history of gastritis. She continued study drug following her surgery.

**APPEARS THIS WAY
ON ORIGINAL**

**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
4/2/02 02:15:36 PM
MEDICAL OFFICER

Thomas Laughren
7/21/02 12:45:04 PM
MEDICAL OFFICER

I agree that this NDA can be approved, once
we reach final agreement with the sponsor on
labeling; see memo to file for more detailed
comments.--TPL

**APPEARS THIS WAY
ON ORIGINAL**

Review and Evaluation of Clinical Data

NDA (Serial Number)	21323
Sponsor:	Forest Laboratories, Inc.
Drug:	Escitalopram oxalate
Proposed Indication:	Major Depression Disorder
Material Submitted:	NDA 21-323/Requested Information NDA 21-323/Amendment
Correspondence Date:	December 19, 2001; February 20, 2002
Date Received / Agency:	December 20, 2001
Date Review Completed	July 11, 2002
Reviewer:	David Gan, MD, Dr.PH, MPH

1. Introduction

Forest Laboratories, Inc. submitted a NDA dated March 23, 2001 for escitalopram (SCT) in the treatment of Major Depression Disorder. The NDA was granted approvable status on January 23, 2002.

In the original SCT NDA, the summary data for change of QTc from baseline for the pooled depression studies did not suggest a QTc-prolonging effect of SCT. However, other data (such as the multiple dose clinical pharmacology study 98107) included in the NDA submission raised the possibility that escitalopram (and citalopram) may have the ability to prolong the QTc interval. As such, on November 30, 2001, DNDP requested additional information about SCT's effect on the QTc interval. In this document, I reviewed the sponsor's response to DNDP's request for information (dated December 19, 2001), as well as additional information provided by the sponsor dated January 9, 2002, February 20, 2002 and May 28, 2002.

Additionally, this review will discuss the identification by the Division of Scientific Investigation of technical problems encountered at some study sites with the ECG machines, leading to duplicates of some tracings, and loss of others.

2. DNDP's Requests and Sponsor's Response regarding ECG data from clinical trials

The following table is a summary of DNDP's requests and the sponsor's response.

1. *For each of the studies (clinical pharmacology and phase II/III) in which ECGs were collected, provide the following information:*

On which visit days were ECGs performed?

ECGs at screening and end of study	Clinical Studies - SCT-MD-01, SCT-MD-02, 99001, 99003
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	Clinical Pharmacology Studies - SCT-PK-01, SCT-PK-02, SCT-PK-03, SCT-PK-04, SCT-PK-05, SCT-PK-06, 98113
ECGs were performed at screening and on Day -1 (baseline), Day 1 (pre-dose and 4 hours post-dose), and Day 8 in each dosing period	Clinical pharmacology studies 98106 (single dose two-way crossover study)
ECGs were performed at screening and on Day -1 (baseline), Day 2, Day 24, and Day 34 in each dosing period	Study 98107 (multiple dose two-way crossover study)
ECGs were performed at screening and on Day -1 and Day 1 in each dosing period, and on Day 3 and Day 14 after the last dose	Study 99166 (three way crossover dose proportionality study)

Were ECGs timed to correlate with Tmax, or another specific time point following dose administration?

ECGs were not timed to correlate with Tmax or any specific time point following dose administration in all studies except for the clinical pharmacology Study 98106 where the 4-hour post dose assessment corresponds approximately to Tmax.

Describe the method by which the ECGs were read (e.g., site investigator read, site cardiologist read, central cardiologist read, etc.)

Retrospectively read by central cardiologists Trained staff manually reviewed and recorded in a computerized database ECG parameters for all subjects. The central cardiologist then reviewed all ECGs from subjects included on this list.	Clinical pharmacology Studies 98106, 98107
Evaluated by central cardiologists ECGs were sent to central lab via mail, overnight courier or transtelephonic modem, an ECG tracking number was assigned to ECG using a label identification system. One single, board certified cardiologist analyzed each ECG.	Four clinical studies (SCT-MD-01, SCT-MD-02, 99001 and 99003), and clinical pharmacology Study 99166
Evaluated by site investigators ECG readings were printed on paper copy and the interpretation was completed by respective site investigators using this copy.	Clinical pharmacology Studies SCT-PK-01, SCT-PK-02, SCT-PK-03, SCT-PK-04, SCT-PK-05, SCT-PK-06 and 98113

If a central cardiologist read the ECGs, were they hand read off a paper copy or read off a digitized version?

Manual digitization of usually up to 3 beats were performed using a Jandel Scientific SigmaScan™ high resolution digitized ECG measurement system with a digitizing pad in which a magnified ECG was analyzed with a cross hair puck that can define the interval within 3 msec of accuracy. The SigmaScan System was calibrated for accuracy prior to each session by measuring a series of 200msec blocks from the background ECG paper grid.

What method was used to correct the QT interval for heart rate?

Bazett's method	all studies
Fridericia's method	clinical pharmacology Studies 98106 and 98107