8.0 Integrated Review of Safety

8.1 Background and Methodology for Safety Review

The evaluation of the safety of citalopram in the treatment of depression consisted of the following:

1) an examination of the entire Phase 1-3 citalopram clinical trials database which is the Integrated Summary of Safety (N_{cit}=4168 for Group 1 studies, 414 for Group 2 studies, and 15,498 for Group 3 studies), including events from ongoing studies to a cutoff date of October 1, 1996 for serious AEs (8.1.3), including deaths (section 8.1.1) and dropouts (8.1.2), and serious postmarketing adverse events reported spontaneously through the cut-off date of October 31, 1996;

2) an examination of safety findings from adverse event, laboratory, vital signs, and ECG data from Group 1 placebo-controlled studies;

3) examination of the literature review performed by the sponsor.

Important findings from the above review processes are organized into a review of systems (8.2), followed by a summary of the key safety findings (8.3).

8.1.1 Deaths

Deaths occurred during Group 1 and Group 3 studies, but not in Group 2 studies. They were reported whether they occurred during or after the protocol-defined follow-up period for reporting (generally within 4 weeks after termination of drug exposure). There were a total of 113 deaths recorded in Group 1 and Group 3 studies during the development program through October 1, 1996. Ninety-five were recorded in patients treated with citalopram, 7 in placebo-treated patients, and 11 in patients treated with other active drugs. A listing of deaths by patient, on citalopram, placebo, and other antidepressants in the development program can be found in Appendix 8.1.1.1.

Crude mortality rates per 100 patients based on total numbers of patients exposed in Group 1 and 3 studies are: 0.48% for citalopram (95 deaths in 19,666 patients); 0.88% for placebo treatment (7 deaths in 792 patients); and 0.70% for active comparator drugs (11 deaths in 1576 patients). Exposure adjusted mortality rates are provided in Table 8.1.1.

The incidence of deaths during the development program (Groups 1 and 3) by treatment by gender, and by age for citalopram-treated patients in the development program is provided in the ISS. In the review of systems (section 8.2) deaths during citalopram treatment are discussed under the appropriate body system.

Table 8.1.1: Incidence of Mortality by Treatment Group For All Group 1 Studies to October 1, 1997					
Treatment Group	**Total Number of Patients**	**Patient Exposure Years**	**Number of Deaths**	**Crude Mortality Incidence (%)**	**Mortality per 100 PEY**
Citalopram	4168	1347.7	35	0.008	2.6
Placebo	691	150.3	2	0.003	1.3
TCA	570	123.9	7	0.012	5.7
SSRI	451	60.4	0	0.000	0.0

8.1.2 Dropouts

8.1.2.1 Overall Profile of Dropouts

Table 8.1.2.1 enumerates citalopram dropouts, placebo dropouts, and active control dropouts from the short-term (≤ 8 weeks), controlled Group 1 studies. They are organized according to the primary reason for dropout as indicated by the investigator, unless after review of case report forms by Forest and Lundbeck, they were reclassified, according to the sponsor, using a more conservative approach. In that approach, the sponsor identified events as ADOs that may not have been classified as such by investigators, or, listed multiple AEs present at early termination as an ADO when the investigator had not indicated which one event resulted in early discontinuation.

The most common reason for dropout among citalopram and active control patients was an adverse event, and in the placebo group, lack of efficacy.

Table 8.1.2.1: Dropout Profile: Enumeration (%) of Dropout by Treatment Group and Reasons for Short-term, Double-Blind, Controlled Group 1 Studies with Citalopram to October 1, 1996				
Reasons for Dropout	**Citalopram N=2744**	**Placebo N=575**	**TCA N=570**	**SSRI N=451**
Lack of Efficacy	121 (4.4%)	71 (12.3%)	22 (3.9%)	23 (5.1%)
Adverse Event	363 (13.2%)	47 (8.2%)	91 (16%)	44 (9.8%)
Noncompliance	64 (2.3%)	25 (4.3%)	9 (1.6%)	7 (1.6%)
Other	197 (7.2%)	57 (9.9%)	40 (7%)	16 (3.5%)
Recovery	31 (1.1%)	5 (0.9%)	3 (0.5%)	21 (4.7%)
Total Dropouts	776 (28.3%)	205 (35.7%)	165 (28.9%)	111 (24.6%)

8.1.2.2 Adverse Events Associated with Dropout

Case report forms for dropouts were reviewed by Lundbeck personnel to identify events designated in the data fields or in comment fields to determine which events were responsible for discontinuation for both citalopram and placebo. Cases in which there was no indication in CRFs as to which event was responsible, resulted in assignment of all events recorded in the CRF that were present at the time the patient dropped out.

Table 8.1.2.2 depicts the AEs which were listed as reasons for premature discontinuation in at least 1% of the citalopram-treated group from Group 1, placebo-controlled, short-term studies (85A, 86A, 86141, 87A, 89303, 89306, and 91206). Adverse events in the psychiatric disorders body system accounted for the majority of the premature discontinuations in these studies; insomnia and somnolence were the most frequent AEs in that body system. The single most frequent AE causing premature discontinuation was nausea.

Dropouts associated with SAEs are discussed in the review of systems (8.2).

Table 8.1.2.2: Number (%) of Dropouts Secondary to Adverse Events from Short-term, Placebo-Controlled Group 1 Studies

Body system/preferred term	Citalopram (N=1063)	Placebo (N=446)
Body as Whole		
Asthenia	11 (1.0)	2 (0.4)
Psychiatric		
Insomnia	34 (3.2)	5 (1.1)
Somnolence	25 (2.4)	5 (1.1)
Suicide attempt	12 (1.1)	5 (1.1)
Anxiety	14 (1.3)	6 (1.3)
Agitation	13 (1.2)	1 (0.2)
Gastrointestinal		
Nausea	45 (4.2)	0
Vomiting	15 (1.4)	0
Mouth dry	11 (1.0)	1 (0.2)
Nervous System		
Headache	22 (2.1)	5 (1.1)
Dizziness	22 (2.1)	3 (0.7)

There were 12 dropouts due to AEs in Group 2 (phase 1) studies (total N=414), none of these dropout events were classified as serious. These will be

discussed in the review of systems.

8.1.3 Other Serious Adverse Events

The Forest medical monitor reviewed all study events to identify those which were serious. Serious AEs were defined as:

- fatal or life-threatening events;
- permanently disabling events/injuries;
- events/injuries that required inpatient hospitalization;
- congenital abnormality/anomaly or cancer;
- an overdose of any drug; and
- pregnancy.

Serious AEs will be discussed under the appropriate section in the Review of Systems (section 8.2). Line listings and narratives were reviewed for all deaths and dropouts in Group 1, 2 and 3 studies. For other SAEs, line listings were reviewed as were most of the narratives if further information was needed to clarify what the event was or to see if other illness or medication was also associated with an event. Not all narratives for events most unlikely to be caused by citalopram such as traumatic injury, appendicitis, suicide attempts, unintended pregnancy, and lack of therapeutic response were read.

Serious AEs reported to the DSU through the spontaneous reporting system (SRS) following the marketing of citalopram, through a cutoff date of October 31, 1996 are included in the NDA database. It is estimated that more than 4 million patients have been treated with citalopram since market introduction. The following adverse events have been reported to be temporally associated with citalopram treatment in at least 3 patients and are not described elsewhere: angioedema, erythema multiforme, hepatic function abnormal, hepatitis, hyponatremia, neuroleptic malignant syndrome, neuropathy, pancreatitis, serotonin syndrome, syndrome of inappropriate antidiuretic hormone secretion, thrombocytopenia, ventricular arrhythmia, and withdrawal syndrome. These and any other serious AEs from the postmarketing SRS that add to information from the ISS will be discussed in the appropriate section in the review of systems.

8.1.4 Other Search Strategies

Adverse events of special interest were defined on the basis of the known pharmacodynamic effects of citalopram and on the basis of critical events associated with depression. These were: suicide attempts and overdose, manic reaction, pregnancy, male ejaculatory dysfunction, female anorgasmia, seizures, and arrhythmias. Patients in Group 1 studies reporting these AEs were identified by the sponsor by searching for a preferred term or reported terms consistent with the presence of the event.

These events will be discussed in the review of systems.

8.1.5 Adverse Event Incidence Tables

8.1.5.1 Approach to Eliciting Adverse Events in the Development Program

For most of the Group 1 studies, AE reporting was done by spontaneous report; for 6 of these 19 studies, in addition to spontaneous reports, a checklist was utilized.

8.1.5.2 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

Treatment-emergent AEs (TEAEs) were defined as new events that emerged after the start of drug treatment or, for events that were present before drug treatment, that intensified after the start of drug treatment.

Adverse events were recorded by clinical investigators using their own terminology. A WHO dictionary of terminology was used to classify reported AEs. The translation of investigator terms to WHO terms appears to be appropriate in general. The differentiation between a few WHO classifications, such as ejaculation disorder and ejaculation failure, edema dependent and edema legs, micturition frequency and polyuria, and pneumonia and pneumonitis, is unclear, as similar events appear to be classified under each term in the above noted pairs. These identical or similar events will be considered as one category for purposes of the review.

8.1.5.3 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

The seven short-term placebo-controlled Group 1 studies vary in their methodologies and design features; rather than pooling them to characterize the AE profile, the largest study among them, 91206, will be used for this review. It is also a fixed dose study that covers the range of doses that are recommended for clinical use. It was carried out at 12 centers in the U.S. in outpatients with moderate to severe depression. Patients randomized to the 10 and 20 mg dosage groups reached the designated dose on the first day of treatment; those in the 40 and 60 mg groups were treated with 20 mg during Days 1-3 and 40 mg during Days 4-7. Patients in the 60 mg group attained that dose on Day 8 and remained at that dose for the remaining 5 weeks of the study. Adjustments in dosage were not permitted. Appendix 8.1.5.3.1 displays the proportions of patients in the various citalopram dose groups and placebo group who experienced AEs that were reported in at least 2% of any of the citalopram dose groups.

Appendix 8.1.5.3.2 displays the categorical incidence of AEs which were reported in citalopram patients in all Group 1 studies, except for those included in Appendix 8.1.5.3.1.

8.1.5.4 Identifying Common and Drug-Related Adverse Events

Treatment-emergent AEs that are considered common and drug-related (i.e. reported in at least 5% of citalopram patients in any dose group at an

incidence at least twice that in the placebo group, based on data from the 2% ADR table (Appendix 8.1.5.3.1) are shown in Table 8.1.5.4.

Table 8.1.5.4: Common and Drug-Related Treatment-Emergent Adverse Events: Study 91206

Adverse event	placebo N=129	10 mg N=131	20 mg N=130	40 mg N=131	60 mg N=129
Body as a Whole					
Fatigue	5%	3%	4%	8%	16%
Fever	1%	5%	5%	4%	2%
Gastrointestinal System					
Abdominal pain	3%	7%	9%	2%	2%
Mouth dry	6%	15%	18%	13%	18%
Nausea	11%	19%	28%	23%	22%
Psychiatric Disorders					
Agitation	2%	0%	2%	2%	5%
Anorexia	2%	6%	8%	5%	9%
Impotence	0%	1%	0%	7%	5%
Insomnia	11%	13%	15%	21%	24%
Libido decreased	1%	2%	4%	6%	5%
Somnolence	4%	9%	13%	22%	19%
Yawning	0%	2%	2%	5%	7%
Central and Peripheral Nervous System					
Dizziness	5%	5%	11%	10%	9%
Tremor	0%	2%	5%	6%	5%
Respiratory System					
Sinusitis	1%	7%	3%	8%	2%
Skin and Appendages Disorders					
Sweating increased	2%	2%	8%	11%	12%
Reproductive System, Female					
Dysmenorrhea	2%	3%	4%	3%	5%

TEAEs that are common and drug-related as defined above were also identified by the sponsor using the pool of short-term, placebo-controlled Group 1 studies. The only events identified were ejaculation disorder and ejaculation failure. These will be discussed in the review of systems.

8.1.5.5 Additional Analyses and Explorations

8.1.5.5.1 Dose-Relatedness

The data from the large fixed dose study (91206) was used to address the dose-relatedness of adverse events. A trend test (Jonckheere's) was applied to the citalopram dose groups (excluding the placebo group) to determine statistical significance for a trend. The events meeting these criteria include: insomnia ($p<0.004$), fatigue ($p<0.000$), somnolence ($p<0.004$), increased sweating ($p<0.001$), yawning ($p<0.004$), and impotence ($p<0.006$).

8.1.5.5.2 Adverse Event/Demographic Interaction

The sponsor examined the relationship between the occurrence of common and likely drug-related AEs, i.e., those events occurring at a frequency ≥ 5% in the citalopram group and ≥ twice the placebo rate, and demographic characteristics. This analysis was done for the Group 1 placebo-controlled, short-term study pool.

The only AEs that fulfilled the definition above were 'ejaculation failure' (4.2% incidence on citalopram and 0.9% incidence on placebo) and 'ejaculation disorder' (2.4% incidence on citalopram and 0.0% incidence on placebo). For the analysis of demographic interactions, the sponsor used all AEs classified as' ejaculation disorder', which encompassed investigator terms 'ejaculation failure', 'impotence', 'delayed ejaculation', 'premature ejaculation', 'painful erections', 'decreased penile sensitivity', 'prostatism', 'prostatitis', and 'strained or drawn up testicles'. The testicular, prostate, and penile problems all occurred at incidences of < 1% in the citalopram group; most of the cases categorized under 'ejaculation disorder' were ejaculation failure. An analysis of the effect of race on these events could not be done since all events, with the exception of possibly one patient of unknown race, were experienced by Caucasian patients.

The effect of age on these TEAEs was evaluated in the following age ranges: < 39 years, 40-55 years, and > 55 years. The sponsor elected these age divisions because only one patient > 65 presented with a treatment-emergent ejaculation problem. For the < 39 year old group, the relative risk of citalopram to placebo was 4.0 (95% C.I.= 0.96-17). In the 40-55 year old group, 6.9% on citalopram and 0% on placebo had an ejaculation disorder. In the > 55 year old group, 5.6% on citalopram and 0% on placebo had an ejaculation disorder. The common odds ration is 8.75 (95% C.I. = 2.63-29.1) and Breslow-Day Chi Square: $\chi^2=1.93$, $p<0.38$.

8.1.6 Laboratory Findings

8.1.6.1 Extent of Laboratory Testing

Laboratory testing in the primary integrated database consisted of clinical chemistry, hematology, and urinalysis. The testing performed during each of the specific studies evaluated and their frequency is shown in Appendix 8.1.6.1. These batteries of tests are adequate to study the effects of citalopram on common laboratory variables.

8.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The pool of the eight short-term, placebo-controlled Group 1 studies (85A, 86A, 87A, 91206, 86141, 89303, 89306, and 91202) was chosen as the primary database to evaluate the effects of citalopram on laboratory variables. Although these studies varied in design somewhat, this pool was felt to be reasonably homogeneous for the purpose of evaluating laboratory test changes. Examination of dropouts due to laboratory abnormalities, however, was conducted across the entire integrated safety database (all 19 Group 1 studies) and the 29 studies in Group 2.

8.1.6.3 Standard Analyses and Exploration of Laboratory Data

Standard analyses consisted of the following:

1) a comparison of mean changes from baseline to final on-drug assessment between citalopram and placebo treatment groups.
2) a comparison of the proportions of patients meeting criteria for significant abnormalities in laboratory parameters between drug and placebo treatment groups.
3) a comparison of the proportions of patients dropping out for laboratory abnormalities between citalopram and placebo.

8.1.6.3.1 Analyses Focused on Measures of Central Tendency

A summary of mean change from baseline to last on-drug visit for each clinical chemistry analyte is presented in Appendix 8.1.6.3.1.1. Measures of mean change from baseline differed significantly between citalopram and placebo patients for three clinical chemistry parameters: bilirubin, calcium, and uric acid. These changes were not clinically significant.

A summary of mean change from baseline to last on-drug visit for each hematology analyte is presented in Appendix 8.1.6.3.1.2. Measures of mean change from baseline differed significantly in citalopram and placebo patients only for platelets; this was not clinically significant.

Urine specific gravity was the only urinalysis variable for which mean change from baseline was evaluated; there was no statistical difference in this parameter between the citalopram and placebo groups. The mean change from baseline to last on-drug visit for it is presented in Appendix 8.1.6.3.1.3.

8.1.6.3.2 Analyses Focused on Outliers

Criteria for identifying patients with potentially clinically significant (PCS) changes in laboratory parameters are listed in Appendices 8.1.6.3.2.1 (chemistry), 8.1.6.3.2.2 (hematology), and 8.1.6.3.2.3. (urinalysis).

The proportions of patients meeting these criteria are displayed in Appendices 8.1.6.3.2.4, 8.1.6.3.2.5, and 8.1.6.3.2.6, respectively. There were no statistically significant differences in the incidence of PCS lab values between citalopram and placebo.

In the three cases of hyponatremia, sodium level decreased to 120, 124, and 125 mmol/L; all of these normalized while continuing on drug treatment. None of these patients had an SAE. None had an associated TEAE, with the exception of one patient who had mild-moderate somnolence.

The highest ALT and AST levels occurred in a patient with infectious hepatitis who dropped out of the study . In the others peak levels ranged . In two patients values normalized while continuing on drug; in the others no follow-up laboratory data are included in the line listing. In the two patients with elevated bilirubin while on citalopram, levels went from in one patient and from in the other. Neither patient was jaundiced. In one patient, bilirubin level normalized while continuing on drug. In the other patient, no subsequent level is included in the line listing.

In the 9 patients with hypoglycemia, blood glucose normalized on continued citalopram treatment. The low glucose was present in only one of several glucose tests over the course of the study in all patients. None of these patients had SAEs, and in most no TEAE was recorded concurrent with the low blood glucose. In one patient there may have been an associated headache; in another diarrhea and dyspepsia were recorded as TEAEs.

In the 4 patients with low leukocyte counts on citalopram, values ranged from The abnormality was present in only one of several tests over the course of the study. In all patients, leukocyte counts normalized on continued drug.

8.1.6.3.3 Dropouts for Laboratory Abnormalities

Fourteen citalopram patients (0.3%) are known to have discontinued citalopram treatment due to laboratory abnormalities during the 19 Group 1 studies (Appendices 8.1.6.3.3, 8.1.6.3.4). The dropout rate was about the same for the placebo group, in which there were 2 dropouts (0.3%). None in Group 2 dropped out because of laboratory abnormalities. The patients who dropped out while on citalopram will be discussed in the review of systems.

8.1.6.4 Additional Analyses and Explorations

Laboratory abnormalities which were classified as serious adverse events in Group 2, Group 3, and ongoing studies were examined and will be discussed in the review of systems. Laboratory abnormalities derived from Lundbeck DSU

postmarketing reports that had not been discussed elsewhere will also be included in the review of systems.

8.1.7 Vital Signs

8.1.7.1 Extent of Vital Sign Measurement in the Development Program

Appendix 8.1.7.1 depicts the vital sign assessments and frequencies of assessment for the six short-term, placebo-controlled Group 1 studies in which vital signs were assessed (vital signs data were not collected in all placebo-controlled Group 1 studies). These studies were all in depressed patients, with the exception of 91202, which was in panic disorder patients. These studies are felt to be adequate to reasonably evaluate the effects of citalopram on vital signs.

8.1.7.2 Selection of Studies and Analyses for Overall Drug Control Comparisons

The pool of the six short-term Group 1 studies in which vital signs were assessed was chosen as the primary database to evaluate the effects of citalopram on vital sign parameters relative to placebo. Although these studies varied somewhat in design characteristics, this pool was felt to be reasonably homogeneous and large for the purpose of evaluating vital sign changes. Examination of dropouts due to vital sign abnormalities, however, included all Group 1, Group 2, and ongoing studies.

8.1.7.3 Standard Analyses and Explorations of Vital Sign Data

Standard analyses consisted of the following:

1) a comparison of the mean changes from baseline between citalopram and placebo treatment groups.
2) a comparison of the proportions of patients meeting criteria for significant abnormalities in vital sign parameters between drug and placebo treatment groups.
3) a comparison of the proportions of patients dropping out for vital sign abnormalities between drug and placebo.

8.1.7.3.1 Analysis Focused on Measures of Central Tendency

Appendix 8.1.7.3.1 depicts mean changes from baseline to final visit on drug for vital sign measures within the pool of short-term, placebo-controlled Group 1 studies. There were statistically significant small mean changes in sitting, standing, and supine pulse rates, sitting systolic blood pressure, and weight between the citalopram and placebo groups. The mean changes were not clinically significant.

8.1.7.3.2 Analysis Focused on Outliers

Appendix 8.1.7.3.2.1 lists the criteria used by the sponsor to identify vital

sign and weight changes of potential clinical significance.

Appendix 8.1.7.3.2.2 displays the proportions of patients in the short-term, placebo-controlled Group 1 studies who had at least one measurement during therapy defined as significant by these criteria. There were no statistically significant differences at the 5% level (t-test) in the incidence of PCS vital sign changes between the citalopram and placebo groups.

8.1.7.3.3 Dropouts for Vital Sign Abnormalities

Thirteen (0.3%) citalopram treated patients who were withdrawn from Group 1 studies in large part because of vital sign abnormalities are discussed in the review of systems. Five were bradycardic (none on placebo), 6 were hypotensive (2 on placebo), and 2 were hypertensive (none on placebo). None of the Group 2 study subjects dropped out because of vital signs abnormalities.

8.1.7.4 Additional Analyses and Explorations

Vital sign abnormalities which were classified as serious adverse events in Group 1, 2 and 3 studies or as a cause of dropout from Groups 1 and 2 were examined and will be discussed in the review of systems.

8.1.8 ECGs

8.1.8.1 Extent of ECG Recording in the Development Program

Appendix 8.1.8.1 depicts the frequency of standard 12-lead ECG assessments for five placebo-controlled Group 1 studies in which ECG data were adequately collected as part of the routine safety evaluations (85A, 91206, 86141, 89304, and 91203). These were all done in depressed patients with the exception of 91203, which was a study in Alzheimer's patients. In addition, the sponsor provides ECG data from three other Group 1 studies in which ECG data were adequately collected as part of the routine safety evaluations (8213, 88A, which were uncontrolled, and 91302 which had an active control). ECGs were discarded for study 92302 due to poor quality, and those from studies 86A and 87A were photocopies that were not assessable. In addition, an evaluation of dropouts and serious AEs related to ECG changes from Group 1, 2, and ongoing studies was done. In addition, a report from entitled "Electrocardiograms from volunteers and patients given citalopram; a comprehensive survey" was reviewed. The information provided was adequate to reasonably evaluate the effects of citalopram on ECG parameters.

8.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The pool of the five Group 1 studies in which ECGs were assessed was chosen as the primary database to evaluate the effects of citalopram on ECG parameters relative to placebo. Although these studies varied somewhat in design characteristics, this pool was felt to be reasonably homogeneous and large for the purpose of evaluating ECG changes. Examination of dropouts due to ECG abnormalities, however, included all Group 1, Group 2, and ongoing studies.

8.1.8.3 Standard Analyses and Explorations of ECG Data

Standard analyses consisted of the following:

1) a comparison of the mean changes from baseline between citalopram and placebo treatment groups.
2) a comparison of the proportions of patients meeting criteria for significant abnormalities in ECG parameters between drug and placebo treatment groups.
3) a comparison of the proportions of patients dropping out for ECG abnormalities between drug and placebo.

8.1.8.3.1 Analyses Focused on Measures of Central Tendency

Appendix 8.1.8.3.1 depicts mean changes from baseline to final visit on drug for ECG parameters within the pool of five placebo-controlled Group 1 studies. The only statistically significant change was in heart rate, which increased by 1.7 bpm on citalopram, and was unchanged on placebo. Findings will be discussed further in the review of systems.

8.1.8.3.2 Analyses Focused on Outliers

Appendix 8.1.8.3.2.1 lists the criteria used by the sponsor to identify ECG changes of potential clinical significance. Appendix 8.1.8.3.2.2 displays the proportion of patients with potentially clinically significant changes in the five placebo-controlled studies. There were no statistically significant differences (Fisher's exact test, $p < 0.05$) between the placebo and citalopram groups.

None of the 9 patients who had a prolonged QT_c recorded (Appx. 8.1.8.3.2.2) had any SAEs, and most of them had no TEAEs. Listed TEAEs in these patients included one patient with asthenia and a bundle branch block, one with nausea and vomiting, one with a mild thyroid condition, and one 86 y.o. with atrial fibrillation. The longest QT_c interval reported in this group was 0.56 sec. All but one had the abnormality recorded at only one time point; QT_c intervals in other ECGs were within normal limits. In Appx. 8.1.8.3.2.2, 11 of the 16 patients with prolonged QRS on citalopram also had a prolonged QRS at baseline. One of the 16 patients with a prolonged QRS had a SAE, which was a myocardial infarction in an 83 y.o. woman after about 4 months on 20 mg. This patient had a prolonged QRS at baseline ; four subsequent measurements on citalopram were . Most of the patients with prolonged QRS had no TEAEs. Listed TEAEs in these patients included three with tachycardia; other TEAEs were primarily psychiatric symptoms. The longest QRS recorded in this group was 0.16 sec; most had normal QRS intervals on other ECGs recorded.

In the eight studies for which ECG data were recorded in the ISS, there were a total of 19 patients who had a normal QT_c at baseline and a $QT_c > 0.500$ sec during citalopram treatment. None of them had a cardiovascular or rhythm

disorder related serious AE. Significant ECG changes will be discussed in detail in the review of systems section.

8.1.8.3.3 Dropouts for ECG Abnormalities

Nine patients in Group 1 studies dropped out of studies due, in large part, to ECG abnormalities; they are discussed in the review of systems. Three had extrasystoles, one with bigeminy. Three had ischemic changes, two had increased QT intervals with U waves, and one had myocardial infarction. One patient prematurely discontinued (died) while on placebo; ECG showed prolonged QT, PVCs, ischemia. No Group 2 subjects dropped out due to ECG abnormalities.

8.1.8.4 Additional Analyses and Explorations

An evaluation of serious AEs related to ECG changes from Groups 1, 2 , 3 and ongoing studies was done, as well as dropouts from Group 1 and 2 studies. This information will be discussed in the review of systems section (8.2.1). The sponsor also evaluated the postmarketing DSU database to October 1, 1996, for ECG abnormalities, much of which was included in the report noted below.

A report entitled "Electrocardiograms from volunteers and patients given citalopram; a comprehensive survey" was reviewed. This is a survey and detailed analysis by an expert reviewer done in 1995, of all available information related to ECG data and cardiovascular safety. At the time, the pharmacovigilance database included spontaneous AE reporting from approximately 600,000 patients in clinical practice and 10,000 patients in clinical trials, as well as data from 42 Group 1 and 3 studies. The external expert identified was Soren Lind Rasmussen, M.D., Specialist ~~in~~ Cardiology. The measurement of each ECG component was done by registered nurses who specialize in cardiology, who were under his supervision and blinded as to treatment group. Computerized selection for parameters falling outside of the limits of normal was then done. The limits used were as shown in Appendix 8.1.8.3.2.1, with the exception of the QT_c interval, for which a more conservative 0.44 sec was used, uncorrected for age.

The ECG survey noted above was reviewed in the DNDP in February, 1996. Also at that time, an adverse events summary which covered from 1979 through December, 1993 and prepared by Lundbeck, was reviewed. Additional summaries and 15-day AE reports from January, 1994 through September 23, 1996 were reviewed. The DNDP review specifically looked for evidence of arrhythmias.

In addition to the 42 Group 1 and Group 3 studies that were examined in the ECG survey, particular attention was given to people in those studies who may have been more susceptible to cardiac effects of citalopram. Susceptability was identified by the external cardiac expert and included those with a cardiac diagnosis prior to treatment (n_{cit} = 277, n_{pbo} = 31). Also considered in the susceptible group were patients receiving concomitant medication known to affect the QT interval (TCAs, neuroleptics, calcium channel blockers, some beta-blockers, beta-agonists, and digoxin. Also considered in the susceptible group were patients with a high baseline QT_c ($\geq$ 0.5 sec). Arrhythmias and

prolonged QT intervals were specifically searched for. Results are noted in section 8.2.1. The report also included a phase 1, randomized, double-blind, placebo-controlled, parallel group study (92104) which was conducted in 23 healthy male volunteers to obtain information on the individual variability of the QT_c, as well as differences between citalopram and placebo at steady state at the maximum recommended dose of citalopram (60 mg). Information from the survey is reviewed in section 8.2.1.

A comparison of ECG parameters in patients < 60 yrs. old and ≥ 60 yrs. old was done using patients from the 8 Group 1 studies in which ECG data were available (section 8.2.1).

8.1.9 Special Studies

8.1.9.1 Ophthalmologic Studies

The effects of citalopram on ophthalmologic function in the clinical development program were evaluated in three ways: 1) data was examined from ophthalmologic exams done pre- and post-citalopram exposure in study 88A; 2) SAEs and TEAEs from Group 1 studies, pertaining to the WHO vision system disorders body system; and 3) evaluation of postmarketing DSU database events collected in the DSU since 1989, the year citalopram entered the European market.

No serious AEs for vision disorders attributable to citalopram were reported during the development program. Reported vision system events in the SRS generally were reversible, and did not suggest ocular pathology associated with citalopram use. Further discussion of this topic is included in the review of systems section (8.2.9).

8.1.9.2 Studies on Psychomotor Function

Three clinical pharmacology studies investigating citalopram effects on psychomotor function were reported. In study 94303, "A double-blind controlled study of psychomotor function in normal volunteers after acute and chronic dosing with citalopram by reference to placebo and dothiepin"; 21 subjects with mean age of 31 years participated. Doses of citalopram tested were 10, 20, and 40 mg; dothiepin dose was 75 mg. Citalopram and placebo were taken for 8 days, dothiepin was taken only on days 1 and 8. For each drug condition, testing was done pre-drug and 2 , 4 , 5, and 8 hours after drug, on the first and final days of drug administration. Tests were critical flicker fusion, choice reaction time, short term memory test, compensatory tracking task, Milford Epworth Speepiness Scale, and an analog mood/side effect rating scale. Citalopram was found to raise critical flicker fusion thresholds, indicating an improvement, without affecting other psychomotor tests. Dothiepin was found to impair psychomotor function and to be more sedating than citalopram.

In studies 8109a and 8109b, single and repeated doses, respectively, of citalopram were compared with placebo and amitriptyline in 12 normal volunteers, mean age = 38 years. Citalopram doses tested were 20 and 40 mg and amitriptyline dose was 37.5 mg in the single dose study. Psychomotor tests

included critical flicker fusion, tapping interval, digit symbol substitution, symbol copying, reaction time, and memory tests. In addition, symptomatic and subjective measures of variables such as alertness were used. In the single dose study, citalopram produced some sedation and tiredness on a mood rating scale as compared to placebo, which was greater for the 20 mg as compared with the 40 mg dose, and much less than that associated with amitriptyline. Citalopram marginally increased visual reaction time at 40 mg, at the 3 hour time point after dosing; the effect of amitriptyline was more marked. The 40 mg dose of citalopram sped up and amitriptyline prolonged the tapping rate. On DSST, performance was slightly though statistically significantly impaired at the 3 hour point after 40 mg; a marked diminuation was seen after amitriptyline. Citalopram enhanced performance on the symbol copying test, while amitriptyline impaired performance at 3 hours.

In the repeated dose study, 12 volunteers were given 40 mg citalopram, amitriptyline 75 mg or placebo, qhs x 9 days. They were tested pre-drug and on the morning after the final dose. Amitriptyline and not citalopram caused drowsiness on a mood scale; none of the psychomotor tests were significantly affected by either drug with the exception of CFF, in which both drugs showed a slight decrease.

In conclusion for the psychomotor testing done, minimal effects on performance were seen after up to 40 mg of citalopram in single doses and repeat doses x 8 days, as compared with placebo in normal volunteers with mean ages in their thirties.

8.1.10 Withdrawal Phenomena/Abuse Potential

Potential withdrawal effects following abrupt discontinuation of citalopram treatment were adequately evaluated in Study 89304, a Group 1, placebo-controlled, longer-term study designed to evaluate maintenance effects of citalopram in patients with depression. This study contained an initial open-label treatment period in which all patients received citalopram (20-60 mg) for up to 8 weeks. Patients who demonstrated a satisfactory clinical response then randomized to double-blind treatment with placebo or citalopram. Patients randomized to placebo (n=150) provided an appropriate group in which to assess treatment emergent adverse events associated with abrupt termination of citalopram, and to compare emergent events in a double-blind clinical trial setting with those in the group of patients randomized to continued treatment with citalopram (n=150). A separate analysis to compare emergent events was conducted at the Week 2 visit covering the first 2 weeks of abrupt withdrawal for patients participating in the double-blind treatment period of Study 89304.

The proportion of patients that experienced one or more TEAEs was similar in the two treatment groups, but the number of events (withdrawal) expressed on a per patient basis was approximately twice as high in the placebo group as in the group which continued citalopram. More placebo treated patients than citalopram treated patients reported an event within the psychiatric disorders body system (15.3% versus 10.7%, respectively) and in the central and peripheral nervous system disorders body system (15.3% versus 9.3%).

Several individual events within the psychiatric and central and peripheral nervous system disorders occurred at a frequency in the placebo patients which was two-fold higher in crude occurrence rate, or represented a 5% absolute difference between the crude occurrence rates compared to the citalopram treated patients. These events, by preferred terms were, in order of decreasing frequency: emotional indifference (5.6% in placebo compared to 0.7% in citalopram treated patients); anxiety (5.6% versus 2.0%); concentration impaired (4.2% versus 0%); migraine (4.2% versus 0.7%); tremor (4.2% versus 0.7%); paresthesia (4.2% versus 1.3%); and amnesia (4.2% versus 2.0%). Thus, the data suggest that several symptoms may be associated with abrupt termination of short-term (8 week) treatment of depressed patients with 20 to 60 mg/day citalopram. These symptoms were generally related to disruption of cognitive function (eg. difficulty concentrating), probable manifestations of increased anxiety (anxiety, paresthesias, increased tremor, increased migraine), and to emotional indifference. These types of events could suggest an overall increase in anxiety that accompanies withdrawal of many psychoactive drug classes, but also could reflect re-emergence of symptoms in depressed patients. Most of the events recorded following citalopram discontinuation were mild in intensity, and no patients randomized to placebo discontinued from Study 89304 during the first two weeks of treatment. The only observed event of potential concern associated with abrupt citalopram discontinuation was an epileptic seizure, reported as mild in intensity, reported for one patient (Patient 3005). Since the seizure occurred within one day after randomization to placebo treatment, at a time when citalopram plasma levels would have decreased little from steady-state, it is unlikely that the seizure could be attributed to reduction of citalopram concentrations. The patient did not leave the study.

In Group 1 and 3 studies, there was one SAE listed as withdrawal syndrome: Study 89404, #72: 37 y.o. female was treated with 20-40 mg of citalopram for 9 weeks, when she was switched to imipramine the day after stopping citalopram. She developed headaches, nausea, vomiting , and dizziness, with symptoms increasing over one week. Imipramine was discontinued, CT scan and lumbar puncture were negative. Information on symptom resolution was not provided; concomitant medication was oxazepam. This may also have been a drug interaction or a response to imipramine.

Citalopram showed no potential to induce physical or psychological dependence in two animal studies. Among seven groups of rats in one study, two groups received water p.o. or saline s.c., two groups received constant dosages 10 and 70 mg/kg citalopram p.o., another group received citalopram starting at 10 and increasing to 70 mg/kg by the end of the 7-week treatment period, one group was treated with p.o. phenobarbital (starting at 10 and increasing to 70 mg/kg), and one group received s.c. morphine (starting at 10 and increasing to 70 mg/kg). On day 37, 5 mg/kg naloxone was administered s.c. At the end of the 7-week treatment period, one subgroup of each treatment group (n=6) was administered water or saline for one week to determine spontaneous withdrawal symptoms. The other two subgroups of citalopram-treated rats were treated with either phenobarbital or morphine (10 mg/kg, s.c.) to determine cross-dependence. Citalopram neither induced

physical dependence nor cross-dependence.

The potential for psychological dependence on citalopram was determined in four cynomolgus monkeys (two/sex). Animals were provided two levels for self-administration of saline or citalopram, via an indwelling jugular catheter. The initial dose of citalopram was 0.075 mg/kg/injection, increasing to 0.15 and 0.3 mg/kg/injection at 2-week intervals. Three of the four monkeys failed to initiate drug-seeking behavior for citalopram. Two animals that showed a low level of citalopram self-administration had a higher response rate for saline administration. The fourth showed a low level of lever pressing, directed solely for citalopram, but because it failed to increase lever-pressing to compensate for an increase in the fixed ratio schedule; its response was also considered to be indiscriminate. A period of involuntary injection of citalopram (0.3 mg/kg/injection every 3 hours x 14 days) failed to induce drug seeking behavior.

There is little evidence to suggest significant withdrawal effects and abuse potential for citalopram. The information in the proposed labeling regarding withdrawal and abuse potential is adequate.

8.1.11 Human Reproduction Data

Pregnancy was of specific interest due to the teratogenicity observed in animal studies; these are summarized briefly below. Citalopram is designated Pregnancy Category C in the proposed labelling on the basis of data from rats. A total of 40 pregnancies reported during citalopram exposure are contained in the DSU data base as submitted in the NDA; 12 of these occurred during Group I studies and the remaining 28 derived from Group 3 and the postmarketing DSU database. Two spontaneous abortions were documented; one due to an ectopic pregnancy in a woman with a history of 4 prior ectopics (patient #595, study 91206), and the other via the postmarketing database about which little is known. In ten additional cases, pregnancy was terminated by elective abortion (nine cases) or due to the mothers deteriorating psychiatric condition (one case). In one other case, outcome is reported as "blighted ovum or pseudocyesis'. The remaining 27 pregnancies generally proceeded to term with no consequences, though 3 women were lost to followup.

Of the 24 pregnancies remaining, 22 produced ultimately healthy infants. In one of the poor outcomes, the mother was reported to have taken citalopram at a dose of 50 mg for 71 days during an unknown period of the pregnancy. The report says only that the infant was born prematurely and weighed 1200 g. The other who was not born healthy had myocardial hypertrophy, slight tricuspid valve insufficiency, and an open foramen ovale. The 27 y.o. mother had taken 20-40 mg of citalopram during the first 2 months of pregnancy, as well as terfenidine, clemastine, terbutaline, and sodium cromoglycate at times during the 1st and 2nd trimesters. The child was delivered prematurely at 31 weeks after decreased fetal movements. When last examined there was no hypertrophy though the foramen ovale was still suspected to be open.

Among the 22 known healthy infants, four were born prematurely. Three of the mothers had been on 40 mg, one for the entire pregnancy, one for the second

trimester, and the other for an unknown time period. The fourth was on 30 mg for an unknown number of months. Two of these had breathing difficulties during the first day, one also had myoclonus which resolved. In one case early delivery was elected reportedly due to the size of the mother's pelvis, another was from premature rupture of the membranes. One of these children had inguinal and umbilical hernias which were surgically repaired with good outcome. Another child was reported to be irritable and tremulous for the first week; the mother had been taking an unknown dose of citalopram during the last 2 months, along with other drugs and had undergone vacuum extraction.

The mothers of healthy infants for which the information is known, took citalopram during the following time intervals: first trimester (n=9), second trimester (n=1), entire pregnancy (n=4), entire pregnancy except the first few weeks (n=2), first and part of third trimesters (n=1), and one (noted above) during the last 2 months.

There were eight reports of fetal abnormalities associated with citalopram treated mothers in the sponsor's pre- and post-marketing database as reported in the NDA and in addition the most recent IND Annual Report. Two, heart malformation and congenital inguinal/umbilical hernia, are noted above. In another case, there was a foot malformation: "slight malformation of soft tissue of right big toe". In a case of meningomyelocele and another case of transposition of the great vessels, no further information were available. One case of cleft palate was reported; the mother was taking 20 mg QD of citalopram during the first "phase" of pregnancy. Another defect reported as "malformation of hand or foot" had no further information. The final case was a chromosomal abnormality (XXY), though it is unknown whether the baby was carried to full term. The mother had taken citalopram 20 mg QD for 4-5 months prior to pregnancy and at least one month after.

A list of birth defects was provided in the consult from the CDER Division of Pharmacovigilance and Epidemiology, from the database search conducted by the WHO Collaborating Center for International Drug Monitoring. The defects noted were the same as those provided in the sponsor's database, including a November 11, 1997 update provided in answer to the DNDP reviewer's questions. They most likely represent the same cases, though case numbers were not provided with the WHO list and it would be necessary to go back to the WHO database for this information if it was deemed necessary to clarify this.

One case of fetal exposure to citalopram is included in the sponsor's literature search. The patient was a 31 y.o. female who was treated for the first 3 weeks of an unknown pregnancy with 20 mg and the next 3 weeks with 40 mg. All drugs were withdrawn after the 6th week and an abortion was performed at 12 weeks. An autopsy gave no indications of dysgenesis, teratogenesis, or developmental problems.

After giving birth the mother of a normal infant continued to take 30 mg of citalopram QD while lactating. The baby was noted to be somnolent, showed impaired suckling and lost weight. Maternal blood citalopram concentration was found to be 204 nmol/L and breast milk concentration was 488 nmol/L.

Three developmental toxicity and teratogenicity studies were conducted in pregnant rats with the same doses of citalopram. In the first study gross external, visceral soft tissue, including cardiac defects, and skeletal anomalies were observed only in fetuses from the high dose group (112 mg/kg/day). In the second teratogenicity study, no external malformations were observed, but visceral and skeletal anomalies were identified for fetuses obtained only from pregnant females given the high dose that were different than the anomalies demonstrated in the first study (e.g. no cardiac anomalies). The high dose in both studies was associated with frank maternal toxicity. On day 15 of gestation, after 10 days of dosing, the average plasma concentration from rats receiving 112 mg/kg/day was 10 times the steady state C_{ave} in humans taking 60 mg. The dose at which malformations was observed in both studies was 21 times the maximum therapeutic human dose based upon mg/m^2. In the third study, doses up to 56 mg/kg/day (65x the maximum daily human dose on a mg/kg basis and 10.4x on a mg/m^2 basis) did not affect fetal morphology, viability, survival, growth, or reproduction. No teratogenic effects were observed in a study conducted in rabbits at doses up to 4.5 times, on a mg/kg basis, the maximum recommended daily human dose.

In conclusion, the population that has been exposed to citalopram is very large (4-5 million people) and as would be expected there are some reports of pregnancy problems and problems with the infants born, including some birth defects. Mothers were often on other medications as well. The number of reported birth defects (8) is rather small and there is no pattern or predominance of any. The cases of the most concern were the cardiac abnormalities (two cases though different defects) and the case of meningomyelocele. Also, there were two infants born who had breathing difficulties the first day, one also had myoclonus, that may ~~have~~ been due to citalopram exposure before and during delivery.

The assignment of Pregnancy Category C appears to be appropriate as per pharmacology reviewer Dr. Huff, though a final report from DNDP Pharmacology is pending.

8.1.12 Overdose Experience

Information on citalopram overdose comes from Group 1 and 3 studies, and from the post-marketing spontaneous reporting system. There were 60 reported overdoses in the DSU database; six of these resulted in death; no concomitant drugs were noted in one of these 6 fatalities (Appx. 8.1.12.2) . The patient with the highest known citalopram overdose (5200 mg) recovered completely. In Group 1 studies, there were 18 patients who attempted suicide by overdosing on citalopram alone or in combination with one or more other agents. In four of these cases, no information about dose or symptoms is available. For Group 3 studies, there were a total of 13 suicide attempts involving an overdose with citalopram.
In four of these cases, citalopram dose was unknown and no information was provided on signs or symptoms associated with overdose. Appendix 8.1.12.1 shows a summary of narrative information on the 23 Group 1 and 3 patients for which dose or symptom information is known.

In patients from Group 1 and 3 studies, known overdoses ingested ranged from 80 mg to 2000 mg (n = 31). All patients recovered. Patients were asymptomatic in 2 cases (Patients 0025 and 0608 from Study 8213).

In overdoses from Group 1 study patients, observed clinical symptoms were consistent with the AE profile for citalopram defined from premature discontinuations due to adverse events and for TEAES for all patients reporting a citalopram overdose except the four who were unconscious or comatose (Subject 0733 in Study 88105; Subject 0913 in Study 89304; Subjects 0606 and I135 in Study 8213) and the one having a seizure (Study 89304, #913). Three of those four had ingested doses of over 1500 mg; patient 733 (study 88105) had ingested 300 mg, but reported information suggests that unconsciousness was more likely attributable to concomitant ingestion of an unspecified benzodiazepine and unknown quantity of alcohol. In addition, blood levels suggested that the patient may not have taken an overdose of citalopram.

The only reported cardiovascular abnormalities in overdoses from Group 1 and 3 studies were: # 3702 (study 89304) who had bradycardia (47 bpm) after ingesting 600 mg along with unknown amounts of oxazepam and prazepam; # 913 (study 89304) who had sinus bradycardia, and ventricular asystoles after ingesting 1520 mg, and #184 (study 88701) in which the ECG showed sinus tachycardia (120 bpm) after ingestion of 200-240 mg and probably alcohol. The QTc interval in #913 (study 89304) was reported as prolonged, though the sponsor notes that 0.458 s in a 51 y.o. woman should not be considered prolonged.

Six cases in the DSU database provided information regarding blood citalopram levels in patients who committed suicide by overdose with citalopram, either alone or in combination with other drugs (Appendix 8.1.12.2). Symptoms were similar to those seen in Group 1 and 3 overdoses, with the exception of three cases of rhabdomyolysis, one of which was associated with the largest citalopram overdose (5200 mg) known The latter patient, a 41 year old male, was treated in the intensive care unit with artificial ventilation for 14 to 18 hours after admission. The patient was unconscious and suffered from convulsions in transit to the hospital. The patient developed minor jerks in all limbs within 24 hr of hospitalization and went on to develop severe acidosis and rhabdomyolysis accompanied by reduced renal function. These effects reportedly resolved and the patient was discharged from the hospital after seven days.

Management of overdose as specified in the proposed labeling: establish and maintain an airway, gastric evacuation, vital signs monitoring, and general supportive care.

The literature review done by the sponsor yielded three references on citalopram overdose including a 1995 review article noting 32 cases. At least some of these cases were included in the DSU database. The review article noted that a seizure was known to have occurred in only one case. Another reference is a letter discussing 6 suicides, with post-mortem serum concentrations ranging well above the therapeutic

level of about 920 nmol/L. Cardiac arrhythmia was postulated as a possible cause of death in these patients, who were found deceased. There is no direct evidence of this reported though and five of the patients were also on other medication. The article also notes a case reported to the Swedish Medical Products Agency, in which QT_c increased in a 44 y.o. woman who overdosed on 840 mg. The third reference was a single case report of an 18 y.o. male who took 1600 mg resulting in a citalopram blood level of and desmethylcitalopram level of he recovered. ECG and labs were normal. The literature reports don't impart any new information otherwise.

8.2 Review of Systems

8.2.1 Cardiovascular

8.2.1.1 Adequacy of Assessment

Within the clinical development program (Groups 1, 2, and 3), cardiovascular AEs were regularly documented. Within the group of short-term, placebo-controlled Group 1 studies, vital signs (orthostatic pulse and blood pressure with the exception of study 91206, in which only sitting BP, pulse were done) were assessed as indicated in Appx. 8.1.7.1. in about 521 citalopram patients. ECGs were recorded in this group of studies as shown in Appendix 8.1.8.1 in about 780 citalopram patients.

The sponsor reports that a search of the ISS was done to capture all likely sources containing arrhythmias. All serious AEs and AEs that led to dropout from a study in the clinical development program were searched, as well as postmarketing reports from the SRS, under the following terms: arrhythmia, death, sudden death, torsades de pointes, ventricular arrhythmia, ventricular fibrillation, cardiac arrest, ECG abnormal, syncope, extrasystoles, palpitation, heart disorder, myocardial infarct, QT_c abnormal, and tachycardia. Also, as part of the evaluation of arrhythmias as an AE of special interest, the sponsor did a search of the ISS for patients receiving citalopram in combination with specific drugs reported to be associated with torsades.

A report entitled "Electrocardiograms from volunteers and patients given citalopram; a comprehensive survey" was reviewed; it is described in section 8.1.8.4 and data are discussed below.

These evaluations are felt to be adequate to evaluate the effect of citalopram on the cardiovascular system.

8.2.1.2 Serious Cardiovascular Events Considered Possibly, Probably, or Definitely Related to Citalopram

Bradycardia

Within the pool of the five short-term Group 1 studies in which vital signs were assessed, there were statistically significant ($p < 0.05$ on t-test) small

mean changes in sitting, standing, and supine pulse rates between the citalopram and placebo groups (Appx. 8.1.7.3.1). On citalopram, mean pulse rate decreased by 2.4 (standing), 2.2 (sitting) and 2.6 (supine) bpm as compared with mean baseline values. These changes were not clinically significant. There was no statistically significant difference in the incidence of PCS vital sign changes, including heart rate, between citalopram and placebo. On the other hand, within the group of short-term, placebo-controlled studies for which ECG information was available, change in mean heart rate from baseline was the only statistically significant variable (Appx. 8.1.8.3.1), increasing by 1.7 bpm on citalopram, and remaining unchanged from baseline on placebo. There were no statistically significant differences between placebo and citalopram in incidence of PCS ECG parameters (including "bradycardia" as defined as < 50 bpm) (Appx. 8.1.8.3.2.2).

One case of bradycardia was identified as an SAE on placebo. Three cases of bradycardia were identified as SAEs in Group 1 and 3 studies while on citalopram:

Study 7902, #236: 60 y.o. male was noted to have a sinus bradycardia on ECG while taking 50 mg citalopram, which he had been taking for at least 2 months. He was asymptomatic and continued treatment. Concurrent meds were atenolol, oxazepam, and nitrazepam.

Study 89411,#774: 74 y.o. male lost consciousness on 5/23/94) which was shown to be secondary to bradycardia for which he had a pacemaker implanted. He had started treatment with citalopram (40 mg) 4/6/94, though treatment was interrupted for at least a 2 week period while the patient was treated for pneumonia, after which he was discharged on 5/20/94. Concomitant medications included flurazepam, lithium, phenytoin, and amitriptyline.

Study 8213, #260: 50 y.o. female experienced sinus bradycardia after taking 40 mg citalopram for one month and was withdrawn from the study. She was also on propanolol and benzodiazepines.

In all of these cases other drugs could have contributed to the bradycardia, especially atenolol, propanolol.

Four additional case of bradycardia from Group 1 studies were identified as a cause of dropout. Ages ranged , duration on drug ranged from 1 day to over 16 months. One patient had Shy-Drager syndrome. Most did not have concurrent symptoms.

In the literature review of citalopram safety conducted by the sponsor, in a notice from the Bivirkningsnaevn (the Danish authority for the investigation of drug side effects) two cases of symptomatic bradycardia (dizziness, fatigue, faintness) were reported. One was in a 93 yr. old man treated with 20 mg x 3 days who also developed a bundle branch block. The other case was a 40 yr. old man treated with 20 mg for one week; ECG showed sinus bradycardia. In both cases, symptoms resolved and ECG normalized after citalopram was discontinued.

In the analysis of TEAEs which occurred in > 1% of any of the citalopram dose groups in study 91206 (Appx. 8.1.5.3.1), bradycardia occurred in 2% of patients at 10 mg and 1% of patients at 40 mg. No bradycardia was recorded on placebo, or on 20 or 60 mg. The low incidence and occurrence of bradycardia in only some dose groups make it unlikely to be drug-related in this study. In the post-marketing DSU database, 4 cases of bradycardia were reported as associated with citalopram use.

The bulk of the evidence indicates that citalopram may cause a slight heart rate reduction, similar to other SSRIs. The reduction is usually not clinically significant; rarely, in a very few older patients who are predisposed to bradycardia, a more significant heart rate reduction may occur. It is recommended that bradycardia be included as an adverse reaction in labeling, under 'Other Events Observed During Premarketing Evaluation'.

Postural Hypotension/Hypotension

In the six placebo-controlled, short-term Group 1 studies in which vital signs were assessed, mean sitting systolic blood pressure decreased by 1.6 mmHg from baseline. This was statistically significant as compared with placebo, though not clinically significant. Standing systolic and diastolic BP both decreased slightly from baseline, though this was not statistically different from placebo. There are though examples of cases in the elderly in which episodes of hypotension were recorded as serious AEs and in which citalopram could have possibly been a contributing factor (all were also on other medications that could have contributed as well):

Study 95A, # 7: 65 y.o. female became hypotensive after initial 40 mg dose. She was also taking doxepine.

Study 8213, #311: 69 y.o. female fell, reportedly secondary to orthostatic hypotension two weeks after starting citalopram. She was on 40 mg and also on levomepromazine, which also could have contributed to the AE.

Study 91304, # 45: 66 y.o. male who felt dizzy and fell one month after beginning citalopram treatment. He was on 40 mg at the time and had also taken chloral hydrate and lorazepam the night of the event.

One case of postural hypotension was identified as an SAE in Group 1 and 3 studies.

There were no statistically significant differences in the incidence of PCS vital sign measures, including blood pressure in citalopram- versus placebo-treated patients in the five Group 1 short-term, placebo-controlled studies.

In Group 1 studies, 6 citalopram patients (and 2 placebo) were withdrawn prematurely due, at least in part, to hypotension. In two cases hypotension (down to 80/40 in one case) occurred shortly after i.v. administration. Two other cases occurred in women in their 50s after 3-9 weeks of treatment with 20 mg; 80/40 was the lowest BP recorded. The two other cases leading to premature withdrawal were in men in their 70s, after about 2 weeks of

treatment with 20-40 mg. BP nadirs were 100/60 and 108/52. Some patients were asymptomatic, others had lightheadedness.

In the post-marketing DSU database, there were 4 cases of postural hypotension reported as associated with citalopram use.

Citalopram may cause a very slight reduction in blood pressure that is usually clinically insignificant. In a very few older patients who are predisposed to hypotension generally from other medications, a more significant blood pressure drop may occur. It is recommended that hypotension and postural hypotension be included as an adverse reaction in labeling, under 'Other Events Observed During Premarketing Evaluation'.

8.2.1.3 Serious Cardiovascular Events Unlikely to be Citalopram-Related

Palpitations/PVCs

Within the pool of short-term, Group 1 placebo controlled studies (N_{cit}=1063, N_{pbo}=446), palpitations were the most common cardiovascular system event, but they occurred at an incidence of 0.063/PEY on citalopram and 0.117/PEY on placebo. Palpitations or extrasystoles in these studies generally were reported in conjunction with symptoms like anxiety, tremor, sweating, panic, and and insomnia.

There were a few SAEs in Group 1 and 3 studies (none on placebo s SAEs) in which symptoms and signs described as palpitations, PVCs, extrasystoles, and irregular extrasystoles occurred, in some cases very shortly after citalopram treatment started:

Study 95208, #1262: 58 y.o. male developed palpitations within minutes of ingesting 40 mg of citalopram. He had a history of hypertension, asthma, and hyperglycemia, and had been taking 20 mg for 2 days, which was increased to 40 mg for 4 days prior to the event. The ECG indicated auricular flutter. The investigator and reviewers felt that the relationship of symptoms to study drug was probable.

Study 87A, #2367: 53 y.o. male, with abnormal baseline ECG (left axis deviation, poor anterior R progression, nonspecific T-wave abnormalities), discontinued treatment with 20 mg citalopram on the second day because of abnormal ECG findings (PVCs and premature or retrograde AV conduction). The investigator and reviewer felt that the relationship to citalopram administration was probable, in exacerbating the patient's tendency to get PVCs.

Study 8213, # 253: 50 y.o. male was hospitalized for "irregular extrasystoles" about 5 weeks after beginning citalopram; outcome was not provided. He was also on other medications which included amitriptyline, dibenzepine, and viloxazine.

Study 91203, #399: 79 y.o. male had a baseline ECG with unifocal ventricular

extrasystoles, judged by the investigator to be of no clinical significance. About 5 weeks after beginning citalopram (20 mg) he complained of tiredness and his ECG showed bigeminy. He recovered after stopping the medication.

In addition to patients #2367 and #399 above, one other patient discontinued prematurely because of extrasystoles; the patient was 75 yrs. old and also had congestive heart failure and angina.

In the post-marketing DSU database, there were 4 cases of palpitations and one case of extrasystoles reported as associated with citalopram use.

Citalopram may contribute to PVCs and/or palpitations in a very few older patients who are predisposed to their occurrence.

Other Arrhythmias/QT Interval Prolongation

In view of the fact that the FDA put the citalopram development program on clinical hold in 1985 because of mortality in a one year dog toxicology study due to cardiac arrhythmias, a summary of information on this topic is included. The arrhythmias in dogs were found to be due to a didemethyl metabolite which lengthened the QT interval. Deaths occurred at 8 mg/kg/day; citalopram levels were 7x greater than average plasma levels in humans receiving 60 mg daily. This metabolite was found to be predominant in dogs, but in humans its plasma concentration was 10% or less than that of citalopram. QT effects in dogs were seen only at concentrations of the metabolite that is at least 50x higher than metabolite levels measured in humans taking 60 mg daily.

In the ECG survey report from (described in section 8.1.8.4), there was no indication of any clinical problem regarding QT_c prolongation or any other change in the myocardial conductive system related to citalopram treatment. For patients that had ECGs both at baseline and with treatment, n_{cit}=1116, n_{pbo}=118, for those with ECGs only during treatment (no baseline), n_{cit}=380, n_{pbo}=97. In addition to the 42 Group 1 and Group 3 studies that were examined in the ECG survey, particular attention was given to people in those studies who may have been more susceptible to cardiac effects of citalopram. Arrhythmias and prolonged QT intervals were specifically searched for. A number of subjects (n=135) had cardiac diagnoses prior to treatment with citalopram; others were receiving concomitant medication with a known potential for affecting QT_c or received such medication just prior to starting citalopram (N=44); others had a $QT_c \geq 0.5$ sec at baseline (N=12). No evidence was found for citalopram-induced QT_c prolongation or any other effects on cardiac conduction in these patients.

In the sponsor's search for arrhythmias among Group 1, 2, 3, studies and the postmarketing DSU database, 12 patients were identified who had the following events: torsades de pointes, ventricular arrhythmias, ventricular fibrillation, QT_c abnormal. Two of these were from trials in the clinical development program and both patients died; 10 were identified via the postmarketing data. There were a total of 6 deaths, three were associated

with torsades, and 3 with fibrillation. The ages of patients who died ranged from 63 to 85. All reported cases of ventricular fibrillation or torsades except DSU #904068 which involved ventricular fibrillation leading to death, also involved another drug (cisapride, haloperidol, amiodarone, and amitripyline) or metabolic condition (acidosis, hypokalemia) with the potential to cause the event. A summary listing the two identified deaths in the development program and three other development program cases that came closest to suggesting a contribution to death by citalopram are listed in Appendix 8.2.1.3. The bulk of the evidence makes its unlikely that citalopram contributed in any large part to these deaths.

Also, as part of the evaluation of arrhythmias as an AE of special interest, the ISS was specifically searched for patients receiving citalopram in combination with drugs reported to be associated with torsades. Other than the cases noted above, no other serious cardiac arrhythmias were identified. Concurrent drugs included: terfenadine (57 cases), astemizole (7 cases), haloperidol (42 cases), cisapride (5 cases), quinidine (2 cases), and sotalol (5 cases). Citalopram's metabolism is mediated by CYP2D6, CYP2C19, and possibly CYP3A4; this is discussed in section 6.0.

Besides the 5 short-term, placebo-controlled studies in which ECG data were available, ECG data was available for three other Group 1 studies (8213, 88A, and 91302). In the total of eight Group 1 studies for which ECG data were recorded, there were a total of 19 patients who had a normal QT_c at baseline and a $QT_c > 0.50$ sec during citalopram treatment. None of them had a cardiovascular or rhythm disorder related serious AE. In addition, there was no difference in crude incidence of QT_c prolongation in patients < 60 and ≥ 60 yrs. old, among those who had a normal baseline QT_c, in these 8 Group 1 studies. This was looked at both by combining data from all doses, and also by splitting out dose ranges (< 20 mg, 20-29 mg, 30-39 mg, 40-59 mg, and 60 mg).

In the five placebo-controlled Group 1 studies in which ECG data were collected (85A, 91206, 86141, 89304, 91203), the crude incidence rate for QT_c prolongation in patients with normal baseline values was 1.1% (N=9) of 797 citalopram treated patients and 0.4% (N=1) for 241 placebo patients; this difference was not statistically significant. There was also no effect of dose found on change in mean QT_c, evaluated in study 91206. In Group 1 studies, two patients dropped out because of increased QT intervals and U waves. One patient was asymptomatic and the other complained of chest pain and had an irregular pulse.

Cardiac Failure

There were 17 patients with cardiac failure listed as an SAE in Group 1 (n=7) and 3 studies on citalopram and one as an SAE on placebo. Fourteen of these were deaths. These cases were all in elderly people, most of whom were reported to have a history of cardiac disease.

Cerebrovascular Disorder

There were 13 cases of cerebrovascular disorder (stroke) listed as an SAE in Group 1 and 3 studies, including 7 deaths. These were in older people, generally with a history of vascular disease, who were also on other medications.

Myocardial Infarction

There were 11 cases of myocardial infarction listed as an SAE in Group 1 and 3 studies, including 3 deaths and one premature dropout with ECG changes. These were all in older people and/or in people with a history of hypertension or vascular disease.

Other Serious Cardiovascular Adverse Events

Of the 95 deaths of citalopram patients in the development program (Groups 1 and 3), 27 (28%) were due to cardiovascular disorders. Nine were due to vascular (extracardiac) disorders (6 cerebrovascular disorder, 1 cerebral hemorrhage, 1 intracranial hemorrhage,and 1 arteriosclerosis); nine other deaths were due to cardiac failure; six deaths are classified under myo-, endo-, pericardial and valve disorders (3 cardiac failure and 3 myocardical infarction) and three were heart rate and rhythm disorders. In most of the deaths there was a history of underlying cardiovascular disease or the time course made it unlikely that a death was contributed to by citalopram. Most of these are noted above.

Within the pool of short-term, Group 1 placebo-controlled studies (N_{cit}=1063, N_{pbo}=446) there was one episode of syncope on citalopram and one on placebo. Syncope or loss of consciousness occurred in 3 cases in citalopram-treated patients in Group 1 studies overall. One was in a 75 y.o. female 20 days after stopping citalopram who was on a diuretic and other medications, another in an 83 y.o. man was shown to be due to very low blood sugar, and the third was a 75 y.o. female with asthma and hypertension who collapsed 20 days after stopping citalopram (after 4 days of treatment with 20 mg). She was also on other medications including spironolactone.

None of the dropouts or serious AEs in Group 2 studies were associated with the cardiovascular system.

Other serious cardiovascular AEs, each of which occurred in 4 patients or less (of the 19,666 in Group 1 and 3 studies) are: circulatory failure, cerebral hemorrhage, phlebitis deep, thrombophlebitis, arteriosclerosis, angina, myocardial ischemia (including 3 dropouts with ECG changes), peripheral ischemic vascular disease.

Two premature withdrawals occurred in one study secondary, at least in part, to hypertension. Peak BPs recorded were 190/110 after 28 days of treatment with 40 mg, and 195/110 after 42 days of treatment with 40 mg. Symptoms included headache, dizziness, and anxiety.