CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20822

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA
NDA #20-822

Sponsor:	Forest Laboratories
Drug:	Citalopram HBr, capsules
Indication:	Depression
Material Submitted:	Safety update, regulatory status update, world literature update
Correspondence Date:	May 22 1998
Date Received:	May 26, 1998

I. Safety Update

The submitted safety update covers the period from the NDA cutoff date, October 1, 1996, through January 31, 1998. Spontaneous reports and deaths and SAEs reported from ongoing clinical studies through March 1, 1998 are also reported.

Four additional studies were completed: 95208, classified as a Group 1 study was a comparison of i.v. versus oral citalopram; the others were Group 2 studies: CIT-PK1-97-02 was a dose proportionality study; 95115 was a PK interaction study with metoprolol; 94123 was a PK interaction study with carbamazepine.

A. Deaths and SAEs

There were no deaths in any of these studies; there were 31 SAEs in the Group 1 study and none in the Group 2 studies.

In ongoing studies, there were 23 deaths (all Group 3 studies) and 296 SAEs reported. The line listing and narratives for all deaths were reviewed. The most frequent causes of death were suicide (n=4) and carcinoma of various organs (n=3). Other causes in greater than one person were cerebral infarction(n=2). Other listed causes occurred in people at least 74 years old and were typical final events with the exceptions of endocarditis in a 61 year old (2 months after starting 20 mg daily; the investigator's opinion was that the event was not related to citalopram) and carcinomas in two people in their 60s.

The report also notes that the term `death' was used in 4 cases in which the cause of death was unknown. The narrative for each of these did not implicate citalopram as a strong contributing factor; contributing factors included: car accident, choking, patient s/p colostomy with significant weight loss on several

other medications though no autopsy was done, and a patient with alcoholism and pneumonia.

The incidence and types of SAEs, including deaths, reported in the safety update from studies and from post-marketing data were similar to those reported in the NDA review. All are represented in labeling with the following exception: One case of epidermal necrolysis was reported in the postmarketing of the NDA review; two additional post-marketing cases of epidermal necrolysis and one pemphigoid reaction were reported in the safety update. The ADR reports filed on the latter cases were all in people over 80 years old and at least 2 of the three were on numerous other medications. There was no strong indication that citalopram was the cause but since at least three cases have been documented, epidermal necrolysis should probably be included in the 'Other Events Observed' section of labeling.

B. Overdose

Three deaths from overdose were reported; at least two of these involved other medications. In the other, a 17 y.o. female with a history of cannabis abuse had ingested 2,800 mg and serum citalopram concentration was 7,384 nmol/L six hours after ingestion. Her QTc was documented to be increased to a max of 533 ms; this was documented after cardiac arrest. She was also noted to have seizures and widened QRS. In one of the other fatal O.D. cases there was a reported ECG abnormality: broadening ventricular complexes.

Two additional nonfatal O.D. cases involved reports of ventricular arrhythmias. One had A-V block and a left bundle branch block on admission and later developed ventricular fibrillation. Her dose was unknown but serum S-citalopram level was > 10,000 nmol/L. In the other case, a 47 y.o. male took 2000 mg of citalopram, temazepam and alcohol and experienced ventricular fibrillation. QTc peaked at 511 ms.

A few other cases of patients with reported increased QT who did not experience arrhythmias and recovered after O.D. were also previously reported to FDA in ADR reports.

C. Pregnancy and Fetal Abnormalities

Eight new pregnancies occurred in clinical studies and 28 were reported from the SRS. Four spontaneous abortions were documented and one additional case of fetal death for which details were not available.

Two cases of fetal abnormality were reported. One was an XXY chromosomal abnormality (Klinefelter's syndrome); the mother was taking citalopram beginning in the third or fourth month of pregnancy. The other was a cleft palate; the mother had taken 20 mg of citalopram daily during the first trimester. There was

also a report of a neonate with somnolence and anorexia who made a complete recovery.

In the NDA review, one case of cleft palate had been reported.

II. Regulatory Status Update

The sponsor reports that citalopram is now approved in 63 countries and that there have been no negative regulatory actions concerning citalopram in any country.

III. World Literature Update

The same conditions were use for the literature update as were used in the NDA submission. The time covered was October 1, 1996 to January 31, 1998. A listing of all citations found including the article abstract were submitted, as well as copies of full articles referenced in the sponsor's update.

The only adverse event that was not included in labeling was priapism; this was also noted in the SRS and was added to the labeling as of June 18, 1998.

IV. Conclusions and Recommendations

No new safety problems strongly associated with citalopram were identified from the safety update.

Two cases of epidermal necrolysis and one case diagnosed as a pemphigoid reaction, together with one case of epidermal necrolysis identified postmarketing in the original NDA review, probably warrant the inclusion of epidermal necrolysis in labeling as noted above.

A few cases of priapism, known to occur with other SSRIs, were noted in postmarketing ADR reports and in the literature. This was added to labeling.

/S/

Susan Molchan, M.D.
June 22, 1998

cc: NDA #20-822
HFD-120
HFD-120/SMolchan
TLaughren
PDavid

7-2-98
I agree that citalopram can now be approved. We have reached agreement with sponsor on final labeling. See memo to file for more details /S/

Review and Evaluation of Clinical Data

Application Information

NDA #:	20-822
Sponsor:	Forest Laboratories, Inc.
Clock Date:	May 12, 1997

Drug Name

Generic Name:	Citalopram
Trade Name:	Proposed: 'Celexa'; second choice, 'Selectin'

Drug Categorization

Pharmacological Class:	Serotonin reuptake inhibitor
Proposed Indication:	Depression
NDA Classification	1 S
Dosage Forms:	10, 20, 40, 60 mg capsules
Route:	Oral

Reviewer Information

Clinical Reviewers:	Susan Molchan, M.D./Gregory Dubitsky, M.D.
Completion Date:	(3/11/98)

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1.0 Material Utilized in Review

1.1

This clinical review entailed an examination of the following items:

NDA Volume(s)	Submission Date	Material
1.82	5/7/97	Table of Contents
1.83	5/7/97	Human PK and bioavailability summary
1.85	5/7/97	Table of Studies
1.94-1.100	5/7/97	Study report: 85A
1.101-1.113	5/7/97	Study report: 91206
1.114-1.118	5/7/97	Study report: 86141
1.119-1.124	5/7/97	Study report: 89303
1.125-1.130	5/7/97	Study report: 89306
1.131-1.148	5/7/97	Study report: 89304
1.149-1.153	5/7/97	Study report: 89305
1.156-1.157	5/7/97	Study report: 86A
1.157-1.161	5/7/97	Study report: 87A
1.279-280	5/7/97	Foreign labeling
1.282	5/7/97	Integrated summary of efficacy
1.294	5/7/97	Integrated summary of safety
1.294	5/7/97	Deaths-listing
1.296-7, 1.301	5/7/97	Dropouts-listings, enumeration
1.298-300	5/7/97	Safety: Laboratory studies, vital signs, ECG
1.301	5/7/97	SAEs-listing
1.302	5/7/97	Deaths-narrative summaries
1.302-303	5/7/97	SAEs-narratives
1.304	5/7/97	Dropouts-narratives
1.304	5/7/97	SRS AEs
1.305	5/7/97	Lundbeck ECG report
1.306	5/7/97	Group 2 adverse events and ADOs
1.307	5/7/97	Clinical literature references
1.308-322	5/7/97	Listing, all Group 1 TEAEs
1.322	5/7/97	Drug abuse and overdose

1.322	5/7/97	Proposed labeling
1.454	5/7/97	Index to CRFs
-	7/31/97	Revised efficacy tables, revised mean dose data for study 89304, trend test on TEAEs-study 91206, adverse event dictionary, revised summary of Group 2 studies, narratives for Group 2 ADOs, revised table and line listings of PCS vital signs parameters, revised line listing of Group 1 ADOs secondary to lab, VS, ECG abnormality
-	8/21/97	Demographic analysis of AEs, revised list of Group 3 studies, revised demographics tables, historical control data for chromosomal aberration tests, revised ISS and ISE volumes
-	9/5/97	Revised vital signs tables and listings
-	10/14/97	Revised PEY data, clarification of SRS data in volume 1.304, requested narratives, clarification of studies included in Group 3
-	10/24/97	Revised overdose information, supplemental efficacy data for study 85A, treatment x center interaction for efficacy data, linear regression of efficacy vs. serum citalopram concentration, study 85A datasets
-	11/7/97	Revised listing of ADOs due to lab, VS, ECG abnormalities, revised patient disposition and duration tables for 85A, clarification of mean daily dose data and change from baseline to endpoint efficacy tables, supplemental demographic and severity efficacy analyses, supplemental information on pregnancy exposures and fetal abnormalities
-	11/18/97	Clarification of number of deaths and missing narratives, revision of adverse dropouts classification for placebo groups, clarification/revision of mortality data for placebo and active controls, provided missing narratives, patient mapping table, additional analyses for the two long-term studies (relapse rates, demographics and relapse), statistical correction of an efficacy measure for study 91206, revised dropouts vs. completers bar charts for efficacy in studies 91206, 85A, requested database and sample programs for 91206, manuscript on cytochrome *in vitro* metabolism of citalopram

-	12/12/97	Requested printout of patients' QRS values; list of studies done under the U.S. corporate IND; clarification of n for NDA Table 8.1.1.2; ITT analysis of placebo studies; additional statistical analysis of MADRS for studies 89304, 89305

Case report forms for the following Group 1 study patients (by study #, site [when available], patient #) were reviewed to audit the completeness and accuracy of data contained in the corresponding patient narrative summaries.

85A-102-2017	91206-102-163	86141-102-113	89303-15-031
85A-102-2187	91206-102-164	86141-602-545	91302-05-420
85A-202-2338	91206-02-148	89306-02-283	8213- -281
8213- -913	91206-02-152	89306-07-532	88105-142-302
88A-102-2137	91206-05-319	89303-10-074	8213- -443

2.0 Background

2.1 Indication

Citalopram HBr is a selective serotonin reuptake inhibitor (SSRI) proposed for the treatment of major depression in a dose range of 20-60 mg daily. Its common treatment-emergent adverse event profile is comparable to that of other SSRIs. The proposed proprietary name is 'Celexa'; second choice is 'Selectin'.

2.2 Related INDs and NDAs

IND is held by for the development of citalopram. Citalopram has actions most like fluoxetine and paroxetine in that it is an SSRI with little or no effect on norepinephrine and dopamine uptake and no or little affinity for other receptors including adrenergic, muscarinic, and histaminergic. No particular toxicities have been associated with citalopram in humans; as with other SSRIs, the potential for serotonin syndrome exists when combined with an MAOI.

2.3 Administrative History

citalopram from and submitted the IND for citalopram on A clinical program was initiated which completed a substantially sized, placebo-controlled, short-term treatment study (Study 85A) and initiated several other clinical studies. The program was put on clinical hold by the FDA on 7/3/85 after unexplained mortality in a one year dog toxicology study being conducted The IND was transferred by after the business relationship between successfully resolved the toxicity questions raised by FDA

Removal of the clinical hold did not include permission to enroll females in clinical studies with citalopram due to reproductive toxicology issues.

Lundbeck successfully resolved the reproductive toxicology issues and FDA removed restrictions on the participation by females in the clinical studies in 1991. resumed full clinical activities in the U.S. with citalopram in 1992, initiating and completing a large, placebo-controlled, short-term treatment study (Study 91206) using a contract research organization

No official "End of Phase II Meeting" was held. A meeting was held 2/29/96 with members of the FDA Division of Neuropharmacological Drug Products (DNDP) to discuss the clinical development, pharmacokinetic/biopharmaceutics and toxicology programs for citalopram. Important outcomes from this meeting related to safety are summarized below.

- FDA indicated that they were interested in any long-term safety or efficacy data regardless of patient population.
- FDA stated that they would not allow a specific claim for safety in the elderly. However, the geriatric studies could be defined in the Precautions section of the label.
- FDA recommended that discussions of human pharmacokinetics and CMC issues take place with the Office of New Drug Chemistry and the Office of Clinical Pharmacology and Biopharmaceutics.
- Although the mouse carcinogenicity study conducted by the sponsor is for a lesser duration than that suggested by current guidelines, this study should be sufficient to meet the preclinical carcinogenicity requirements if : (1) the rat study is negative; and (2) the mouse study is not suggestive. This issue should be reviewed and presented to the Carcinogenicity Assessment Committee.
- FDA agreed with the recommendation that long-term ophthalmic examinations in the one-year clinical study should be performed.
- FDA stated that it was their belief that citalopram is a teratogen. Additional studies that demonstrated negative teratogenic findings could go into the label along with the studies that had positive findings.
- FDA emphasized the importance of characterizing the P450 isozyme potential of citalopram.

A pre-NDA meeting was held with members of the FDA DNDP 10/31/96 to discuss the organization and presentation of data in the clinical section of the citalopram NDA. Issues discussed are summarized below.

- The proposed grouping of clinical studies (Group 1, Group 2, and Group 3; refer to Section 5.1.1 for definition of these groups) based on design and conduct characteristics was accepted by the FDA.
- Patient narratives would be provided for all deaths and serious adverse events reported in the development program. Patient narratives for dropouts due to adverse events would be provided only for citalopram treated patients in Group 1 studies.
- Serious adverse event information would be summarized from the following sources: literature, spontaneous reporting system, and clinical trials. Further, the HAM-D Suicide Item (Item 3) would be used to assess emergent

suicidality.
• Analyses would be provided on the influence of age and gender on adverse event rates for all Group I studies. The WHO-ART dictionary would be an acceptable coding dictionary, and will be provided as an appendix.
• A full report of safety and efficacy would be provided for Studies 85A and 91206. A brief report, in addition to the existing Lundbeck study report, would be provided for the remainder of the Group I studies.
• The cutoff date for the literature search and clinical safety information would be 10/1/96.
• Forest would submit a proposal for discussion with the FDA on preclinical ophthalmological findings after reevaluation of existing findings.
• Specific claims regarding an indication for efficacy in the geriatric population would likely not be allowed, though results of the geriatric studies may be described.

A teleconference was held with members of the FDA DNDP on 12/3/96 to discuss the presentation of the clinical data and the ISE/ISS table formats for the Citalopram NDA. Issues discussed are summarized below.

• The 19 studies designated as Group I studies will be the basis for the primary efficacy and safety claims. Group 2 studies contain the clinical pharmacology and pharmacokinetic studies. Remaining studies are classified as Group 3. The only information to be presented in the ISS for the Group 3 studies will be patient narratives for all serious adverse events (including deaths).
• Specific changes in the safety tables were determined as per DNDP instructions

Forest received a letter dated 1/27/97 from the FDA DNDP that was a follow-up to the 10/31/96 preNDA meeting and the 12/3/96 teleconference referenced above. Important issues related to safety are summarized below.

• Issues not contained in the Forest minutes of the 10/31/96 meeting and the 12/3/96 teleconference were summarized by FDA. Forest responded to these issues in the 2/25/96 correspondence, referenced below.
• FDA agreed that case report forms do not have to be submitted for all patients in the Group 3 studies, and case report forms do not have to be submitted for patients receiving reference drug or placebo in the Group I and 2 studies. However, these case report forms should be available at the request of the FDA.

Forest sent a letter dated 2/25/97 to the FDA DNDP to clarify issues presented in the FDA letter to Forest dated 1/27/97. Important issues related to safety are summarized below.

• Patients meeting potentially clinically significant criteria for labs, vital signs, and ECGs will be presented in the NDA.
• Adverse event listings will be provided and organized by event and by patient.
• Adverse event incidence tables will be broken down by age (> 60/≤ 60), race (where data are available), and gender.

• The emergence of suicidality will be analyzed by providing for Group I studies broken out by placebo-controlled and active-controlled studies as follows: (1) mean change from baseline to termination in HAM-D Item 3; (2) percent of patients with an increase from baseline in suicidality on the HAM-D Item 3 at any point during the trial (MADRS Item 10 will be used if HAM-D scale was not employed in a given trial); and (3) summary of percentages of patients with AE listing/ termination records of suicidal attempts, suicidal ideation and actual suicides.
• Dose by duration and demographics tables will be submitted only for Group 1 studies.
• Plans for addressing study pools for adverse drug reaction tables are as follows: citalopram versus placebo, citalopram versus tricyclic and related antidepressants, and citalopram versus SSRIs, across the 17 Group 1 studies with a control treatment. In addition, the placebo-controlled studies will be subdivided into short-term versus long-term groupings.
• A tabular display will be generated of the occurrences of potentially clinically significant abnormalities for clinical chemistry, urinalyses, hematology, vital signs, and ECGS.
• Regarding the termination page of the CRF, "loss to follow-up" and "lack of compliance" will be combined into a single category: Lost to Follow-Up. A complete patient listing of premature discontinuation with the reasons and all associated comments will be provided in the NDA.

Forest received a letter dated 3/4/97 from the FDA DNDP that resolved which CRFs need to be translated for the NDA submission. The outcome from this letter was that FDA will accept non-translated CRFs for efficacy measures, but safety information must be translated.

2.4 Proposed Directions for Use

Directions for use conveyed in the sponsor's proposed labeling are as follows:

Citalopram should be administered at a dose of 20 mg once daily. Clinical trials demonstrating antidepressant effectiveness studied the recommended therapeutic dose range of 20-60 mg/day. Patients not responding to 20 mg may benefit from dose increases, in 20 mg/day increments, up to a maximum of 60 mg/day. Dose changes should occur at intervals of at least one week.

Citalopram should be administered once daily, in the morning or evening, with or without food.

In elderly patients, dosage should not exceed 40 mg/day. In patients with hepatic impairment, dosage should not exceed 40 mg/day. No dosage adjustment is necessary for patients with mild or moderate renal impairment, but should be used with caution in patients with severe renal impairment.

2.5 Foreign Marketing

Citalopram was first introduced commercially in 1989 in Denmark. Citalopram has received marketing approval for depression in 49 countries as of 1/1/97. As of the NDA submission date (5/12/97), marketing approval is pending for

depression in 24 additional countries. No foreign regulatory authority has refused approval of citalopram for reasons related to safety. There have been no withdrawals of citalopram from marketing by any foreign authority for any reason related to safety or efficacy. withdrew a dosing recommendation for citalopram 10 mg/day in France before obtaining marketing authorization due to insufficient evidence of efficacy. There have been no warning letters sent to physicians requested by foreign regulatory authorities of adverse effects, and no major changes in marketing status or labeling information with respect to depression.

Citalopram was approved in Austria for use in chronic pain, but the indication was withdrawn following publication of the results from a study on chronic tension-type headache that did not support efficacy for this indication. Citalopram remains on the market in Austria for depression. Marketing applications for use of citalopram in the treatment of panic attacks are approved in Austria, Denmark, Finland, Sweden and the U.K.

Dosage formulations for citalopram that are available for marketing include: tablets (10, 20, and 40 mg) and intravenous solution (40 mg/mL).

3.0 Chemistry

The chemical name of the drug product, citalopram hydrobromide is 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile, HBr. Citalopram is a racemate consisting of a 50:50 mixture of the S-(+) and R-(-) enantiomers.

The chemistry section has been reviewed by Janusz Rzeszotarski, Ph.D., who says that there are no important chemistry issues with citalopram.

4.0 Animal Pharmacology

Citalopram's antidepressant activity has been suggested in a variety of animal models.

The efficacy of citalopram appears to reside in the (+), or S, enantiomer based on both *in vitro* and *in vivo* studies. The S-(+) enantiomer of demethylcitalopram (DCT) has approximately of the activity of the respective citalopram enantiomer on serotonin uptake inhibition, with the activity of the didemethyl metabolite (DDCT) lower than that of both citalopram and its demethyl metabolite in *in vitro* studies.

Toxicology

Citalopram dose in the following text is expressed as the free base, e.g., 80 mg free base equals 100 mg citalopram salt. Oral LD_{50} values were 726 mg/kg in male and 901 mg/kg in female rats. The oral single dose NOEL was 20 mg/kg in male and female dogs. Signs of toxicity for rats generally included salivation, reduced spontaneous activity, low respiration rate, mydriasis, tremors and tonic/clonic convulsions. For dogs given high single doses of citalopram, clinical signs generally included restlessness, dry nose,

tachycardia, clonic convulsions, hyperpnea, hypersensitivity to touch, and salivation. Citalopram daily doses of 240 and 80 mg/kg/day were selected as the highest doses for longer term studies in mice (26 weeks) and rats (13 weeks), respectively. At these doses, achieved plasma levels in mice were 27x and in rats ≥ 10x greater than the average plasma levels in humans (370 nM) receiving a maximum daily therapeutic dose of 60 mg. No clinical signs of toxicity were observed in the 26-week mouse study, and a transient incidence of salivation and tortuous tail was observed in the 13-week rat study.

The highest dose selected for chronic oral studies in dogs was 8 mg/kg/day, where the citalopram plasma levels achieved were 7x greater than the average plasma levels in humans receiving a maximum daily therapeutic dose of 60 mg. At this high dose, 2 male and 3 female dogs (out of a total of 9) unexpectedly died.

In subacute toxicity studies in dogs, oral and intravenous doses ≥16 mg/kg/day induced toxicity manifested as sedation at citalopram plasma levels of , and agitation or vocalization, convulsions, tachycardia, T-wave polarity, QT prolongation or S-T changes at higher levels, and finally severe (sometimes fatal) cardiac arrhythmia at The lowest citalopram plasma levels associated with sedation was 8x greater than the average citalopram plasma level in patients receiving a maximum daily therapeutic dose of 60 mg.

Very high plasma concentrations of citalopram and DDCT caused fatal arrhythmias in dogs. DDCT was proarrhythmogenic at plasma levels of 1,000 nM in the presence of citalopram at 3,000 nM. These plasma values are 8x and 50x greater than average plasma levels of parent drug and metabolite in humans at a 60 mg/day therapeutic dose. In the isolated perfused guinea pig heart, micromolar concentrations of citalopram caused appearance of only PQ interval changes, while similar concentrations of DDCT produced PQ, QT, and ST interval changes. QT effects for DDCT were seen only at concentrations of 1.0 μM or greater which is 50x higher than DDCT levels measured in humans at a 60 mg/day maximum recommended dose. The cardiac toxicity appeared to be concentration-dependent for both citalopram and DDCT. The highest level of DDCT measured in humans was 60 nM which is 16x less than that associated with proarrhythmogenic activity in the dog.

Citalopram induced hepatic fatty change in male rats, related to extensive first pass metabolism of citalopram. This does not present a risk to humans since first pass metabolism in humans is negligible. Citalopram induced phospholipidosis in several rat studies and in one mouse study. This change was reversible, was not accompanied by adverse morphologic or functional effects.

Citalopram was weakly positive in the bacterial reverse mutation assay, and was a weak inducer of chromosomal aberration in Chinese Hamster lung cells.

In reproduction studies of pregnant rats administered citalopram late in gestation to postnatal day 21no adverse effects on fertility were seen. One teratogenicity study in rats demonstrated visceral soft tissue and skeletal

malformations and cardiac defects at 112 mg/kg/day. In a second study, cardiac defects were not observed though visceral and skeletal anomalies were. The dose at which malformations was observed was approximately 21 times the maximum the therapeutic human dose based on body surface area (mg/m^2). Further discussion of this is in section 8.1.11.

Citalopram was not antigenic in mice or guinea pigs and a 0. I % solution was locally tolerated in rabbits when administered intravenously or perivascularly. This concentration is 6-12x higher than that administered intravenously in clinical studies and suggests that citalopram presents no local concern to patients when administered intravenously.

Absorption, Distribution, Metabolism, Elimination

Citalopram was well-absorbed in mice, rats, dogs, and monkeys. Systemic bioavailability ranged from 50 to 90% due to species-specific first pass metabolism. After citalopram administration, radioactivity was concentrated in pigmented tissue, lung, liver, kidney, spleen, harderian and salivary glands, and the gastrointestinal tract. Low levels of radioactivity, citalopram itself, and its major metabolites were observed in brain. Citalopram crossed the placental barrier, with fetal distribution similar to adults. Small amounts of citalopram were secreted through the milk of lactating mice.

Citalopram is metabolized by the mixed function oxidase system, with formation of demethyl and didemethyl metabolites. Induction of this system appeared in animals after multiple dose administration. The plasma levels of the metabolites relative to citalopram are higher in animals, particularly rodents, than in man. Citalopram has a short half-life in animals; in mice it is 1.5 hours, rats: 3 hours, and dogs: , compared to 33 hours in humans. The didemethyl metabolite has the longest $t_{1/2}$ (1.5 to 2 days) in animals.

Citalopram is rapidly cleared from plasma in animals. There was complete recovery from urine and feces by 48 hours following administration of ^{14}C-citalopram by oral gavage to rats. Maximal excretion in urine occurred at 2-8 hours and in feces at 8-24 hours. Elimination was by both renal and hepatic routes for both parent and the major metabolites.

The animal pharmacology section has been reviewed by Robin Huff, Ph.D.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

The clinical program for citalopram started in 1976. One-hundred-eighty-six studies in the citalopram development program were completed or ongoing as of March, 1997. These are summarized in the 'Table of All Studies' in Appendix 5.1.

Forest and the FDA agreed to organize the clinical trials data into the following categories: Group 1 studies (19 high quality Phase 2/3 trials which will be used as the core support for the efficacy and safety of citalopram in depressed patients); Group 2 studies (29 pharmacokinetics and pharmacodynamic studies conducted in normal volunteers and patients); and Group 3 studies (119 studies consisting of all other clinical trials); Drug Surveillance Unit (DSU) data; and 19 ongoing studies.

The studies included in Group 1 have complete case report forms (CRFs) with data entered into an electronic database, were monitored according to GCP, used the standards from DSM-III or DSM-IIIR for patient diagnosis, and were conducted using informed consent. Exceptions to these criteria were study 8213, which did not meet GCP standards with respect to the monitoring of non-French study sites, and studies 88105 and 86141, which did not use DSM criteria for diagnosis.

Group 3 studies did not meet the standards of Group 1 studies because of one or more of the following considerations: 1) the study was conducted with minimal or no CRFs; 2) the study monitoring was not consistently documented; 3) did not sponsor the study or provide study drug. Only serious adverse events (AEs), including deaths, are summarized in the NDA submission for Group 3 studies.

The DSU data base was established in 1982 to collect and organize all serious AEs in the citalopram clinical trial program (from 1976 to the present) in addition to events reported from non-clinical trial use (e.g. marketing use) and from reports of serious AEs published in the medical literature. Serious AEs are defined (in 8.1.3) as per the requirements of 21 CFR 312.32. As of December 31, 1996, over 4,000,000 patients are estimated to have received citalopram based largely on European sales of the drug in the 49 countries where it is marketed. The current DSU database for citalopram contains over 1,000 serious AE reports.

The 19 studies labelled as "ongoing" are those started within the past 4 years for which a final study report has not been issued; safety data to the cutoff date of October 1, 1996 is included in the NDA submission. Ongoing study 93401 is classified as a Group 1 study and ongoing study 95220 is classified in Group 2. Efficacy results for 93401 are not available but all safety results are included in the Integrated Summary of Safety (ISS). All serious AEs as of October 1, 1996 from the 19 ongoing studies are included in the DSU database.

An enumeration of all Group 1 subjects is shown in Table 5.1.1.1, and of all Group 2 subjects in Table 5.1.1.2:

Table 5.1.1.1: Patient Enumeration by Study Type			
Group 1 (Phase 2/3) Studies			
Study Type	**Citalopram**	**Placebo**	**Other**
Short-term (≤ 8 weeks), placebo-controlled in depressed patients			
Flexible Dose	105	107	16
Fixed Dose	958	339	-
Subtotal	1063	446	16
Long-term (> 8 weeks), placebo-controlled in depressed patients			
Fixed Dose	257	116	-
Short-term, active-controlled in depressed patients			
Flexible Dose	667	-	387
Fixed Dose	331	-	342
Long-term, active controlled in depressed patients			
Flexible Dose	167	-	178
Uncontrolled in depressed patients			
Flexible Dose	1449	-	-
Placebo-controlled, patients other than depression			
Fixed-dose (check actual study)	516	129	98
Total Unique Patients	**4168**	**575**	**1021**

Note: 391 patients participated in uncontrolled study 89304, 226 went on to participate in long-term, placebo-controlled study 89304 (152 on citalopram and 74 on placebo). Subjects who participated in both studies are counted only once in the total. In addition, all subjects who participated in long-term placebo-controlled study 89305 had participated in short-term placebo-controlled studies 89303 and 89306; each individual is counted only once in the total. In addition, 65 patients who participated in uncontrolled study 88A had participated in other studies and are counted once in the total.

Table 5.1.1.2: Patient Enumeration by Study Type: Group 2 (Phase 1) Studies			
Study Type	Citalopram	Placebo	Active Control
Single Dose	122	0	0
Multiple Dose	250	77	132
Total	**372**	**77**	**132**

5.1.2 Demographics

Demographic characteristics of all subjects in Group 1 studies are summarized in Table 5.1.2.1. Of the Group 1 citalopram patients, 24.8% were age 60 or older. Most of those whose race was specified were Caucasian; many studies did not collect data on race. Females outnumbered males by a ratio of about 2:1. Demographic characteristics of all subjects in Group 2 (phase 1) studies are summarized in Table 5.1.2.2.

Table 5.1.2.1
Demographic Characteristics for Patients in Group 1 Studies (Phase 2/3) (N=5764)

	Citalopram (N=4168)	Placebo (N=575)	TCA (N=570)	SSRI (N=451)
Age: < 40	1252 (30%)	242 (42%)	85 (15%)	204 (45%)
40-59	1578 (38%)	215 (37%)	107 (19%)	196 (43%)
60-64	303 (7%)	22 (4%)	9 (2%)	27 (6%)
≥ 65	1032 (25%)	94 (16%)	369 (65%)	23 (5%)
unknown	3 (<1%)	2 (<1%)	-	1 (<1%)
Age (years)				
Mean	51	45	63	42
Range				
Sex				
Male	1384 (33%)	240 (42%)	155 (27%)	144 (32%)
Female	2784 (67%)	335 (58%)	415 (73%)	307 (68%)
Race				
White	1624 (39%)	322 (56%)	476 (83%)	264 (58%)
Non-white	80 (2%)	30 (5%)	2 (<1%)	3 (1%)
Not specified	2464 (59%)	223 (39%)	92 (16%)	184 (41%)
Weight (lb)				
Mean	67	72	66	68
Range				

Table 5.1.2.2:
Demographic Characteristics of All Group 2 (Phase 1) Subjects (n=415)

	Citalopram (N=372)	Placebo (N=77)	Active Control (N=132)
Age (years)			
Mean (SD)	34.7 (17.7)	47.3 (20.3)	27.0 (9.8)
Range			
Not Recorded	44	23	13
Sex N (%)			
Female	99 (31%)	32 (49%)	30 (28%)
Male	221 (69%)	33 (51%)	78 (72%)
Not Recorded	52	12	24
Race N (%)			
White	69 (78%)	40 (91%)	26 (93%)
Non-white	19 (22%)	4 (9%)	2 (7%)
Not Recorded	284	33	104

5.1.3 Extent of Exposure

Duration of exposure and dose for those who received citalopram in Group 1 (phase 2/3) and in Group 2 (phase 1) studies is profiled in Tables 5.1.3.1. and 5.1.3.2. Each subject is enumerated according to mean daily dose and duration of exposure.

Among citalopram patients in Group 1 studies, about 20.4% (850) were exposed to drug for longer than 24 weeks. 346 of these received a mean daily dose of 40 mg/day or above.

Table 5.1.3.1: Number (%) of All Patients Receiving Citalopram According to Mean Daily Dose and Duration of Therapy in Group 1 Studies

Duration (days)	Mean Citalopram Dose (mg/day)				Total N	(%)
	< 20 mg	20-39 mg	40-60 mg	> 60 mg		
1-7	17	70	18	9	114	(2.7)
8-14	49	94	34	4	181	(4.3)
15-28	50	152	125	14	341	(8.2)
29-84	391	1146	643	32	2212	(53.1)
85-168	57	299	105	9	470	(11.3)
169-336	29	190	168	11	398	(9.5)
337-1152	67	197	125	11	400	(9.6)
> 1152	3	18	31	-	52	(1.2)
Total	663	2166	1249	90	4168	(100)
(%)	(15.9)	(52.0)	(30.0)	(2.2)	(100)	

Table 5.1.3.2: Number (%) of All Subjects Receiving Citalopram According to Mean Daily Dose and Duration in Group 2 Studies					
Duration of Exposure (Days)	Citalopram Mean Dose (mg/day)				Total N (%)
	< 20	20-39	40-60	> 60	
≤ 1	0 (0)	50 (16)	6 (2)	0 (0)	56 (18)
2-7	0 (0)	33 (11)	38 (12)	0 (0)	71 (23)
8-14	0 (0)	2 (<1)	52 (17)	0 (0)	54 (17)
15-30	0 (0)	0 (0)	97 (31)	0 (0)	97 (31)
> 30	0 (0)	0 (0)	32 (10)	0 (0)	32 (10)
Total N (%)	0 (0)	85 (27)	225 (73)	0 (0)	310 (100)*

* Citalopram dosing and duration data were available for only 310 of the 372 citalopram treated subjects.

The sponsor has proposed a maximum dose of citalopram of 60 mg daily. From Table 5.1.3.1, 1249 patients were exposed to mean daily doses in the 40-60 mg range, and 90 patients were exposed to doses greater than 60 mg.

Person-time exposure for citalopram, placebo and active comparators for all Group 1 studies, up to the primary safety cut-off date (October 1, 1996), is as follows:

Treatment	N	Patient-Years
Citalopram	4168	1347.7
Placebo[a]	691	150.3
TCAs	570	123.9
SSRIs	451	60.4

[a]The discrepancy between the placebo N in the above table and the N is tables 5.1.1.1 and 5.1.2.1 arises from the addition of placebo treated patients from studies 89304 and 89305, in which some patients transferred in a crossover regimen from placebo to citalopram or vice versa. Tables 5.1.1.1 and 5.1.2.1 reflect the total unique number of patients in Group 1 studies, with the assignment of the noted 89304 and 89305 participants to the citalopram count.

5.2 Secondary Source Data

5.2.1 Non-IND Studies

Most of the studies in the submitted NDA were non-IND studies.

5.2.2 Post-Marketing Experience

The DSU data base was established by in 1982 to collect and organize all serious adverse events (AEs) in the citalopram clinical trial program (from 1976 to the present). It also contains events reported to Lundbeck from non-clinical trial use (e.g. marketing use) and reports of serious AEs published in the medical literature. A listing is provided for post-marketing spontaneous reports of deaths and serious AEs, through October 31, 1996. As of December 31, 1996, over 4,000,000 patients are estimated to have received citalopram based largely on European sales of the drug in the 49 countries where it is marketed. The current DSU database contains over 1000 reports of SAEs from sponsored clinical trials and from spontaneous reports. The sponsor states that serious AEs recorded through the spontaneous reporting system (SRS) generally reflect the pattern and nature of the SAEs recorded un the clinical development program, and that no new critical safety issues were uncovered. The submitted summary of these events was reviewed, with any important information included in the review of systems (section 8.2). In addition, events of special interest for the safety of citalopram accumulated through the SRS were integrated by the sponsor into the discussions of these events (suicide attempts including overdose, pregnancy and fetal malformations, seizures, ventricular arrhythmias, and vision system effects). Important information from these data will be included in the review of systems section, as will events listed by the company as occurring in at least three patients that were temporally associated with citalopram use and not described elsewhere in the ISS.

5.2.3 Literature

The company states that an article published in Reviews in Contemporary Pharmacotherapy (Vol. 6:315-25, 1995) serves as a baseline from which updates from the literature are summarized. Published literature in the last five years related to citalopram was searched through October 1, 1996. Reprints are provided for all references cited in the ISS (vol. 1.307). The clinical literature review was conducted

The search included the terms "citalopram" and "nitalapram", the originally proposed generic name), "Lu-10-171", and "Lu-10171". The following citation databases were searched: Medline, Excerpta Medica, Biological Abstracts, and Derwent Drug File. The above noted terms were combined with the following restriction terms: "clinical trials$", "efficacy$", "kinetic$", "pharmacokinetics$", "toxicol$", "metaboli$", "pharmacology", "pharmacolo$", and "human". The references for articles which contained new information relevant to safety that did not derive from Lundbeck-sponsored clinical trials are noted and summarized.

The results of the computerized search (title/author/abstract printout) were reviewed by Forest Labs (W. Stern, Ph.D. And G. Schwartz, Ph.D.)

. has 10 years of experience in the drug development industry; has 11 years of experience in the drug development industry, following a career in academic medical research. Their C.V.s were reviewed and they are felt to be adequately qualified to conduct and evaluate the literature search. Potential articles

were selected for the review; of this group, the full articles were reviewed to generate the literature summary for the NDA.

5.3 Comment on Adequacy of Clinical Experience

Data from the large number of clinical trials (186) and post-marketing experience with citalopram since January, 1989 are adequate for determining the safety of the drug at the proposed doses. Data substantiating efficacy for the treatment of depression comes from two short-term studies (studies 85A and 91206) and two long-term studies (studies 89304, 89305); it is also sufficient.

5.4 Comment on Data Quality and Completeness

Twenty case report forms (CRFs) selected at random were compared to the corresponding narrative summaries to assess the accuracy and completeness of data contained in the summaries. No deficiencies were found. Thus, the safety review relied primarily on narrative summaries.

The principal investigator at site for study 91206 (Richard Borison, M.D., Ph.D) was indicted on 2/19/97 for diversion of research funds. There is no evidence that the integrity of that data is compromised, and the number of patients from the site is small relative to the full study (45 of 650 patients, or 7%). Efficacy analyses were done both with and without inclusion of that site, and conclusions were not changed, as discussed in section 7 in the efficacy section of the review.

No other inadequacies in data quality were noted.

6.0 Human Pharmacokinetics

The sponsor reports that citalopram exhibits linear kinetics within the dose ranges tested, though the biopharmacology reviewer has raised questions on the adequacy of the studies done regarding this. Citalopram is characterized by rapid absorption in the gastrointestinal tract and slow elimination. Citalopram's half-life (1.5 days) justifies once-daily dosing. Steady-state concentrations are achieved within one week of daily dosing.

Citalopram is rapidly absorbed in humans, with time to peak plasma or serum concentration (T_{max}) averaging four hours following single or multiple oral administrations. The times to peak plasma or serum concentration of the demethyl and didemethyl metabolites were variable and occurred at approximately 2 to 9 hours and 2 to 11 hours, respectively, after oral administration. Neither renal nor hepatic impairment had any influence on the T_{max} values for citalopram. Maximal concentrations of the demethyl and didemethyl metabolites were about of the citalopram concentration, respectively. The bioavailability of citalopram was nearly complete (80% ± 13%), following a single 40 mg oral dose relative to an intravenous dose.

A high- or non-fat meal immediately preceding oral administration of 30 mg

citalopram did not alter the rate and extent of citalopram absorption nor its disposition, compared to the fasting state.

Following oral administration, ^{14}C-citalopram was rapidly absorbed into the systemic circulation and then slowly eliminated, consistent with data obtained in single and multiple dose studies. As expected for a basic, lipophilic drug, citalopram partitioned into organs, achieving tissue levels in animals that exceeded those in plasma by as much as ten-fold. The volume of distribution was approximately , further indicating widespread tissue distribution.

The binding of citalopram and its demethyl and didemethyl metabolites to human plasma proteins was approximately 82, 74, and 78%, respectively. Thus, potential displacement of citalopram from plasma protein binding sites by other drugs would have little effect on its half-life or plasma levels.

Metabolism of citalopram is by the mixed function cytochrome P450 system, with successive N-demethylations to demethylcitalopram (DCT) and didemethylcitalopram (DDCT). In subjects with sparteine and mephenytoin oxidation polymorphisms, the relationship between citalopram pharmacokinetics and spartein/mephenytoin metabolism was studied and found likely not to be clinically significant. Therefore, there is no need for individualized dosing based on these phenotypes. In *in vitro* microsomal tests, the principal cytochromes mediating citalopram demethylation were $IIIA_4$ and IIC_{19}, with a possible small contribution of IID_6.

The relative amounts of citalopram, DCT and DDCT recovered in urine (48 hour total) after a single 40 mg dose were approximately 10%, 5%, ~~and 0.9%~~, respectively, for both oral and intravenous routes. Following a multiple dose regimen of citalopram the relative amounts excreted in the urine at steady state were approximately 23%, 19%, and 4%, respectively.

Following oral administration of ^{14}C-citalopram, 85% of the radioactivity was recovered in urine (409 hours collection) and feces (337 hours collection). Protracted renal elimination accounted for approximately 75%, whereas fecal elimination accounted for 10.5% of the dose recovered in the excreta.

DRUG-DRUG INTERACTIONS

Concomitant administration of imipramine, lithium, and levomepromazine had no effect on T_{max} values of citalopram or its metabolites. In contrast, cimetidine caused a statistically significant decrease in the T_{max} value of citalopram and an increase in that of DCT.

In an evaluation of the effects of psychotropic drugs on serum citalopram concentrations in psychiatric patients, individual neuroleptics (perphenazine, thioridazine, periciazin, chlorpromazine, haloperidol, zuclopenthixol, and levomepromazine) had no effect on serum citalopram or its demethyl derivative. Only alprazolam among the benzodiazepines tested (including oxazepam, diazepam, temazepam, clonazepam, lorazepam, chlorazepam, and chlordiazepoxide)

had any effect on citalopram and DCT concentrations, increasing them by 20% and 48%, respectively. Among the antidepressants administered concomitantly with citalopram, clomipramine exerted the most effect, increasing citalopram and DCT concentrations by 94% and 250%, respectively.

Concomitant administration of cimetidine caused a significant increase in the average steady-state levels of citalopram and DCT by 43% and 11%, respectively, as determined by AUC values and a significant decrease (30%) in the oral clearance of citalopram. Additionally, the renal clearances of citalopram and DDCT were decreased by approximately 30%. Minimal adjustments in citalopram dose may be needed when used in combination with cimetidine.

Drugs which did not appear to have any clinically significant pharmacokinetic interactions with citalopram and may be coadministered with citalopram include digoxin, carbamazepine, imipramine, lithium, levomepromazine, and warfarin. Citalopram inhibited metoprolol metabolism without an apparent effect on its cardiovascular pharmacodynamics. Citalopram is contraindicated with monoamine oxidase inhibitors, as are all SSRIs.

PHARMACOKINETICS IN SPECIAL POPULATIONS

The pharmacokinetics of steady-state citalopram in elderly subjects are similar to that in young subjects. After 5 weeks of citalopram 40 mg/day, mean C_{max} and AUC were, respectively, 13% and 23% higher in elderly subjects compared to younger subjects, though there were no statistically significant differences in C_{max}, T_{max}, AUC, or $t_{1/2}$. In the proposed labeling, a maximum dose of 40 mg is recommended in the elderly based on clinical experience, though it is unclear what this experience is, as there was no age difference identified in the incidence of common and likely drug-related AEs (section 8.1.5.5.2).

The half-life of citalopram was approximately twice as long with clearance reduced by 37% in patients with reduced hepatic function compared to normal volunteers. This suggests that the use of citalopram in reduced hepatic function patients should be approached with caution and a lower maximum dose is recommended.

In patients with mild to moderate reduced renal function the oral clearance of citalopram is reduced by 17% compared to normal subjects while its rate and extent of absorption are minimally affected; these changes were not statistically sugnificant. Consequently, no dosage adjustment for these patients is warranted. No information is available for patients with severely reduced renal function.

The pharmacokinetics of citalopram is being reviewed by Iftekhar Mahmood, Ph.D. He has noted some problems with some of the sponsor's claims and the adequacy of studies. His report is pending.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

The Group 1 studies provide the primary basis for evaluating the efficacy of citalopram in the treatment of depression. Group 2 studies were essentially Phase 1 pharmacokinetic/pharmacodynamic trials and Group 3 studies did not meet the quality standards of Group 1 trials because of one or more of the following deficiencies:

- minimal or no case report forms.
- study monitoring was not consistently documented.
- Lundbeck did not sponsor the study or provide study drug.

Among the 19 clinical trials classified under Group 1, two studied patients with indications other than depression,[1] two were uncontrolled studies in depressed patients,[2] and six were active-controlled studies in depressed patients.[3] These ten trials are not capable, by design, of providing an adequate demonstration of antidepressant efficacy.

Among the 9 placebo-controlled studies in depression, two were small (≤20 patients treated with citalopram) and had been prematurely terminated.[4] These two trials were also not felt to be capable of providing convincing evidence of efficacy.

Thus, this section will focus on the remaining seven placebo-controlled depression studies: five short-term trials (85A, 91206, 86141, 89303, and 89306) and two longer-term, relapse prevention trials (89304 and 89305).

The efficacy analyses presented in this review focus on the following widely accepted instruments for measuring an antidepressant effect: Hamilton Depression Rating Scale (HAM-D) total score, item #1 of the HAM-D (depressed mood score), and the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Additionally, the Clinical Global Impression (CGI) severity score, a standard global measure of illness severity, is presented. With respect to the latter scale, older studies in the Group 1 database used a 5 point scoring system while more recent ones used a 7 point scale. Please note that the sponsor converted the 7 point scores collected in all seven placebo-

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[1]Studies 91202 and 91203.

[2]Studies 8213 and 88A.

[3]Studies 89422, 91302, 92301, 88105, 92302, 93401.

[4]Studies 86A and 87A.

controlled studies to a 5 point scale in preparing ISE data displays. This conversion, which involved combining two pairs of 7 point scores under 5 point scores, was done as follows (7 point scores are bolded):

5 point score	7 point scores
1	not ill (1)
2	borderline (2) and mildly ill (3)
3	moderately ill (4)
4	markedly (5) and severely ill (6)
5	extremely ill (7)

This conversion process is not expected to appreciably affect the conclusions regarding antidepressant efficacy.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Placebo-controlled Controlled Studies in Depression

7.2.1.1 Study 85A

Investigators/Locations

The three principal investigators and study center locations are identified in Appendix 7.2.1.1.

Objectives

The objective of this study was to assess the safety and efficacy of citalopram relative to placebo in moderately to severely ill patients with major depression or in the depressed phase of bipolar illness.

Population

Study participants were outpatients in the age range who had a DSM-III diagnosis of major depression or bipolar disorder, depressed. The study protocol also specified that patients must meet DSM-III criteria for melancholia. However, examination of the Patient Selection Criteria checklist used by the investigators did not appear to incorporate this requirement (see Appendix 1 of the study report). Females must have been post-menopausal or surgically sterilized. Patients must have had a 24-item HAM-D total score of ≥25 at the end of the placebo washout phase and must have discontinued all psychotropic medication before entry into the study. The following exclusion criteria were used:

- history of DSM-III schizophrenic disorder, schizoaffective disorder, organic mental disorder, or dysthymic disorder.
- presence of psychotic features.

- significant medical or neurological disease.
- history of a seizure disorder.
- drug or alcohol abuse or dependence within six months.
- use of an MAOI within two weeks of the study.

Design

This was a 3-center, randomized, double-blind, placebo-controlled, parallel group study. After a single-blind, one week placebo run-in, eligible patients were randomized to receive either citalopram (flexible doses in the range 20-80 mg/day) or placebo for four weeks of double-blind treatment. All study medication was taken as a single daily dose in the evening. Citalopram dosing began at 20 mg/day and titration to the maximum tolerated dose was to be accomplished in 20 mg/day increments every 3-4 days within the first two weeks; however, 13 citalopram and 5 placebo patients had dose increases during weeks 3 and 4.

Analysis

The protocol for this study did not specify a primary efficacy variable; the ISE indicates that the principal measurement of efficacy was the 24-item HAM-D total score. The efficacy intent-to-treat (ITT) population included all randomized patients who had assessments at baseline and at least one post-baseline assessment. Between-group differences in changes from baseline for efficacy measures were tested using an ANCOVA model with treatment and center as main effects, treatment by center as an interaction effect, and baseline value as the covariate.

Baseline Demographics

Baseline demographic data is displayed in Appendix 7.2.1.1. Treatment groups were comparable with respect to mean age, age range, gender composition, and race.

The vast majority of patients (~95% of each group) had a diagnosis of major depression, as opposed to bipolar depression, at baseline.

At baseline, only 85% of both citalopram and placebo patients met the criteria for melancholia despite the protocol requirement that all patients have DSM-III melancholia.

Baseline Severity of Illness

Groups did not significantly differ with respect to baseline HAM-D total or depressed mood item scores or CGI severity ratings.

Patient Disposition

This study enrolled 180 patients. Of these, 169 patients met

criteria for inclusion in the efficacy ITT population: 82 were randomized to citalopram and 87 to placebo. The number of completers at weeks 1, 2, 3, and 4 is displayed in Appendix 7.2.1.1. Of the ITT samples, 59% of both the citalopram and placebo groups completed the study. At least two-thirds of the patients in each group were in-study on week 3. A smaller proportion of citalopram patients dropped out due to lack of efficacy compared to placebo (7% versus 25%, respectively). Conversely, more citalopram than placebo patients dropped out due to an adverse event (25% versus 8%, respectively).

Dosing Information

Mean dose by visit is displayed in Appendix 7.2.1.1. At final visit, the mean citalopram dose was 62.4 mg/day. Further information on dosing in this study will be presented in Section 7.3.3 (Choice of Dose).

Concomitant Medications

Concomitant psychotropic medications were prohibited during the study, except that chloral hydrate was permitted intermittently as needed for sleep disturbance. One citalopram and four placebo patients received a sedative/hypnotic agent during the study. Also, one placebo patient received an unspecified antidepressant drug during the study. This usage is unlikely to bias the efficacy results in favor of citalopram.

Efficacy Results

This review focused on the least-squares adjusted mean change from baseline in the HAM-D total score, HAM-D depressed mood item, and CGI severity score as the primary measures of efficacy. Results for these measures, using both the last observation carried forward (LOCF) and observed cases (OC) datasets, are summarized in Appendix 7.2.1.1.

There was consistent statistical superiority favoring citalopram over placebo on the HAM-D total score and depressed mood item from week 1 onward for both the LOCF and OC datasets.

Between-group differences were less consistent for the CGI severity score but were statistically significant at week 4 for both LOCF and OC. The differences at week 2 were highly significant ($p \leq 0.0024$) but became less marked at weeks 3 and 4 due to substantial mean improvement in the placebo group.

There did not appear to be a significant treatment-by-center interaction in this study based on the mean change from baseline in HAM-D total score in the LOCF sample ($p=0.8194$ at week 4).

The sponsor proposes to describe in the Clinical Trials of

labeling a superiority of citalopram over placebo with respect to certain HAM-D factor subscores (melancholia, psychomotor retardation, cognitive disturbance, and sleep disturbance). These factors are defined in the ISE as follows:

Factor	HAM-D Items Subsumed by Subfactor
Melancholia	Depressed mood Feelings of guilt Work and activities Retardation Anxiety, psychic Somatic Symptoms, general
Retardation	Depressed mood Work and activities Retardation Genital symptoms
Cognitive Disturbance	Feelings of guilt Suicide Agitation Depersonalization/derealization Paranoid symptoms Obsessive/compulsive symptoms
Sleep Disturbance	Early insomnia Middle insomnia Late insomnia

The retardation, cognitive, and sleep factors of the HAM-D have been previously described[5] but there is no known documentation to support the melancholia cluster of symptoms as a distinct factor. For these reasons, findings with respect to the melancholia factor should not be described in labeling.

Regarding the retardation, cognitive, and sleep disturbance factors, Week 4 data are summarized in Appendix 7.2.1.1. Differences between drug and placebo were statistically significant for both LOCF and OC analyses for all three variables. Visit-wise LOCF data were not provided but the observed cases analysis indicates consistent superiority over time.

Conclusions

Study 85A demonstrated adequate superiority of citalopram over placebo in the treatment of depressed outpatients.

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[5]Guy W. ECDEU Assessment Manual for Psychopharmacology. Revised, 1976. U.S. Department of Health, Education, and Welfare.