CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20822

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 9, 1998

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approval Action on Forest Laboratories, Inc. NDA 20-822
Celexa (citalopram HBr) for the management of depression

TO: File NDA 20-822
&
Robert Temple, M.D.
Director, ODE1
HFD-101

This memorandum conveys to the file my recommendation, offered as Director of the Division responsible for the application's review, for the approval of Forest Laboratories' NDA 20-822 which allows for the marketing of Celexa Tablets
as an antidepressant drug product.

My substantive comments about the NDA were provided in my memorandum to the file of 5/4/98. Dr. Laughren's July 2, 1998 memorandum to the file summarizes both the matters considered by the review team and the substance of its interactions with the sponsor over the interval following the issuance of the approvable action letter. No new evidence or finding has emerged as a result of these activities that would cause me to alter my prior conclusion that Celexa has been shown to be safe for use and effective in use.

I have, however, asked for, and gained the firm's agreement to accept, some minor modifications of the proposed product labeling. These changes were made because the labeling presented by the review team for my endorsement differed in both form and content from the labeling under which I recommended (5/4/98) that the product be declared approvable.

For the most part, the draft developed jointly by the sponsor and the

review team differed in only minor respects from that which I had originally endorsed.

The decision to place the discussion of the findings of the dog cardiovascular study in the very last section of labeling is not a placement that I prefer, but it is one that I can nonetheless accept because it does not affect my conclusion that Celexa can, within the meaning of the Act, be deemed safe for use under labeling carrying that discussion in the location that it does.

However, given the placement of the discussion, and the heading of the section, (i.e., Animal Toxicology), I found it to be an inappropriate section in which to discuss clinical findings. Moreover, not only did the last paragraph of the draft assert that the findings of the dog studies were irrelevant to human use, a conclusion a bit too strong from my perspective, but it also presented almost promotional assertions concerning how extensive clinical experience gained elsewhere in the world documents citalopram's safety for use. I am not fond of such arguments because they rely on the absence of evidence to support affirmative contrary assertions.

Another aspect of the labeling provided for my endorsement that I found less than satisfactory was the OD section of the labeling. The draft provided began with a statement that there were no fatalities in clinical trials at overdoses (i,e, ODs) of up to 2000 mg, and only later, as a clause in the second sentence, did it acknowledge that there have been 12 fatalities.

I found this placement off point; the clinical information of primary importance is that overdoses with Citalopram alone can sometimes prove fatal, not that most reported cases of overdoses survive, nor that when deaths do occur that they typically involve overdoses with multiple drugs. The latter attribute applies to a substantive proportion of overdoses reported with almost every marketed drug, a finding explained by the impulsive nature of so many non-accidental ODs. Moreover, estimates of the proportion of overdoses with a drug that prove fatal are meaningless given the imprecise usage of the term overdose.

I also found it less than satisfactory that the OD section did not make note of the fact that some ODs have been associated with QTc prolongation exceeding 500 msec. I was concerned not only because this is important in its own right, but because OD is the very situation in which citalopram's didesmethylated metabolite (DDCT) might be elevated in humans to levels where it could cause QTc prolongation as it did in the dog.

Dr. Laughren subsequently informed me that the sponsor claims (in an oral presentation) to have examined blood samples obtained from human ODs for the presence of elevated DDCT levels and found none. However, the numbers of samples assayed are few (2 cases to be precise), the circumstances under which the blood samples were taken relative to the OD unknown, and accordingly, the level of reassurance provided by this experience of limited value.

Accordingly, we approached the sponsor with a number of requests for further modifications of the OD and Animal Toxicology sections of Celexa labeling.

Among the requests was one asking the sponsor to rework the opening sentence of the OD section to make more prominent the fact that fatalities could occur. Another was that the OD section contain (at the end of a sentence describing the EKG findings in OD) a reference pointing the reader to the Animal Toxicology section. I was mindful that the placement of a reference in the OD section to the Animal toxicology section implied that a link between DDCT and death in OD was a distinct possibility. Although I believed it was not improper to suggest such a possibility (if for no other reason than to stimulate interest in measuring the DDCT metabolite in OD cases where QTc prolongation was observed), I was also aware that the link was based on a rational possibility, not an empirical finding. Accordingly, I was well aware that the sponsor would probably object. On the other hand, I felt the last paragraph of the animal section extolling the reassuring post-marketing clinical experience gained elsewhere in the world with Citalopram served as more than reasonable counterweight to the implication I intended the reader to consider.

Direct negotiations with the sponsor about these several matters (teleconference of 7/8/97) produced a compromise. I agreed to drop my request for a link in the OD section to the animal toxicology section in exchange for their agreement to delete the exculpatory last paragraph in the Animal Toxicology section. We made a number of other minor changes to ensure that any clinical information contained only in that paragraph would be presented in other, more appropriate, sections of product labeling (e.g., post-introduction reports, adverse reactions, or in the revised OD section.)

I made clear to the sponsor, however, that the text of labeling might undergo further revision at the Office level. In any case, I am now satisfied that Celexa, if marketed under this labeling, will, within the meaning of the Act, be safe for use and effective in use, under the conditions of use recommended.

Recommendation:

Issue the approval action letter and attached labeling

/S/

Paul Leber, M.D.
July 9, 1998

cc:
NDA 20-822
HFD-120
Temple
HFD-120
Katz
Laughren
Molchan
Dubitsky
Fitzgerald
Huff
Rosloff
David
Seevers
Guzewska
Rzeszotarski
HFD-713
Sahlroot
Choudhury
HFD-860
Sahajwalla
Mahmood

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 2, 1998

FROM: Thomas P. Laughren, M.D. /S/
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Celexa (citalopram) for the Treatment of Depression

TO: File NDA 20-822
[**Note:** This overview should be filed with the 5-22-98 submission.]

1.0 BACKGROUND

In our 5-12-98 approvable letter, we requested a safety update, a foreign regulatory update, a world literature update, a gender subset analysis for study 91206, a report on findings pertinent to the occurrence of pulmonary hypertension and/or valvulopathy, and a commitment to conduct several phase 4 studies

We also (1) identified our preferred dissolution methodology and specifications, (2) noted that we could approve only an 18 month expiration date, (3) explained our rationale for a cardiovascular risk Warning statement, and (4) explained our rationale for our dosing recommendations. We also attached our proposal for labeling.

Forest responded to our approvable letter with a 5-22-98 submission, including (1) a safety update, (2) an alternative labeling proposal, and (3) responses to the other questions and requests in our letter.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks, including both exchanges of draft labeling and teleconferences (6-10-98; 6-16-98; 6-19-98), in order to resolve most of the less controversial differences in labeling prior to our face-to-face

meeting with Forest on 6-26-98. At that meeting, we reached tentative final agreement on labeling, with the exception of exact wording for the cardiovascular statement. We reached final agreement on the cardiovascular risk statement on 7-2-98. This mutually agreed upon final labeling [LABCTLDP.AP4] is included with the approval letter.

Dr. Susan Molchan reviewed the clinical sections of the 5-22-98 response to the approvable letter, including the safety update, the literature update, and the regulatory status update.

2.0 SAFETY UPDATE

The safety update included reports of deaths, serious adverse events, adverse dropouts, and other adverse events. The safety update covered a period from 10-1-96 through 1-31-98 for the integrated database; spontaneous reports and deaths/SAEs from ongoing studies were reported through 3-1-98.

-There were an additional 23 deaths and 296 SAEs from clinical studies, all from group 3 (large open marketing studies), most in elderly individuals; there were 4 suicides. Dr. Molchan concluded that none of these deaths could be reasonably attributed to citalopram treatment, and I agree.
-New overdose reports included 3 deaths, 2 of which involved co-administered drugs but 1 apparently involved only citalopram (17 y/o female) and was associated with a QTc of . Two nonfatal overdoses also were associated with cardiac findings, including 1 with VF and another with a QTc of 511.
-There were 3 reports of epidermal necrolysis, which although confounded, nevertheless need to be noted in labeling.
-Dr. Molchan reviewed the deaths and other serious adverse events, and concluded that these additional data did not alter her view about the approvability of citalopram and, with the exception of the reports of epidermal necrolysis, did not reveal any new information that would impact on the labeling of citalopram. I agree.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from 10-1-96 to 1-31-98, including both clinical and preclinical references. Dr. Molchan reviewed abstracts for these references and concluded that they contained no findings that would adversely affect conclusions about citalopram's safety. The only new event emerging from this search and not in the originally proposed labeling was priapism, and this has now been incorporated.

4.0 FOREIGN REGULATORY UPDATE

The sponsor has noted that citalopram is approved in 63 countries at the present time. They have warranted that no negative regulatory actions have been taken with regard to this drug.

5.0 GENDER SUBSET ANALYSIS

The sponsor conducted a subset analysis of the efficacy data for study 91206 on the basis of gender, and found no evidence supporting the effectiveness of the 20 mg dose in women.

6.0 PULMONARY HYPERTENSION/VALVULOPATHY

Forest searched their clinical trials and spontaneous reporting database for cases suggestive of either pulmonary hypertension or valvulopathy, and claim to have found none. They are aware of no echocardiographic data for citalopram and they do not plan to collect any. They are also aware of no gross anatomic or microscopic data from cardiac valves in citalopram-exposed subjects, and they have no plans to collect any. Given the lack of evidence suggestive of an association of either event for the other SSRIs we have looked at, I am inclined to think this response is sufficient.

7.0 REQUEST PHASE 4

8.0 BIOPHARMACEUTICS

The sponsor accepted our proposed dissolution method and specifications.

9.0 CMC

Forest referred to a 4-2-98 amendment containing data in support of a 24 month expiration date. We have reviewed these data and we are in agreement with a 24-month date.

10.0 LABELING

The major issues in our labeling negotiations involved the cardiovascular risk statement and recommendations for dosing. We were able, during several teleconferences, in a face-to-face meeting on 6-26-98, and in subsequent negotiations to reach agreement on final labeling. We did agree to place the cardiovascular risk statement in Animal Toxicology rather than in Warnings, on the basis

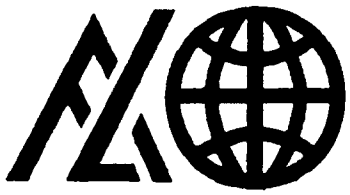
of a lack of any persuasive human data supporting a concern for a risk of QTc prolongation. At the time of sending our approvable letter, the only clinical finding that tended to support this concern was a suggested higher incidence of outliers on QTc (patients exceeding 500 msec on QTc) for citalopram compared to placebo. Upon further examination, it was clarified that the difference is diminished when corrected for duration of exposure, is not statistically significant, and a substantial majority of citalopram patients meeting this criterion had prolonged QTc's at baseline. Regarding the possible role of DCT, the sponsor has agreed to conduct an additional in vitro test (guinea pig heart) to explore its role in QTc prolongation.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Forest has submitted sufficient data to support the conclusion that Citalopram is effective and acceptably safe in the treatment of depression. I recommend that we issue the attached approval letter with the version of labeling for which we were able to reach mutual agreement with the sponsor.

cc:
Orig NDA 20-822
HFD-120
HFD-120/TLaughren/PLeber/GDubitsky/SMolchan/PDavid/SHardeman
HFD-100/RTemple

DOC: MEMCTLDP.AP1



FAX: (212) 750-9152
DIRECT LINE: 212 224 6820

May 22, 1998

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
CDER, HFD-120, Woodmont II
Document Control Room, 4th Floor
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Re: **NDA#20-822 - Class 1 Resubmission - Response to Approvable Letter**
Product: **Celexa™ (citalopram hydrobromide) tablets 10mg, 20mg, 40mg& 60 mg**

Dear Dr. Leber:

Reference is made to the May 12, 1998 approvable letter for Celexa™. Forest hereby amends NDA #20-822 pursuant to 314.110(a) (1) to issue a complete response to the approvable letter and proposed labeling. Pursuant to the CDER MAPP 6020.4, this resubmission would qualify as a Class 1 resubmission because it consists of only draft labeling, a final safety update, a stability update, responses to proposed phase 4 committments, minor clarifying information, and some minor re-analysis of data previously submitted to the NDA.

The various items in the approvable letter will be addressed in the same numerical order as received. Supporting data will be provided in the appendices to each section. Please note that this supporting data has already been submitted to the Division either as part of the original NDA or amendment to the NDA or to the Citalopram IND Per the May 20, 1998 telephone conversation with Mr. Paul David, copies of these data are provided in this amendment for reviewer convenience.

CLINICAL

1. Labeling

Forest has provided revised labeling in Section V of this amendment. These revisions are based on the suggestions of the Division and on interpretations of the data available as revisited by Forest Justifications are provided at the end of the annotated version of the PI. Per the May 14, 1998 conversation with Mr. Paul David, an electronic version of both the labeling and the annotated labeling is provided in Section V.

2. Safety Update

A final safety update is provided in Section IV per Forest's March 18, 1998 proposal to the Division. This safety update utilizes a clinical trial cut off date of January 31, 1998. Spontaneous reports and deaths and serious adverse events reported from ongoing clinical studies through March 1, 1998 are also reported.

3. Regulatory Status Update

An update of all regulatory actions regarding citalopram worldwide is provided in section II. Citalopram is now approved in 63 countries worldwide. Labeling (and English translations where needed) is provided where labeling is available. There have been no negative regulatory actions concerning citalopram in any country.

4. World Literature Update

An updated report on the world's archival literature is provided as Appendix 2 to Section IV (Safety Update). An explanation of the algorithms used to search and the credentials of the individual conducting the literature search is included. Any references addressing the safety of citalopram, either as preclinical or clinical data, are included with English translation when necessary.

5.

7. Cardiovascular Risk

Forest requests that the Cardiovascular Risk section be deleted from the **WARNINGS** section of the package insert. Our overall assessment of the preclinical and clinical cardiovascular findings is that the observations of QTc changes, Torsades de Pointes, and sudden death in the dog are clinically irrelevant. This assessment is based on review of the results of extensive investigative toxicology studies and an unusual wealth of clinical data within the NDA and the enclosed safety update encompassing greater than 23,000 citalopram-treated clinical patients over a 20-year period and some eight million postmarketing citalopram exposures since the drug was approved in Europe 9 years ago.

Importantly, we conclude that the clinical use of citalpram in these studies and throughout the postmarketing experience was not associated with QTc prolongation or an increase in the risk of serious cardiac arrhythmias in man. We acknowledge the Division's comments regarding the toxicity findings in dogs. Whereas the mechanism of the findings in dogs may not be precisely known, the lack of clinical evidence for increased cardiac risk suggests that the dog results have no human equivalent. While additional preclinical studies may be useful to understand why dogs are susceptible to cardiovascular toxicity during citalopram exposure, these studies will not change the conclusion that citalopram use has not been associated with increased cardiovascular risk in man.

A full discussion of the preclinical and clinical data supporting this assessment is presented in Section V, Attachment 9. Forest agrees that the issue of cardiovascular risk would benefit from additional discussion among ourselves, representatives from , and the Division at the scheduled June 25 meeting.

8. Valvulopathy

A search through the Citalopram clinical database and the spontaneous reporting system did not yield any cases of pulmonary hypertension or any valvular problems that developed during Citalopram exposure.

Forest Laboratories are not aware of any echocardiographic data for patients exposed to Citalopram. No echocardiography studies are planned at this time.

Forest is not aware of any gross anatomic or microscopic data from cardiac valves for patients exposed to Citalopram. There are no plans to try to obtain such data.

9.

10. Maximum Recommended Dose/Highest Tablet Strength

Reference is made to supplement 78 to IND submitted on April 13, 1998. This supplement provided a justification for a recommended therapeutic dose of 20 mg. A copy of this proposal is included as Attachment 29 to Section V.

Based on the analysis of patient response in controlled short term and long term studies, Forest believes the 20 mg dose to be an efficacious dose and the rapid forced titration to 40 mg/day, proposed by the Division, does not allow for the use of the lowest effective dose in patients who can respond acutely and maintain their response on a 20 mg/day regimen.

Forest also proposes that the Division include the 60 mg dosage strength. This dose was clearly shown to be safe and effective in study 91206. While we anticipated the majority of depressed patients will respond to a 20 to 40 mg dose, the 60 mg strength should be recommended to those patients requiring a higher dose or who are more severely depressed. This issue is fully discussed in Attachment 30 to Section V, to support the revised labeling.

PHARMACOLOGY

MANUFACTURING AND CONTROLS

1. Expiration Date

We have acknowledged your notification of an 18 month expiration date. However, based on prior communication with the agency, Forest had begun packaging product with a 24 month expiration date. It was our understanding, after discussion with the chemistry reviewer, that in order to use a 24-month expiration date we must have 18-month stability data available (see Section I, Appendix 4, Attachment 1). Please note that we submitted a 18-month stability data to the Agency on April 2, 1998 (see Appendix 4, Attachment 2) with a statement that this data qualifies us for a 24-month expiration date. As we already packaged some of the batches (Physician Samples) with a 24-month expiration date, we are requesting your permission to use these batches based on the following:

According to February 1987 "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics" our original application contains a post-approval stability commitment to (1) perform stability studies; (2) report results of stability studies as they become available (e.g., in periodic reports); and (3) withdraw from the market any lots which may fail to meet our approved specifications (see Appendix 4, Attachment 3). In addition, our application also contains 6-month accelerated stability data

which supports a 5-year expiration date. We now provide stability reports for the 20 mg and 40 mg strengths from indicating the product to be stable for 5 years (see Appendix 4, Attachment 4). This information, we believe, should satisfy the guideline requirements to approve expiration dating with the data that do not cover the full expiration period.

In addition, based on the available data (previously submitted on April 2, 1998, see Attachment 2), which includes test results from 18 months storage Celexa Tablets 10, 20, 40 and 60 mg packaged in bottles and blisters are projected to be stable for at least 36 months at room temperature. The projections using these data are given in Attachment 5. In all cases, the regression plots show, at the lower 95% confidence limit, the assay is well within specification at the 24 month time point. Therefore, Forest requests that expiration dating of 24 months be granted for Celexa.

2. Nomenclature

submitted the name citalopram to USAN on May 19. A copy of the USAN approval letter will be forwarded to the Division when it is received by Forest.

BIOPHARMACEUTICS

1. (Re: Carbamazepine)

Forest believes that further studies to access the effect of steady state carbamazepine on citalopram pharmacokinetics are not needed. This issue is fully discussed in Section V, Attachment 13.

2. (Re: Enantiomers)

On March 30, 1998, Forest submitted the final report for CIT-PK-1-97-02, A Dose Proportionality and Pharmacokinetics Study of Citalopram in Healthy Young Volunteers to the NDA. We agree to analyze the samples from this study to determine the dose proportionality of the individual isomers. Forest also agrees to conduct a gender analysis for both isomers. This data will be provided within 6 months after approval.

3. (Re:Dissolution Sampling Times)

The dissolution data on pages 6-00179 through 6-00189 of the NDA (see Section I, Appendix 5, Attachment 1) represent all available dissolution data (collected during the 15 years of product development) for batches used in bioavailability and clinical studies. Dissolution profiles (10, 20, and 30 minutes) have been performed on clinical formulations at since January, 1992, whereas dissolution on the marketed formulation ! Before January, 1992, dissolution profiles were only performed on special request. When was used, the sampling time was for both clinical and marketed formulations. Data presented in Attachment 1 reflect the evolution and focus towards establishing a dissolution specification of at 30 minutes.

To characterize the dissolution profiles of citalopram tablets later in the development process, demonstrating the *in vitro* equivalence of product manufactured by Forest to that from (see Section I, Attachment 2), samples were taken at 10, 20, 30, 45 and 60 minutes in various dissolution medium; except when water is used as the medium, then samples were taken at 10, 20, 30, 60, 90 and 120 minutes. These time points were selected to provide additional data to better define the rate of release and the point at which the asymptote is reached.

4. *In Vivo* Drug Interaction Study

CYP3A4 and CYP2C19 are the primary isoenzymes involved in the metabolism of citalopram to DCT. The support for this statement is provided by independent studies with human liver microsomes.

Fluvoxamine is a significant inhibitor of both 3A4 and 2C19. An independent *in vivo* study submitted in the NDA, evaluated the effect of fluvoxamine administration on the metabolism of citalopram. In this study, doubling of the citalopram concentration was not associated with an increase in clinically significant adverse events.

A comparison of adverse event incidence in Group 1 citalopram patients receiving concomitant medications known to inhibit 3A4 (erythromycin, miconazole, fluconazole, clotrimazole, ketoconazole, itraconazole, gestodene, fluvoxamine, and ethnylestradiol) versus all other Group 1 citalopram-treated patients was performed. There was no evidence of a clinically important difference in adverse event incidence or type between the two groups.

These results are fully discussed in Section V, Attachment 2.

Based on the lack of known clinical significance of the 3A4 and 2C19 inhibitors on citalopram metabolism, Forest does not believe an *in vivo* study would warrant further investigation. We would be happy to discuss this with the Division.

5. Dissolution Specifications

Forest agrees to the recommendation by the Office of Clinical Pharmacology and Biopharmaceutics for the dissolution and specification method expressed in the approvable letter.

A field copy of this amendment is being submitted to the Brooklyn, N.Y. district office.

Per the request of Mr. Paul David, 4 desk copies are provided for volumes 1 (cover letter) and 5 (annotated labeling) of this submission.

Forest is anxious to work with the Division to proceed to final labeling in a timely fashion. We are hopeful that many of the minor differences can be resolved through one or more telephone conferences prior to our June 25 meeting with the Division on the more substantive issues. Additional briefing materials will be sent at least two weeks prior to the June meeting.

Please do not hesitate to contact me at 212-224-6820 if you have any questions regarding this submission.

Sincerely,

Kathryn Bishburg

Kathryn Bishburg, Pharm.D.
Director, Regulatory Affairs
FOREST LABORATORIES, INC.

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: May 4, 1998

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable Action on Forrest Laboratories, Inc. NDA 20-822
Celexa (citalopram HBr) for the management of depression

TO: File NDA 20-822
&
Robert Temple, M.D.
Director, ODE1
HFD-101

Introduction[1]

Forrest Laboratories' NDA 20-822 allows for the marketing of Celexa Tablets (a racemic formulation of citalopram bromide) as an antidepressant drug product; the NDA's PDUFA goal date is 5/12/98.

The IND for Citalopram (IND) was opened in 1983 by . It is of note that clinical testing under the IND was suspended for almost 4 years during the late 1980's because of concerns about the product's safety arising from reports of sudden and unexpected deaths in a 1 year chronic dog toxicology study (see below). Although the Division subsequently agreed that the findings of additional preclinical tests and accumulating clinical experience were sufficient to allow domestic clinical testing to resume, the factors that may have contributed to the deaths in the dog toxicology remain a matter of speculation, a fact that I am persuaded must be considered in the agency's assessment of Citalopram's risks of use.

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[1] An earlier draft version of this memorandum, dated April 14, 1998, was provided to Dr. Temple at the time the Division's review package was first sent to the Office. The current memorandum differs in only minor respects from the draft of April 14, 1998.

Citalopram is currently marketed in more than 50 countries[2].

The Review Process

The NDA review team was led by Dr. Thomas Laughren; the findings of the review team are summarized in his supervisory memorandum of 3/26/98. The primary clinical review was conducted jointly by Drs. Gregory Dubitsky and Susan Molchan (3/11/98); the consulting statistician was Jaobrata Choudhury (2/26/98). The pharm/tox review was conducted by Dr. Robin Huff[3] (2/13/98); an overview of the major findings of the preclinical evaluation of citalopram is provided in Dr. Glenna Fitzgerald's supervisory memorandum of 4/8/98 and her addendum of 4/30/98.

Pharmacology of citalopram.

Citalopram [CT] is a sparingly water soluble compound with a molecular weight of 405 daltons. It's sole proton donating site has a pKa of 9.5. The S (+) enantiomer of citalopram is a monamine reuptake inhibitor that exhibits a greater capacity to affect the transport of serotonin as compared norepinephrine and dopamine, and, accordingly, is classified pharmacologically as an SSRI. In common with other SSRI's (e.g., fluoxetine, paroxetine, fluvoxamine, sertraline, etc.), citalopram has effects in preclinical models that are indicia of probable antidepressant activity in humans. The (+) enantiomer of citalopram's desmethylated metabolite, mondesmethyl citalopram [DCT], the major circulating human metabolite, has about percent of its parent's activity.

Pharmacokinetics

Following its oral administration as Celexa Tablets, approximately 80% of

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[2] Citalopram

[3] During the drug's development

an administered dose of citalopram reaches the systemic circulation. Food has no effect on the drug's absolute bioavailability. About 80% of plasma citalopram is protein bound; its volume distribution is about 12 L/kg.

The major metabolites of citalopram are desmethylcitalopram [DCT] and didesmethyl citalopram [DDCT]. At steady state, the concentrations of these metabolites are no more than half the value of CT. N-demethylation of CT is, based on evidence obtained from in vitro studies with human liver microsomes, thought to occur primarily via CYP3A4.

The elimination of half-life of CT is approximately 35 hours while that of DCT is about 80 hours. The systemic clearance of citalopram following Intravenous administration to human volunteers was about 0.33 Liters/min. Renal clearance is about 60 mL/min.

Preclinical toxicology findings of potential clinical interest

Unexpected /unanticipated deaths in dogs

In a one year dog chronic oral toxicity study, unexpected / unanticipated deaths occurred in 5 of 10 high dose (8 mg/kg) animals. Among the 5 deaths, 4 occurred within 2-3 hours of drug administration during weeks 17,18, 27 and 27. The 5th death occurred in dog who died during the 31st week of dosing during an interval from more than 9 to less than 25 hours after the last dose of citalopram was administered. Unexpected deaths were not observed in dogs assigned to the control, low, or mid dose groups.

These findings are strong evidence that citalopram and/or one or more of its metabolites has (have) a capacity to cause sudden death in dogs, albeit by an unknown mechanism. Accordingly, since the initial report of the dog study, there has been considerable interest in identifying the mechanism responsible, in no small part in an effort to gauge whether or not the mechanism responsible for the deaths might be operative in humans.

An adverse action of citalopram and/or one of its metabolites on cardiac

repolarization has long been suspected to the mechanism involved. Dogs in the high dose group that died experienced, on average, a 10% increment (? over baseline) in QT interval; importantly, this average increase was detected under conditions of surveillance that were not designed to capture maximum degrees of QT prolongation (i.e., EKGs were not obtained at Tmax).

A subsequent special cardiovascular dog study undertaken in an effort to understand how and why citalopram might have caused deaths in the chronic toxicology study adduced results that were only arguably reassuring. In this experiment citalopram and its didesmethylated metabolite (DDCT) were administered intravenously both alone and in combination. Although QT interval prolongation was only detected in dogs receiving DDCT,"pro-arrhythmic" effects were detected in all 3 groups receiving active drug treatment.

In discussing the results of this special study, the sponsor makes much of the fact that deaths were not observed in dogs given only high doses of citalopram. The firm argues that the deaths observed were due to an interaction between citalopram and DDCT, an interaction, it asserts is unlikely to occur in humans because DDCT is not present in any appreciable amounts in human plasma under the conditions of use likely to obtain in human patients administered Celexa under the directions of use recommended in its proposed labeling.

Unfortunately, even if the firm's explanation is generally correct, and whether it is or not is unknowable, it in no way excludes the possibility that QT intervals might be prolonged to a clinically important degree following the administration of citalopram (e.g,. in patients who, for one reason or another, develop higher than expected plasma levels of DDCT).

Accordingly, whatever one may conclude about the deaths in dogs and the role played by citalopram relative to DDCT in their genesis, the finding in dogs remains a signal that is not fully understood. Thus, it remains a finding that must in some manner be factored into the regulatory assessment of the evidence bearing on citalopram's safety for use. (see

below)

In vivo lifetime Carcinogenicity Studies

The 18 month mouse study was negative; the 24 month rat study detected a small increase in the incidence of "carcinomas" in the small intestine and evidence of retinal degeneration.

Mutagenicity

Citalopram is mutagenic in two in vitro assays.

Teratogenicity

Although the sponsor and the review team disagree about citalopram's capacity to cause terata (see Dr. Fitzgerald's discussion--pages 3 and 4 of her 4/8/98 review), I am persuaded that the conclusions offered in the Division's draft labeling for Celexa fairly represent the findings vis a vis the drug's effect on embryogenesis and in-utero growth and development.

Essentially, citalopram was found to have teratogenic effects in mice, but not in rabbits.

CLINICAL

Effectiveness in Use

The set of controlled clinical trials intended to document the effectiveness of citalopram in depression provide mixed results. Nevertheless, despite its weaknesses and limitations, the evidence adduced in 4 of the 7 "independent" adequate and well controlled clinical trials provides, in aggregate, proof in principle of citalopram's effectiveness in use as an antidepressant. This experience is not, it should be noted, unusual; other commercial drug development efforts have also had a number of seemingly adequate and well controlled clinical trials fail for reasons unknown. It is widely believed, however, that

these "failures" are probably a result of the heterogenous nature of depressed patients and their highly variable response to antidepressant treatment.

Acute antidepressant action

Study 85 A, a flexible dose, 4 week long, balanced comparison of citalopram (20-80 mg/day; mean of 62 mg/d among completers) and placebo in some 180 depressed outpatients provides clear evidence of a beneficial effect.

Study 91206, a fixed, multilevel dose, 6 wk long, placebo controlled study enrolling approximately 600 depressed outpatients provides clear evidence that 40 mg a day and 60 mg a day (given hs) are effective in use.

Study 86141, a 6 wk long placebo controlled, flexible dose (10-30 mg/d) study in elderly depressed patients), Study 89303, a fixed dose (20 and 40 mg/d), 6 wk study in some 190 depressed patients and Study 89306, a 6 wk long, placebo controlled, fixed dose (20 and 40 mg/d) comparison all failed to provide results confirming the positive findings of Studies 85 and 91206.

Maintenance of clinical remission in recently recovered depressed patients

Two, more or less, identically designed "relapse prevention" studies provide positive findings that provide additional and independent support for a conclusion that citalopram exerts an antidepressant effect.

Study 89304, randomized 226 recently depressed patients who were deemed to have recovered (MADRS ≤ 12) after 8 weeks of open treatment on citalopram at doses of 20-60 mg/d to their original dose of citalopram (N=152) or to placebo (N=74). Treatment effect was assessed in terms of the time to recurrence of depression (MADRS ≥ 25). The mean time to relapse was 18 weeks among placebo randomized as compared to 21 weeks among citalopram randomized patients ($p = 0.04$) Although not a primary

outcome measure, the crude proportion of relapsers was 24 % among placebo and 14% among citalopram patients.

Study 89305, randomized "responders" who had participated in trials 89304, and 89306, both of which, as noted above, failed to demonstrate an effect of citalopram to placebo to one of two fixed doses of citalopram (N= 48 to 20 mg, N=57 to 40 mg) or placebo and followed them for 24 weeks. As in study 89304, the primary outcome was assessed in the time domain (time to MADRS of ≥ 22). Again, the results favored both active treatments over placebo at statistically significant levels. The two active treatments levels were not distinguishable from each other.

Conclusions about effectiveness.

There is clear evidence from more than one adequate and well controlled clinical investigation that citalopram exerts an antidepressant effect. The size of that effect, and more importantly, the clinical value of that effect, is not something that can be validly measured, at least not in the kind of experiments conducted. Accordingly, substantial evidence in the present case, as it has in all other evaluations of antidepressant effectiveness, speaks to proof in principle of a product's effectiveness in use.

Safety for Use

For the most part, the clinical evidence that bears on citalopram's risks of use supports a conclusion that citalopram has been shown to be "safe for use." This does not mean, of course, that citalopram has been shown to be free of risk, although it does represent a conclusion that the risks known to be associated with its use are those that 'experts' in the management of depression would likely find acceptable in an effective antidepressant drug product given the natural history of untreated depression and the set of alternative treatments currently available for depression in the armamentarium.

Evidence reported from clinical trials and open clinical experience establishes that citalopram causes virtually the same set of dysphoric adverse clinical effects that are caused by other members of the SSRI

drug class (adverse reports concerning signs and symptoms referable to the CNS, the GI tract, sexual drive and sexual performance).

The lack of reports of unusual and/or unique serious adverse clinical events or laboratory test findings cannot be attributed to a limited opportunity to evaluate the drug in clinical use. To the contrary, the numbers of patients observed[5] under treatment are, as judged by the size of typical NDA safety cohorts, large and, thus, by any reasonable standard, sufficient for the evaluation of citalopram's risks of use.

Accordingly, the evidence extant is an almost all respects sufficient to support the conclusion reached by the Division review team that the drug will be safe for use under the conditions of use recommended in the labeling proposed by the Division.

The unexpected and sudden deaths that occurred in the one year dog study, remain a disquieting matter, however.

As noted in earlier discussion, the evidence adduced in the special intravenous dog cardiovascular study, although it may offer insights into why and how the combination of citalopram and DDCT might prove especially lethal for dogs, does not exhaust the mechanisms through which citalopram (and/or one or more of its metabolites) might kill or increase the likelihood of a potentially fatal cardiac arrythmia in dogs, let alone humans.

On the other hand, I would acknowledge that most of the clinical evidence available that speaks to citalopram's potential to cause injury via a cardiac mechanism seems reassuring . EKGs conducted on some 797 citalopram patients participating in the "Group 1 placebo controlled studies" (**Appendix 8.1.8.3.1** of the clinical review document) revealed that these subjects, as a group, experienced a 2 msec mean decrease from

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[5] Dr. Laughren gives a nice overview of the extent of the experience derived from 186 studies. For purposes of evaluation, these were distributed, based on their quality and reliability, into 3 tiers and each tier was examined (in theory) to a degree and depth proportional to its informational value. Thus, greatest emphasis was placed on information gained from 19 "high quality phase 2 and 3 clinical trials for which CRFs were available, representing almost 4200 human subjects.

baseline in the duration of their QTc intervals.

Although they are not described in the primary clinical review document, two additional clinical studies reported to the NDA are also of interest. conducted a special study (92104) in 1993 that titrated 12 volunteers over a period 10 days to a daily dose of 60 mg and followed them forward in time for an additional 21 days. Changes in QTc between days 29-31 and days 2 to 3 were not statistically significant. A much larger fixed dose comparison trial conducted with several hundred subjects (Study 91206) also failed to find an effect of citalopram on the mean QTc interval.

On the other hand, some of the clinical evidence is not so reassuring. An evaluation of the EKGs obtained on patients participating in the set of Group 1 placebo controlled studies (**Appendix 8.1.8.3.2.2**) reveals that 1.1% of citalopram randomized, but only 0.4 % of placebo assigned patients, developed QTc intervals ≥ 500 mSec. While a 2.75 fold relative risk is hardly large, it must also be considered that the EKGs used to estimate the crude proportions meeting this criterion were obtained under casual conditions not intended to capture maximum prolongation of QTc intervals. Moreover, the proportion cited for citalopram is for all citalopram assigned patients (i.e., the tabulation ignores dose and time at risk).

To assist in the evaluation of this problem, I sought the counsel of Dr. Charles Ganley of HFD-110; Dr. Ganley is well known to the Division, having acted as our expert consultant in regard to questions bearing on the effects of drugs on cardiac repolarization on numerous past occasions.

Because his consultation was sought relatively late in the review process Dr. Ganley has so far offered his views only verbally and informally. Basically, he agrees the findings in the dog study have an arguable interpretation. He believes, too, that an in vitro study assessing the effects of CT, DCT and DDCT on K channels would be helpful, and recommends, too, that we consider asking the firm to conduct further human clinical pharmacology studies at doses exceeding those recommended in product labeling. In the course of discussions held with Dr. Ganley, the review team also agreed that we do not really have as good

an understanding of the extent to which subgroups in the population vary in the manner and extent to which they metabolize citalopram as we might like. Variability is of concern, because if DDCT is the noxious QTc prolonging agent the sponsor's special dog study reveals it to be, it is important to determine if DDCT, which is ordinarily present in relative small quantities in human plasma, accumulates to an appreciable extent in some subgroup in the population, either naturally, or under some specific condition of use (e.g, in concomitant use with a drug inducing formation of DDCT).

Conclusions regarding Safety for Use.

A conclusion that citalopram is safe for use is supportable, but only if the drug is marketed under product labeling that describes the findings of the dog studies and discusses the uncertainties associated with their interpretation. A more vexing question for me, one that I have not yet resolved completely, is whether or not additional investigations of citalopram's effects on cardiac repolarization are required, and if so, what form they should take, and whether they should be carried out prior to or after approval of the NDA.

A frank discussion with the sponsor about these matters may prove the best way to resolve them. Accordingly, the action letter forwarded for issuance by the Office explains our concerns and offers, in the post-approvable period, to meet with its representatives to discuss their resolution.

Labeling

A draft version of labeling under which I believe it would be responsible to conclude that citalopram has been shown, within the meaning of the Act, to be both effective in use and safe for use is attached to the approvable action letter that was forwarded to the Office on April 15, 1998 for issuance. For the most part, the intent of the text of the draft labeling is self evident.

One aspect of the labeling deserves special mention. The Clinical Efficacy Trials subsection within the Clinical Pharmacology section not only describes the clinical trials providing evidence of citalopram's antidepressant effects, but makes mention of adequate and well controlled clinical studies that failed to do so. I am mindful, based on prior discussions of the issue, that the Office Director is inclined toward the view that the provision of such information is of no practical value to either the patient or prescriber. I disagree. I believe it is useful for the prescriber, patient, and 3rd party payer to know, without having to gain access to official FDA review documents, that citalopram's antidepressants effects were not detected in every controlled clinical trial intended to demonstrate those effects. I am aware that clinical studies often fail to document the efficacy of effective drugs, but I doubt the public, or even the majority of medical community, are aware of this fact. I am persuaded they not only have a right to know, but should know. Moreover, I believe that labeling that selectively describes positive studies and excludes mention of negative ones can be viewed as being potentially "false and misleading."

Recommendation.

Issue the approvable action letter and draft labeling that was forwarded to the Office on 4/15/98.

/S/

Paul Leber, M.D.
May 4 1998

cc:
NDA 20-822
HFD-120
Temple
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Katz
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Guzewska
Rzeszotarski
HFD-713
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Choudhury
HFD-860
Sahajwalla
Mahmood

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 26, 1998 /9/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Celexa (citalopram) for the Treatment of Depression

TO: File NDA 20-822
[**Note:** This overview should be filed with the 5-7-97
original submission.]

1.0 BACKGROUND

Citalopram is a selective serotonin reuptake inhibitor (SSRI) that is being proposed for use in the treatment of depression, at an initial target dose of 20 mg/day, up to a maximum dose of 60 mg/day. At present, 4 other SSRIs are marketed in the US, including fluoxetine, sertraline, paroxetine, and fluvoxamine.

IND for citalopram was originally submitted 6-28-83.

. This concern was subsequently resolved with (1) additional dog data suggestive of a toxic interaction between citalopram and a metabloite (DDCT) not present to any extent in humans, and (2) relatively safe passage with citalopram in approximately 1600 human subjects exposed in clinical trials. Lundbeck resumed control of the IND on 8-3-87 and the IND was permitted to resume 10-24-89, after the toxicity questions were satisfactorily resolved.

However, the resumption of testing in women of childbearing potential (WCBP) was further delayed by concerns about possible teratogenicity associated with citalopram. Finally, on 6-18-92, these concerns were addressed by modifications in the clinical protocols, the investigator brochure, and consent forms, and testing was resumed in WCBP.

The original NDA 20-822 for citalopram was submitted 5-12-97.

We decided not to take citalopram to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

There was some difficulty in gaining acceptance by the nomenclature committee for the sponsor's proposed names for this product. Dr. Temple has overruled the committee on the currently preferred name, Celexa, and that will be the accepted name.

The chemistry group has concluded that this NDA is approvable from their standpoint. At the time of this memo, I am aware of only one unresolved chemistry issue, i.e., we have not yet received an inspection report from the facility. This reported is expected imminently.

3.0 PHARMACOLOGY

All other findings can be addressed through labeling.

4.0 BIOPHARMACEUTICS

The biopharm group has concluded that this NDA is approvable from their standpoint. At the time of this memo, I am aware of five biopharm issues requiring comment by the sponsor:

-The sponsor has not provided a rationale for the sampling scheme in their dissolution studies. We will request this in the approvable letter.

-Given the apparent prominent role of the CYP3A4 pathway in the clearance of citalopram, I think it would be useful for the sponsor to consider an in vivo interaction study involving citalopram and a potent 3A4 inhibitor, e.g., ketoconazole.

-A steady state interaction study with carbamazepine should be done.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

There were reports on a total of 17 clinical trials in depression, including 2 uncontrolled trials, 6 active controlled trials showing no difference between treatments, and 2 placebo controlled trials that were too small to be considered adequate. Thus, our review of citalopram focused on the remaining 7 placebo-controlled depression studies. Five of these were short-term (85A, 91206, 86141, 89303, and 89306) and 2 were long-term (89304 and 89305).

Our analyses of short-term studies focused on several standard outcomes for depression, including: HAMD Total score; HAMD Item 1; MADRS Total score; and CGI. For the 2 relapse prevention trials, we focused on time to relapse.

The efficacy data were reviewed by Greg Dubitsky, M.D. of the clinical group and Japo Choudhury, Ph.D. of the biometrics group.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study 85A

This was a randomized, double-blind, parallel group, 4-week study comparing citalopram (dose range 20-80 mg/day, at hs) with placebo in depressed outpatients. There were approximately 90 patients per group, with 59% of both groups completing to 4 weeks. The mean citalopram dose for completers to 4 weeks was 62 mg/day. Citalopram was superior to placebo on HAMD Total score, HAMD Item 1, and CGI Severity, generally both for LOCF and OC analyses. Dr. Dubitsky considered this to be a positive study, and I agree.

5.1.2.2 Study 91206

This was a randomized, double-blind, parallel group, 6-week study comparing citalopram (at 4 fixed doses of 10, 20, 40, and 60 mg/day, at hs) with placebo in depressed outpatients. There were approximately 120 patients per group, with roughly of all groups completing to 6 weeks. Citalopram, at doses of 40 and 60 mg/day, but not at doses of 10 and 20 mg/day, was superior to placebo on HAMD Total score, HAMD Item 1, and the MADRS Total score, generally with stronger results for LOCF than for OC analyses. Findings for CGI Severity were less consistently in favor of citalopram. There was no indication of greater efficacy for the 60 mg/day dose vs the 40 mg/day dose. Dr. Dubitsky considered this to be a positive study for the 40 and 60 mg/day dose groups, and I agree.

5.1.2.3 Study 86141

This was a randomized, double-blind, parallel group, 6-week study comparing citalopram (dose range 10-30 mg/day, at hs) with placebo in elderly depressed inpatients or outpatients. There were approximately 100 citalopram patients compared to 50 placebo patients, with ~~66% of~~ citalopram vs 76% of placebo patients completing to 6 weeks. The mean citalopram dose for completers to 6 weeks was 24 mg/day. Citalopram was not consistently superior to placebo on any of the key outcomes. While the reasons for the negative outcome for this study are unknown, about a fourth of patients did not meet criteria for major depression, and the citalopram dose was lower than that used in the previous 2 positive studies. This study does not provide support for the antidepressant efficacy of citalopram.

5.1.2.4 Study 89303

This was a randomized, double-blind, parallel group, 6-week study comparing citalopram (at 2 fixed doses: 20 and 40 mg/day, at hs) with placebo in depressed inpatients or outpatients. There were approximately 65 citalopram patients per treatment group, with of subjects completing to 6 weeks. Citalopram was not consistently superior to placebo on any of the key outcomes for either the 20 or 40 mg/day doses. While the reasons for the negative outcome for this study are unknown, there was a substantial placebo response, making it difficult to distinguish drug from placebo. This study does not provide support for the antidepressant efficacy of citalopram.

5.1.2.5 Study 89306

This was a randomized, double-blind, parallel group, 6-week study comparing citalopram (at 2 fixed doses: 20 and 40 mg/day, at hs) with placebo in depressed inpatients or outpatients. There were approximately 90 citalopram patients per treatment group, with about 75% of subjects completing to 6 weeks. Citalopram was not consistently superior to placebo on any of the key outcomes for either 20 or 40 mg/day. While the reasons for the negative outcome for this study are unknown, there was a substantial placebo response, making it difficult to distinguish drug from placebo. This study does not provide support for the antidepressant efficacy of citalopram.

5.1.2.6 Study 89304

This was a double-blind, randomized, parallel group relapse prevention trial in stable depressed outpatients or inpatients who had responded during an initial 8-week open-label phase involving treatment with citalopram in a dose range of 20-60 mg/day, at hs. Response was defined as a MADRS Total score of $\leq$ 12 at the end of the open-label phase. Eligible patients (n=226) were randomized to citalopram (n=152) at the same dose established during the stabilization phase or placebo, and followed for 24 weeks. The primary outcome was time to relapse, defined as an increase in the MADRS Total score to at least 25. Citalopram was superior to placebo on relapse rate (14% for citalopram vs 24% for placebo; p=0.04) and time to relapse (mean time to relapse for citalopram was 21 weeks vs 18 weeks for placebo; p=0.04).

5.1.2.7 Study 89305

This was a double-blind, randomized, parallel group relapse prevention trial in stable depressed outpatients or inpatients who had responded while receiving citalopram (20 or 40 mg/day, at hs) during an initial 6-week, double-blind acute treatment phase (studies 89303 or 89306). Response was defined as a MADRS Total score of $\leq$ 12 at the end of the 6-week acute treatment phase. Eligible patients (n=147) were randomized to citalopram (n=48 to 20 mg/day and n=57 to 40 mg/day) or placebo, and followed for 24 weeks. The primary outcome was time to relapse, defined as an increase in the MADRS Total score to at least 22. Citalopram was superior to placebo on relapse rate (8% for citalopram 20 mg/day; 12% for citalopram 40 mg/day; 31% for placebo; p=0.006 for 20 mg/day vs pbo and p=0.022 for 40 mg/day vs pbo) and time to relapse (p=0.01 for 20 mg/day vs pbo and p=0.02 for 40 mg/day vs pbo).

5.1.3 Comment on Other Important Clinical Issues Regarding Citalopram

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 2 positive short-term trials, i.e., 85A and 91206, only study 91206 had a design that is pertinent to the question of dose/response. In that study, involving fixed doses of 10, 20, 40, and 60 mg/day, only the 40 and 60 mg/day doses were superior to placebo. There was no clear advantage of the 60 mg/day dose over the 40 mg/day dose.

In labeling, the sponsor has proposed 20 mg/day as the target dose, with dose increases only if patients don't respond at that dose. Dr. Dubitsky has recommended titrating up to 40 mg/day as the

target dose, with an increase to 60 mg/day in patients who do not respond at 40. I agree that 40 mg/day is a more appropriate target dose, given the limited data we have. In most studies, citalopram was initiated at 20 mg/day and safely titrated in 20 mg/day increments every 3 days, and so, it would not be unreasonable to recommend 20 mg/day as the initial dose with an increase to the 40 mg/day target dose by day 4. Although steady state for citalopram is reached on average after about 1 week, given the time it takes for an antidepressant response to SSRIs, I agree with Dr. Dubitsky's suggestion for a 2-4 week interval of treatment at 40 mg/day before considering an increase to 60 mg/day for nonresponding patients. Although there are data regarding the safe use of citalopram at doses up to 80 mg/day, there are no data on which to base any recommendations for pushing the dose further in patients not responding at 60 mg/day. Thus, labeling should indicate the limits on information available for dosing at the high end of the dose range.

Clinical Predictors of Response

The sponsor conducted subset analyses based on age, gender, race, and baseline severity of illness to explore for predictors of response. For all these analyses, there was only 1 suggestion of an interaction, i.e., a reduced effect in the elderly. This was likely a chance finding.

Size of Treatment Effect

An estimate of effect size, based on a comparison of mean change from baseline in HAMD total score (LOCF analysis) for citalopram and placebo revealed a difference of approximately 3 HAMD units. While it is difficult to judge the clinical significance of this difference, similar findings for other SSRIs and other recently approved antidepressants have been considered sufficient to ~~support~~ the approvals of those other products.

Duration of Treatment

There were 2 relapse prevention trials (89304 and 89305) that demonstrated a lower rate of relapse in patients randomized to citalopram compared to those randomized to placebo. This information can be included in the appropriate sections of labeling, i.e., Indications and Use, Clinical Trials, and Dosage and Administration.

5.1.3 Conclusions Regarding Efficacy Data

In summary, I consider studies 85A and 91206 positive support for the claim of short-term antidepressant efficacy for citalopram. While 3 other placebo-controlled short-term trials (86141, 89303, and 89306) were negative, and not easily interpretable since there were no active control arms, I feel there were sufficient reasons to speculate about the negative outcomes and, therefore, not count these studies against citalopram. In further support of the antidepressant effectiveness of citalopram were the 2 positive relapse prevention trials. Overall, I consider these results sufficient to support claims of both short-term and long-term antidepressant effectiveness of citalopram.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for citalopram, including the original submission and the numerous amendments in response to our requests for additional information, were reviewed by Dr. Molchan. This original review was based an integrated database (with a cutoff date of 10-1-96, for both routine data and also deaths and other serious adverse event reporting), and a cutoff date for postmarketing reports of 10-31-96.

The development program for citalopram spanned many years and included over 186 studies. For purposes of preparing the NDA, these studies were divided into 3 groups: (1) 19 high quality phase 2/3 studies for which CRFs were available; (2) 29 phase 1 pk/pd studies; and (3) 119 lower quality, often uncontrolled studies that were not well monitored and for which CRFs were generally not available. Only deaths and serious AEs were available for group 3 patients. Note: 19+29+119=167; the remaining 19 studies are (or were ongoing) at the time of submission of the NDA.

4168 human subjects were exposed to citalopram in the group 1 studies; this was the basis for the sponsor's integrated safety database. 372 patients were exposed to citalopram in group 2 studies, and approximately 15,500 were exposed to citalopram in group 3 studies. Patients in phase 2-3 studies (group 1) were roughly 2/3 female, predominantly white, and predominantly middle-aged. There were approximately 1000 patients over age 60. Approximately 82% of citalopram-treated patients in these phase 2-3 studies received mean citalopram doses in a range of 20 to 60 mg/day, and approximately 80% of exposures were for 6 months or less. Nevertheless, there were approximately 850 patients who received citalopram for 6 months or more, including about 425 who received citalopram for greater than 1 year.

In addition, extensive post-marketing data were available. The estimated exposure to citalopram worldwide was 4 million patients as of 10-31-96. The sponsor provided a report on the postmarketing data, and we also asked DPE to provide information on citalopram. The information from DPE was entirely consistent from that received from the sponsor.

Adverse Event Profile for Citalopram

Overall, the side effect profile of citalopram is as expected for an SSRI, i.e., the adverse events that emerge as drug related include the usual GI events (nausea, vomiting, anorexia, and dry mouth), CNS (dizziness, insomnia, agitation, somnolence, fatigue, tremor, and yawning), and sexual (impotence, delayed ejaculation, and decreased libido). Citalopram is associated with a very modest decrease in pulse rate also observed for other SSRIs.

Although not observed with this drug, citalopram will carry the usual contraindication for SSRIs of coadministration with MAOIs, given the reports of sometimes fatal NMS-like syndromes for other drugs in this class. In addition, it will have Precautions statements for hyponatremia, activation of mania, and seizures, as is also the standard for other SSRIs.

There has been extensive human experience with this drug, both pre- and post-marketing, and no unexpected serious adverse events have emerged. In particular, the early concern about possible cardiovascular risk has not been apparent in broad experience with this drug. Drs. Molchan and Dubitsky have concluded that the safety data for citalopram reveal it to have an acceptable safety profile, and I agree.

5.3 Clinical Sections of Labeling

We have substantially rewritten the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Molchan reviewed the published literature for citalopram included in the NDA and did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, citalopram is marketed for depression in 49 countries as of this date, and applications are pending in 24 additional countries. It has not been withdrawn anywhere. We will ask for an update on the regulatory status of citalopram in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take citalopram to the PDAC.

9.0 DSI INSPECTIONS

Several sites from the key studies supporting the approvability of citalopram were inspected, revealing no findings that would preclude relying on the data derived from these studies.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft dated 5-7-97.

10.2 Foreign Labeling

We have reviewed foreign labeling for citalopram and discovered no new concerns that we were not already aware of.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, a regulatory status update,

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Forest has submitted sufficient data to support the conclusion that citalopram is effective and acceptably safe in the treatment of depression. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 20-822
HFD-120
HFD-120/TLaughren/PLeber/GDubitsky/SMolchan/PDavid
HFD-100/RTemple

DOC: MEMCTLDP.AE1