21046

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 021046

Trade Name: CELEXA 10 mg/ml ORAL SOLUTION

Generic Name: CITALOPRAM HYDROBROMIDE

Sponsor: FOREST LABORATORIES, INC.

Approval Date: 12/22/99

INDICATION(s): TREATMENT OF DEPRESSION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-046

Forest Laboratories Inc.
Attention: Amy Rubin
Director, Drug Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 073115

DEC 2 2 1999

Dear Ms. Rubin:

Please refer to your New Drug Application dated October 30, and received November 2, 1998, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celexa (citalopram hydrobromide) 10 mg/5 ml oral solution.

We acknowledge receipt of your submission dated October 29, 1999. This submission constituted a complete response to our September 2, 1999 approvable letter.

We also acknowledge receipt of your additional communications dated October 1, October 12, October 29, and December 13, 1999. The 2 month primary User Fee goal date for this application is January 1, 2000.

This new drug application provides for a new oral solution formulation of citalopram hydrobromide.

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling below. Accordingly, the application is approved effective as of the date of this letter.

LABELING

Below are the revisions to the Celexa labeling to incorporate this new formulation and other safety related revisions. We note your agreement to this labeling in a telephone conversation dated December 14, 1999, between Mr. Paul David, of this Agency, and Ms. Tracey Varney of Forest. Your final labeling for Celexa solution should be identical to your currently approved labeling for Celexa tablets except for revisions to the following sections of labeling (double underline font denotes additions):

DESCRIPTION

Celexa (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated (±)-1-(3-

dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr with the following structural formula:

[Structural formula here]

The molecular formula is $C_{20}H_{22}BrFN_2O$ and its molecular weight is 405.35.

Citalopram HBr occurs as a fine white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol.

Celexa (citalopram hydrobromide) is available as tablets or as an oral solution.

Celexa tablets are film coated, oval, scored tablet containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base.

The tablets also contain the following inactive ingredients: Copolyvidone, Corn Starch, Crosscarmellose Sodium, Glycerin, Lactose Monohydrate, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Microcrystalline Cellulose, Polyethylene Glycol, and Titanium Dioxide. Iron Oxides are used as coloring agents in the pink (20 mg) tablets.

Celexa oral solution also contains citalopram HBr equivalent to 2 mg/ml citalopram base. It also contains the following inactive ingredients: Sorbitol, Purified water, Propylene Glycol, Methylparaben, Natural Peppermint Flavor, and Propylparaben.

CLINICAL PHARMACOLOGY-Pharmacokinetics

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalopram in plasma, based on the half-life, is expected to be 2.5 times the plasma concentrations observed after a single dose. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent.

PRECAUTIONS-Drug Interactions

Sumatriptan
There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised.

ADVERSE REACTIONS
Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The table below, displays the incidence of sexual side effects reported by at least 2% of patients taking Celexa in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Celexa (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Decreased Libido	3.8% (males only)	≤ 1% (males only)
Impotence	2.8% (males only)	≤1% (males only)

In female depressed patients receiving Celexa, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively.

There are no adequately designed studies examining sexual dysfunction with citalopram treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

HOW SUPPLIED

Tablets:

20 mg
Bottle of 30 NDC # 0456-4020-30
Bottle of 100 NDC # 0456-4020-01
Bottle of 500 NDC # 0456-4020-05
10 x 10 Unit Dose NDC # 0456-4020-63

Pink, oval, scored film coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "20 mg".

40 mg
Bottle of 30 NDC # 0456-4040-30
Bottle of 100NDC # 0456-4040-01
Bottle of 500NDC # 0456-4040-05

10 x 10 Unit DoseNDC # 0456-4040-63

White, oval, scored film coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "40 mg".

Oral Solution:

10 mg/5 ml, peppermint flavor – (120 ml) NDC 0456-4130-04

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

1. Expiration Date

   The Agency is approving an expiry date of 18 months at this time.

2. Methods Validation

   Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you are in the process of fulfilling your pediatric study requirement at this time.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-046." Approval of this submission by FDA is not required before the labeling is used.

Additionally, please submit one market package of the drug product when it is available.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

/S/

Russell Katz, M.D.
Division Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-046

DAVD

Forest Laboratories Inc.
Attention: Keith Rotenberg, Ph.D.
Drug Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 073115

SEP - 2 1999

Dear Dr. Rotenberg:

Please refer to your pending New Drug Application dated October 30, and received November 2, 1998, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celexa (citalopram hydrobromide) 10 mg/5 ml oral solution.

We acknowledge receipt of your submissions dated January 25, March 2, March 22, March 23, March 29, April 14, April 30, May 25, and August 27, 1999. The 10 month User Fee goal date for this application is September 2, 1999.

We have completed our review of your application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to respond to the following items:

LABELING

We have reviewed your proposed draft labeling submitted in your October 30, 1998 submission. It provides for additions to the **DESCRIPTION, CLINICAL PHARMACOLOGY-Pharmacokinetics,** and **HOW SUPPLIED** sections of labeling to incorporate this new formulation. This labeling is acceptable.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Deficiencies Pertaining to Drug Substance:
DMF

Deficiencies Pertaining to the Drug Product:

4. Please provide the FDA with the COA

5. Please explain why glass containers are listed as Items Packaged on the Packaging Projection

8. Please justify the differences in the (known & unknown) specifications for Citalopram HBr Oral Solution and Citalopram HBr Coated Tablets. Table 16 summarizes the relevant specifications for the two drug formulations.

Table 16: Comparison of Specifications for Citalopram HBr Oral Solution & Citalopram HBr Coated Tablet

1 page(s)
REDACTED
TRADE Secret/
Confidential/
Commercial

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Mr. Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

/S/ 9/2/44

Russell Katz, M.D.
Acting Division Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Review and Evaluation of Clinical Data
NDA #21-046

Sponsor:	Forest Laboratories
Drug:	Citalopram Hydrobromide
Dosage Form:	Oral Solution
Indication:	Depression
Correspondence Date:	October 30, 1998
Date Received:	November 4, 1998
PDUFA Date:	September 2, 1999

I. Background

The sponsor has submitted an application to market an oral suspension formulation of Celexa (citalopram hydrobromide), a selective-serotonin reuptake inhibitor currently approved in tablet form for the treatment of depression. The rationale for this new formulation is that it may provide a more convenient dosage form for patients who have difficulty swallowing tablets. The oral solution formulation is marketed in 9 foreign countries, including the U.K., France, the Scandinavian and other European countries.

In support of this application, the sponsor has referenced information in the original citalopram NDA (#20-822) and provided Chemistry, Manufacturing, and Control information. Bioequivalence to the currently marketed tablet formulation was evaluated by Biopharmacology reviewer Dr. Mahmood. Chemistry data will likewise be evaluated by CMC reviewer Dr. Lorenzo Rocca and will not be addressed further here.

Of note is the October, 1998 DSI inspection that included biopharmaceutic study CIT-PK1-97-09. Deficiencies were found in the accuracy of measured concentrations of active drug ingredients and their metabolites. This issue has been reviewed by Dr. Mahmood and he considers it resolved.

This review will focus on safety data from one pharmacokinetic study and one taste study that were not reviewed in the submission of the original NDA.

II. Summary of Safety Review

A. Methodology

Safety data from four of the bioequivalence/bioavailability studies (83-N-0046, 91102, 88117, 91303) were reviewed with the original NDA submitted for citalopram tablets (#20-822). Adverse events and dropouts due to AEs were reviewed. There were no deaths and one serious AEs associated with dropout involving a fall leading to hospitalization in a 74 y.o. woman. The event was considered unlikely to be related to citalopram. No specific AEs were associated with the solution formulation. Safety data from the other two studies (one taste studies and one bioequivalence/bioavailability study) submitted with the current NDA were examined separately with the objective of detecting any adverse occurrences not adequately addressed in current Celexa labeling. Serious adverse events were defined as per 21 CFR 312.32(a).

Appendix I summarizes the four bioequivalence/bioavailability studies completed using the oral liquid formulation, as well as the two taste studies.

B. Safety Findings

1. Study CIT-PK1-97-09

This was a randomized, open-label, single dose, two-way crossover study in 24 healthy volunteers. The 60 mg tablet formulation was compared with 60 mg solution after a 14 day interval. There were no serious AEs. One subject dropped out of the study due to AEs (abdominal cramps, nausea, diarrhea). There were no clinically significant laboratory abnormalities. The adverse event profile was similar to that for the tablets. Two subjects had potentially clinically significant decreases in BP. One subject's diastolic BP fell from 63 to 49 mmHg 4 hours after ingestion of the solution. In another, systolic BP fell from 96 to 87 mmHg 4 hours after the solution. The sponsor asserts these were not associated with clinically important events. Pre- and post-dose one-week after drug administration) ECGs were normal. No unlabeled TEAEs were reported.

2. Study CIT-PK1-97-05 (Taste study)

This was a randomized, double-blind, four-way cross-over study of citalopram solution (10 mg) in 20 healthy subjects. Doses were adminsitered at 1 hour intervals.

No AEs were reported and no changes noted in vital signs.

III. Discussion and Conclusions

The safety data from the six studies noted above revealed no findings which would preclude approval of this formulation or warrant any change to the clinical sections in current Celexa labeling.

The Division Biopharmacology reviewer, Dr. Mahmood agrees that the solution is bioequivalent to the currently marketed tablet formulation.

The suspension will be supplied in a concentration of 10 mg/5 ml. Since Celexa tablets are dosed in minimum increments of 20 mg, this concentration should permit reasonably accurate measurement of comparable doses of the suspension using a teaspoon or medication cup.

In conclusion, provided that the CMC reviewer finds that the product excipients are deemed to be safe, the liquid formulation is expected to be as safe as the marketed tablet formulation. From a clinical standpoint, I have no objection to the approval of this NDA.

/S/

Susan Molchan, M.D.
May 26, 1999

5.26.99

/S/

/S/

cc: NDA #21-046
HFD-120
HFD-120/SMolchan
TLaughren
PDavid

Appendix I.

Citalopram: Oral Liquid Formulation								
Protocol Number, Investigator(s), Country Publication(s), Group Number	***Completion Status (Start Date)***	***Study Design/Population***	***Treatment/Doses*****	***Number Entered Each Treatment******	***Treatment Length***	***Age Range (mean)***	***Number Male/Female (%)***	***Document Location:***
Bioequivalence/Bioavailability Studies								
83-N-0046 S. de Dennis USA	Complete (1984)	Single dose -two-way crossover oral Healthy male subjects	3 x 10 mg tablets 20 mg 1.5 mg/mL aqueous solution	16 subjects 16 subjects	2 single doses at 14 d interval	20 - 33 y (25.9)	16 males (100)	NDA #20-822 Vol. 1.58, p. 6-02095
91102 O. Blin France	Complete (Nov 7, 1991)	Single-dose, two-way crossover Healthy subjects	1 x 40 mg tablet 1 mL 40 mg/mL aqueous solution	12 subjects 12 subjects	2 single doses at 14 d interval	21 -34 y (25.8)	8/5 (62/38)	NDA #20-822 Vol. 1.59, p. 6-02641
CIT-PK1-97-09-000 S Zeig USA	Complete Mar 24, 1998	Single center, randomized, open-label, single dose, two-way crossover study Healthy subjects	1 x 60 mg tablet 60 mg citalopram as an oral aqueous solution (10 mg/5 mL)	23 24	2 single doses at 14 d interval	19 - 35 y (27)	16/8 (67/33)	NDA #21-046 Vol. 1.14, p. 6-00667
Early Studies								
88117 J-C Scotto France	Complete	Multiple dose, two-way crossover Depressed subjects	10 mg tablets 40 mg/mL aqueous solution 20 - 80 mg/day	11 subjects enrolled; 10 subjects completed	4 weeks	Not stated	11 females (100%)	NDA #20-822 Vol. 1.81, p. 6-11205
Taste Studies								
91303 Bouchard, Burnat, Laqueille, Lazartigues, Peyrouzet, Raikovic, Sananes, Danic France	Complete (Dec 3, 1991)	Open-label, multicenter, noncomparative Healthy subjects	Citalopram 40 mg/mL aqueous solution, 20-30 mg/d	37 subjects enrolled, 35 subjects evaluated	6 weeks	36 - 86 y (70.9)	11/26 (30/70)	NDA #20-822 Vol. 1.214, p. 8-47357
CIT-PK1-97-05-000 H. Offenberg USA	Complete (Nov. 25, 1997)	Double-blind, randomized, four-way crossover design Healthy subjects	Citalopram Hbr 10 mg/5 mL free base dose	20 subjects 12 elderly 8 young	4 X 10 s at 1 h intervals	65 - 76 y (70.6) 20 - 22 y (21.1)	6/6 (50/50) 4/4 (50/50)	NDA #21-046 Vol. 1.11, p. 6-00049

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: August 26, 1999

/S/

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 hydrobromide) Oral Solution (10 mg/5 mL)

TO: File NDA 21-046
[Note: This memo should be filed with the 10-30-98 original submission.]

Celexa is an SSRI approved for the treatment of depression, and is available as 20 and 40 mg immediate release tablets. This NDA provides support for a citalopram solution for oral administration at a concentration of 10 mg/5 mL.

The application has been reviewed by Lorenzo Rocca, Ph.D. from the chemistry group, Iftekhar Mahmood, Ph.D. from the biopharm group, Robin Huff, Ph.D. from the pharmacology group, and Susan Molchan, M.D. from the clinical group. All 4 reviewers have concluded that the application is approvable.

While this NDA has been deemed approvable from a chemistry standpoint, the letter details numerous deficiencies that must be corrected before the application can be approved.

Bioequivalence between the immediate release citalopram and the oral solution was established in study CIT-PK1-97-09-000. A reanalysis of the data from that study was requested by DSI, and this also passed.

Approvability regarding pharmacology/toxicology requirements is based on the fact that all the excipients in the oral solution are GRAS.

Finally, the clinical review focused on safety data available from 5 bioavailability/bioequivalence studies and 1 taste study and revealed no findings of concern.

In conclusion, I agree that this NDA is approvable, and I recommend that we issue the attached approvable letter with our proposed labeling.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 21-046
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PDavid

DOC: NDA21046.01

APPEARS THIS WAY
ON ORIGINAL

Rocca

AUG 18 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 21-046 **CHEM REVIEW: #1** **REVIEW DATE: 8/18/99**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE /ACTION
ORIGINAL	11/2/98	11/2/98	11/9/98
N(BC) Amendment	1/25/99	1/26/99	1/27/99 / NAI on 5/27/99
N(BC) Amendment	3/2/99	3/4/99	3/9/99 / NAI on 5/27/99
N(BC) Amendment	4/14/99	4/16/99	4/20/99 / NAI on 5/27/99
N(BC) Amendment	4/30/99	5/3/99	5/7/99 / NAI on 5/27/99
N(BC) Amendment	5/25/99	5/26/99	5/28/99 / NAI on 5/28/99

NAME AND ADDRESS OF APPLICANT

Forest Laboratories
909 Third Avenue
New York, New York 10022-4731

DRUG PRODUCT NAME

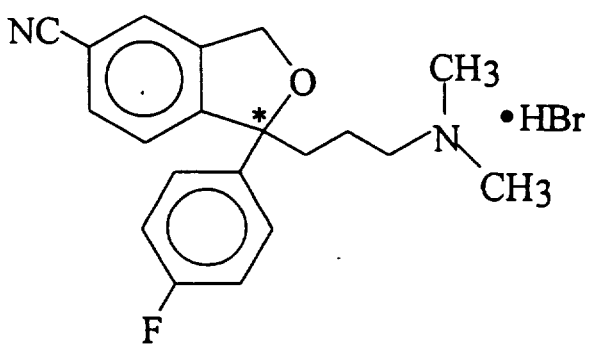
Proprietary: Celexa™ (citalopram hydrobromide) Oral Solution 10mg/5mL
Non proprietary/USAN: Citalopram Hydrobromide Oral Solution
Code Name/Number: [redacted]0-171
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Depression
DOSAGE FORM: Oral solution
STRENGTHS: 10mg/5mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x Rx ___OTC
SPECIAL PRODUCTS: ___Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr
USAN Name: Citalopram Hydrobromide
Chemical Formula: $C_{20}H_{22}BrFN_2O$
Molecular Weight: 405.35
CAS Registry Number: 59729-32-7

Synonyms: Cipramil™, Cipram™, Seropram™, Elopram™, Prisdal™



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CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 21-046 is approvable. The Applicant must address the deficiencies before the NDA can be approved for CMC.

/S/ 8/18/99

Lorenzo A. Rocca, Ph.D., Review Chemist

APPEARS THIS WAY ON ORIGINAL

/S/ 8/18/99

Robert H. Seevers, Ph.D., Chemistry Team Leader

cc:
Orig. NDA 21-046
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/RSeevers
File: C:\lr\NDA\NDA21046\N21046Review1.doc

APPEARS THIS WAY ON ORIGINAL

DAVID

SEP - 1 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 21-046 **CHEM REVIEW: #2** **REVIEW DATE: 8/31/99**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE /ACTION
ORIGINAL	11/2/98	11/2/98	11/9/98
N(BC) Amendment	1/25/99	1/26/99	1/27/99 / NAI on 5/27/99
N(BC) Amendment	3/2/99	3/4/99	3/9/99 / NAI on 5/27/99
N(BC) Amendment	4/14/99	4/16/99	4/20/99 / NAI on 5/27/99
N(BC) Amendment	4/30/99	5/3/99	5/7/99 / NAI on 5/27/99
N(BC) Amendment	5/25/99	5/26/99	5/28/99 / NAI on 5/28/99

NAME AND ADDRESS OF APPLICANT

Forest Laboratories
909 Third Avenue
New York, New York 10022-4731

DRUG PRODUCT NAME

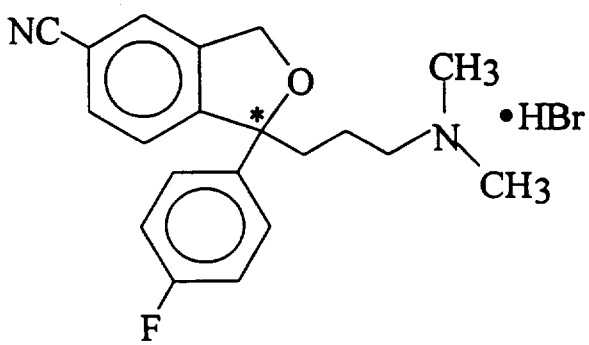
Proprietary:	Celexa™ (citalopram hydrobromide) Oral Solution 10mg/5mL
Non proprietary/USAN:	Citalopram Hydrobromide Oral Solution
Code Name/Number:	10-171
Chem. Type/Ther. Class:	3S

PHARMACOLOGICAL CATEGORY/INDICATION:	Depression
DOSAGE FORM:	Oral solution
STRENGTHS:	10mg/5mL
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	x Rx ___OTC
SPECIAL PRODUCTS:	___Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr
USAN Name: Citalopram Hydrobromide
Chemical Formula: $C_{20}H_{22}BrFN_2O$
Molecular Weight: 405.35
CAS Registry Number: 59729-32-7

Synonyms: Cipramil™, Cipram™, Seropram™, Elopram™, Prisdal™



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Confidential
Commercial

[redacted]

CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 21-046 is approvable. The Applicant must address the deficiencies before the NDA can be approved for CMC.

[redacted]

8/31/99

Lorenzo A. Rocca, Ph.D., Review Chemist

[redacted]

9/1/99

Robert H. Seevers, Ph.D., Chemistry Team Leader

cc:
Orig. NDA 21-046
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/RSeevers
File: C:\Data\lr\NDA\NDA21046\N21046Review2.doc

DAVID

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NOV 26 1999

NDA 21-046 **CHEM REVIEW: #3** **REVIEW DATE:** 11/26/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE /ACTION
ORIGINAL	11/2/98	11/2/98	11/9/98
N(BC) Amendment	1/25/99	1/26/99	1/27/99 / NAI on 5/27/99
N(BC) Amendment	3/2/99	3/4/99	3/9/99 / NAI on 5/27/99
N(BC) Amendment	4/14/99	4/16/99	4/20/99 / NAI on 5/27/99
N(BC) Amendment	4/30/99	5/3/99	5/7/99 / NAI on 5/27/99
N(BC) Amendment	5/25/99	5/26/99	5/28/99 / NAI on 5/28/99
N(AZ) Amendment	10/29/99	11/1/99	11/4/99 / Reviewed 11/26/99

NAME AND ADDRESS OF APPLICANT

Forest Laboratories
909 Third Avenue
New York, New York 10022-4731

DRUG PRODUCT NAME

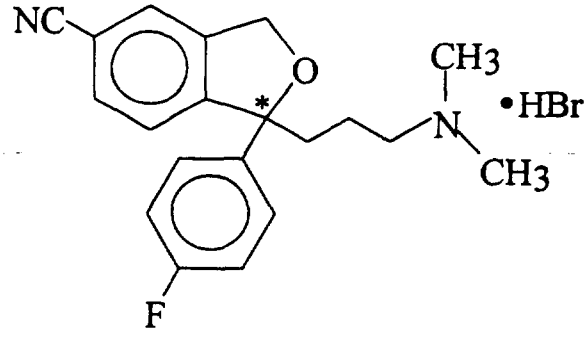
Proprietary: Celexa™ (citalopram hydrobromide) Oral Solution 10mg/5mL
Non proprietary/USAN: Citalopram Hydrobromide Oral Solution
Code Name/Number: 10-171
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Depression
DOSAGE FORM: Oral solution
STRENGTHS: 10mg/5mL
ROUTE OF ADMINISTRATION: Oral
DISPENSED: x Rx ___OTC
SPECIAL PRODUCTS: ___Yes x No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA

CA Name: (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr
USAN Name: Citalopram Hydrobromide
Chemical Formula: $C_{20}H_{22}BrFN_2O$
Molecular Weight: 405.35
CAS Registry Number: 59729-32-7

Synonyms: Cipramil™, Cipram™, Seropram™, Elopram™, Prisdal™



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TRADE
Secret

CONCLUSIONS & RECOMMENDATIONS: Concerning the chemistry, manufacturing, and controls (CMC), NDA 21-046 is approvable. The Applicant must address the following deficiencies before the NDA can be approved for CMC.

/S/ 11-26-99

Lorenzo A. Rocca, Ph.D., Review Chemist

/S/ 11/26/99

Robert H. Seevers, Ph.D., Chemistry Team Leader

cc:
Orig. NDA 21-046
HFD-120/Division File
HFD-120/PDavid
HFD-120/LRocca
HFD-120/RSeevers
File: C:\Data\lr\NDA\NDA21046\N21046Review3.doc

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ON ORIGINAL

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Review of **NDA 21-046**

Drug: **citalopram** (Celexa™), oral solution

Sponsor: Forest Laboratories, Inc.
909 Third Avenue
New York, NY 10022-4731

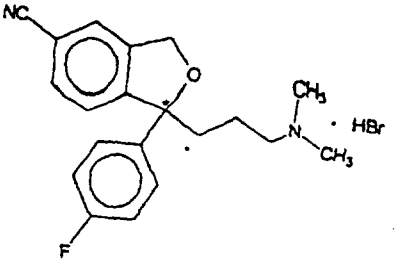
Review Date: January 4, 1999

Reviewer: Robin Huff

Class: selective serotonin reuptake inhibitor (SSRI)

Indication: depression

Structure:



Chemical Name: 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr

Molecular Formula: C20H21FN2O HBr

MW: 405.35

Related INDs/NDAs IND [redacted] NDA 20-822 (Citalopram tablets)

The review of NDA 20-822 for citalopram oral tablets is cross-referenced in support of approval of NDA 21-046 for citalopram oral solution. Approval of the oral solution is being sought on the basis of bioequivalence. Relying on the data submitted in NDA 20-822, which was approved on July 17, 1998, NDA 21-046 is approvable with respect to the pharmacology/ toxicology portion. This recommendation is based on the fact that all [redacted] in the citalopram oral solution are [redacted] and is made with the condition that [redacted] in the oral solution [redacted] ICH Q3B Guideline on Impurities in New Drug Products. Specific impurity and degradation data will be submitted for chemistry review. For sections of labeling that incorporate preclinical data, the sponsor is proposing to use the exact wording approved for NDA 20-822.

/S/

Robin A. Huff, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

cc: NDA21046
HFD-120
/G. Fitzgerald gg 7 6/1/99
/R. Huff
/P. David

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DAVID

COMPLETED MAY 2 1 19

GP-2154

MAY 2 1 1999

REVIEW FOR HFD-120
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review #2 of NDA 21-046
Response to Microbiology Deficiencies
May 20, 1999

1. **APPLICATION NUMBER:** 21-046

   APPLICANT: Forest Laboratories Inc.
   909 Third Avenue
   New York, NY 10022-4731

2. **PRODUCT NAMES:** citalopram hydrobromide oral solution

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** oral dosage, 10 mg/5 ml.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Treatment of depression.

B. 1. **DATE OF INITIAL SUBMISSION:** November 2, 1998

2. **AMENDMENT:** April 30, 1999

3. **RELATED DOCUMENTS:** fax transmission 5/19/99

4. **ASSIGNED FOR REVIEW:**

5. **DATE OF CONSULT REQUEST:** May 12, 1999

C. **REMARKS:**

The submission responds to deficiencies presented to the Applicant as a result of Microbiologist's Review #1.

D. CONCLUSIONS:

The submission is recommended for approval on issues concerning microbiology.

/S/ 5/20/99

Brenda Uratani, Ph.D.
Review Microbiologist

APPEARS THIS WAY

/S/ 5/20/99

cc:

APPEARS THIS WAY
ON ORIGINAL

NDA 21-046
HFD-120/ Div. File
HFD-805/ Uratani
HFD-120/L. Rocca, P. David
drafted by: Brenda Uratani, 5/20/99
R/D initialed by P. Cooney, 5/20/99

REVIEW FOR HFD-120
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review #1 of NDA 21-046
January 22, 1999

1. **APPLICATION NUMBER:**

   APPLICANT: Forest Laboratories Inc.
   909 Third Avenue
   New York, NY 10022-4731

2. **PRODUCT NAMES:** citalopram hydrobromide oral solution

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** oral dosage, 10 mg/5 ml.

4. **METHOD(S) OF STERILIZATION:**

5. **PHARMACOLOGICAL CATEGORY:** Treatment of depression.

B. 1. **DATE OF INITIAL SUBMISSION:** November 2, 1998

2. **AMENDMENT:**

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** December 14, 1998

5. **DATE OF CONSULT REQUEST:** December 7, 1998

C. **REMARKS:**

The drug product is in a [redacted] oral dosage form. Microbiological specification and testing for the drug product are the subject of this review.

D. CONCLUSIONS:

The application is approvable pending resolution of microbiology issues.

/S/ 1/26/99

APPEARS THIS WAY
ON ORIGINAL

Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 1/26/99

cc:

APPEARS THIS WAY
ON ORIGINAL

NDA 21-046
HFD-120/ Div. File
HFD-805/ Uratani
HFD-120/L. Rocca, P. David
drafted by: Brenda Uratani, 1/22/99
R/D initialed by P. Cooney, 1/22/99

COMPLETED JUL 2 0 1999

Citalopram Hydrobromide
Oral solution (10 mg/5 mL)
NDA 21-046

Forest Laboratories
New York, NY 10022

JUL 19 1999

Submission Date: October 30, 1998, March 29, 1999
Reviewer: Iftekhar Mahmood, Ph. D.
Indication: Antidepression

TABLE OF CONTENTS

INTRODUCTION

Citalopram (CT) is an orally administered selective serotonin reuptake inhibitor. Citalopram is a racemic bicyclic phthalane derivative. Molecular formula of citalopram is $C_{20}H_{22}BrFN_2O$ and its molecular weight is 405. Citalopram is a white powder and is sparingly soluble in water. The pK_a of citalopram is 9.5.

The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. Human studies have shown that higher concentrations [redacted] of the (R)-enantiomer are achieved in the plasma compared to the (S)-enantiomer, possibly due to the larger clearance of the (S)-compared to the (R)-enantiomer.

Citalopram is absorbed with a T_{max} of 1 to 6 hours in healthy subjects. The absolute bioavailability of citalopram is 80% . Following a single oral dose (30 mg tablet) of citalopram, the mean C_{max} and T_{max} were 42.2 ng/mL and 4.5 hours, respectively. The mean C_{max} and T_{max} of demethylcitaloprim (a metabolite of citalopram) were 5.3 ng/mL and 24.8 hours, respectively. Food has no effect on the pharmacokinetics of

citalopram tablets. The volume of distribution of citalopram is 12.3 L/kg. Citalopram is 82% bound to human plasma proteins over the concentration range of 100 to 2400 ng/mL. The major metabolites of citalopram are desmethylcitalopram (DCT) and didesmethyl citalopram (DDCT). The DCT levels are approximately [redacted] than that of the parent compound whereas DDCT levels are only about 10% of citalopram levels. DCT is [redacted] than the parent compound as a serotonin reuptake inhibitor. Minor metabolites of citalopram are N-Oxide and propionic acid. Approximately 85% of the radioactivity was recovered in urine (75%) and feces (10%). CT, DCT, DDCT, CT-glucuronide + DDCT-glucuronide, deaminated propionic acid-glucuronide, and N-oxide accounted for 26%, 19%, 9%, 20%, 12% and 7% of the radioactivity recovered in urine, respectively. The systemic clearance of citalopram is 330 mL/min. Renal clearance is about 60 mL/min. The elimination half-life of citalopram is approximately 35 hours.

Compared to a single oral dose study (40 mg), following multiple dosing the C_{max} and AUC [redacted] increased by [redacted] whereas the oral clearance [redacted] The percent of dose excreted unchanged in urine was 23% following multiple dosing compared to 10% after a single dose. The elimination half-life of CT, DCT and DDCT following multiple dosing was 41, 49 and 102 hours, respectively.

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Study Title: A single dose, open label, bioequivalence study comparing citalopram as an oral solution with citalopram as a tablet in human volunteers (CIT-PK1-97-09-000).

Objectives:

The objective of this study was to assess the bioequivalence of a citalopram (10 mg/5 mL) oral solution (test product) with citalopram tablet (reference product), under fasting conditions.

Formulations:

Citalopram 60 mg Tablets and citalopram solution (10 mg/5 mL).

Study Design

The study was a single dose, open label, randomized, two-way cross-over bioequivalence study with a two week washout period. Subjects were randomly assigned to two dosing sequences and fasted overnight Twenty four healthy adult volunteers (16 males and 8 females) were enrolled in the study. Twenty-three subjects completed the study (15 males and 8 females) . Blood samples were collected pre-dose and at the following times after dosing: 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 and 192 hours. Plasma concentrations of citalopram, demethylcitalopram and didemethylcitalopram were measured by a validated method with a fluorescence detector. The

Pharmacokinetic Analysis:

Non-compartmental analysis was performed to estimate pharmacokinetic parameters, AUC_{0-t}, $AUC_{(0-\infty)}$ and C_{max} and these parameters were used to determine comparative bioavailability (bioequivalence) between solution and tablets. Bioequivalence criteria were assessed using two one-sided tests on the log transformed values on AUC_{0-t}, $AUC_{(0-\infty)}$ and C_{max}.

Results:

Pharmacokinetic parameters of citalopram for individual subject have been shown in Appendix I. Tables 1-2 summarize C_{max} and AUC of citalopram and its metabolite demethylcitalopram following oral administration of a 60 mg tablet or solution. The C_{max} and AUC values for citalopram and demethylcitalopram between tablet and solution were comparable. The two, one-sided tests procedure showed that the 90% confidence intervals

(Tables 1 & 2) for log-transformed $AUC_{(0-\infty)}$ and C_{max} of citalopram solution were within 80-125% of the reference tablet.

TABLE 1

Pharmacokinetic parameters of citalopram following a 60 mg oral dose of citalopram tablet or solution (n = 23)

Parameter	Oral Solution	Tablet	90% CI
C_{max} (ng/mL)			95 - 104
$AUC_{(0-t)}$ (ng*hr/mL)			95 - 104
$AUC_{(0-\infty)}$ (ng*hr/mL)			96 - 103

TABLE 2

Pharmacokinetic parameters of demethylcitalopram following a 60 mg oral dose of citalopram tablet or solution (n = 23)

Parameter	Oral Solution	Tablet	90% CI
C_{max} (ng/mL)			90 - 104
$AUC_{(0-t)}$ (ng*hr/mL)			93 - 104
$AUC_{(0-\infty)}$ (ng*hr/mL)			95 - 106

Conclusions:

Based on the data analysis, the oral solution of citalopram meets the bioequivalence criteria with citalopram tablet.

Reanalysis of data:

The Division of Scientific Investigations (DSI) inspected Forest Lab's bioanalytical facility at Farmingdale, NY. The inspection indicated irregularities and deficiencies in the analytical procedure (details in Appendix II). Based on the report submitted by the DSI to the OCPB, the Sponsor was requested to reassess the confidence interval on log transformed C_{max} and AUC excluding subjects # 1, 2, 9 and 10. The reanalysis of the

data also indicated that the oral solution of citalopram is bioequivalent to citalopram tablet (Tables 3 & 4).

TABLE 3

Pharmacokinetic parameters of citalopram following a 60 mg oral dose of citalopram tablet or solution (reanalysis, n = 19)

Parameter	Oral Solution	Tablet	90% CI
C_{max} (ng/mL)			95 - 106
$AUC_{(0-t)}$ (ng*hr/mL)			95 - 106
$AUC_{(0-\infty)}$ (ng*hr/mL)			96 - 104

TABLE 4

Pharmacokinetic parameters of demethylcitalopram following a 60 mg oral dose of citalopram tablet or solution (reanalysis, n = 19)

Parameter	Oral Solution	Tablet	90% CI
C_{max} (ng/mL)			87 - 104
$AUC_{(0-t)}$ (ng*hr/mL)			93 - 104
$AUC_{(0-\infty)}$ (ng*hr/mL)			96 - 107

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Recommendation:

The analysis of data indicates that the oral solution of citalopram meets the bioequivalence criteria with citalopram tablet.

Iftekhar Mahmood, Ph.D. /S/ 7/19/99

RD/FT initialed by Chandra Sahajwalla, Ph.D /S/ 7/19/99

Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-046, HFD-120, HFD-860 (Mahmood, Sahajwalla, Mehta), HFD-340 (Viswanathan), CDR-Biopharm, and FOI (HFD-19) files.

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ON ORIGINAL

Table A-5
Pharmacokinetic Parameters of Citalopram Following a Single Dose Oral Administration of a 60 mg Citalopram Oral Solution in Young Healthy Volunteers

Subject #	Gender	Cmax	Tmax (hr)	AUC0-t	AUC0-inf	t1/2 (hr)	CL/F (L/hr)
1	M						
2	M						
3	M						
4	M						
5	M						
7	M						
8	M						
9	M						
10	M						
11	M						
12	M						
13	M						
14	F						
15	F						
16	F						
17	F						
18	F						
19	F						
20	M						
21	M						
22	M						
23	F						
24	F						
Mean		79.54	4.09	2831.00	2975.28	33.36	21.54
SD		18.19	1.59	856.15	895.80	6.33	5.04
%CV		22.87	38.98	30.24	30.11	18.98	23.42
Min							
Max							

Study Protocol

Table A-6
Pharmacokinetic Parameters of Citalopram Following a Single Dose Oral Administration of a 60 mg Citalopram Tablet in Young Healthy Volunteers

Subject #	Gender	Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng.hr/mL)	AUC0-inf (ng.hr/mL)	t1/2 (hr)	CL/F (L/hr)
1	M						
2	M						
3	M						
4	M						
5	M						
7	M						
8	M						
9	M						
10	M						
11	M						
12	M						
13	M						
14	F						
15	F						
16	F						
17	F						
18	F						
19	F						
20	M						
21	M						
22	M						
23	F						
24	F						
Mean		80.28	4.00	2855.25	2990.67	33.55	21.42
SD		18.90	1.31	832.84	869.43	6.76	5.17
%CV		23.54	32.86	29.17	29.07	20.16	24.11
Min							
Max							

Table A-9
Pharmacokinetic Parameters of Demethylcitalopram Following a Single Dose Oral Administration of a 60 mg Citalopram Oral Solution in Young Healthy Volunteers

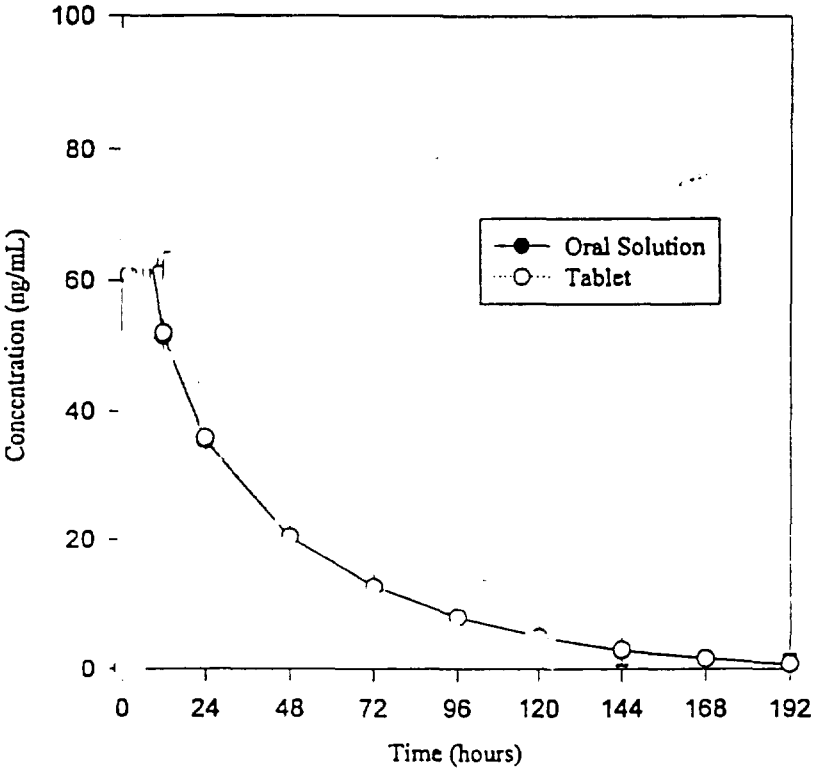
Subject #	Gender	Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng.hr/mL)	AUC0-inf (ng.hr/mL)	t1/2 (hr)
1	M					
2	M					
3	M					
4	M					
5	M					
7	M					
8	M					
9	M					
10	M					
11	M					
12	M					
13	M					
14	F					
15	F					
16	F					
17	F					
18	F					
19	F					
20	M					
21	M					
22	M					
23	F					
24	F					
	Mean	11.27	20.00	971.41	1206.80	60.93
	SD	2.98	20.62	228.97	258.06	20.02
	%CV	26.45	103.08	23.57	21.38	32.86
	Min					
	Max					

Table A-10
Pharmacokinetic Parameters of Demethylcitalopram Following a Single Dose Oral Administration of a 60 mg Citalopram Tablet in Young Healthy Volunteers

Subject #	Gender	Cmax (ng/mL)	Tmax (hr)	AUC0-t (ng.hr/mL)	AUC0-inf (ng.hr/mL)	t1/2 (hr)
1	M					
2	M					
3	M					
4	M					
5	M					
7	M					
8	M					
9	M					
10	M					
11	M					
12	M					
13	M					
14	F					
15	F					
16	F					
17	F					
18	F					
19	F					
20	M					
21	M					
22	M					
23	F					
24	F					
		11.74	14.17	983.12	1204.10	59.37
		3.20	12.22	234.16	259.72	23.14
		27.25	86.22	23.82	21.57	38.98

Study Protocol

Figure A-1
Mean Plasma Citalopram Concentrations Following
Single oral Dose Administration of Citalopram Hydrobromide 60 mg Oral
Solution or Tablet in Young Healthy Male and Female Volunteers



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Study Protocol

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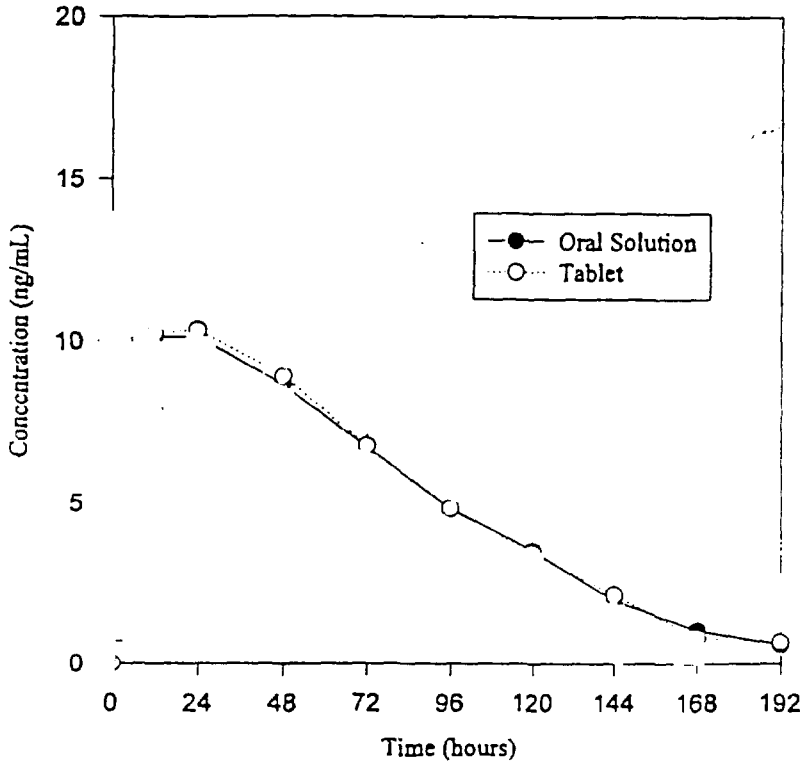
Figure A-2
Mean Plasma Demethylcitalopram Concentrations Following Single oral Dose Administration of Citalopram Hydrobromide 60 mg Oral Solution or Tablet in Young Healthy Male and Female Volunteers



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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21046	**Trade Name:**	CELEXA (CITALOPRAM HYDROBROMIDE) 10MG/5M
Supplement Number:		**Generic Name:**	CITALOPRAM HYDROBROMIDE
Supplement Type:		**Dosage Form:**	Solution; Oral
Regulatory Action:	AE	**Proposed Indication:**	Depression

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
_X_ Other Age Groups (listed): 7-17 y.o.
____Children (25 Months-12 years)
_X_ Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
This is an AE action providing for a new formulation, solution, of an already marketed solid (tablet) dosage form, i.e., a bioequivalence approval. Pediatric WR issued 4-28-99, requesting submisison of 2 pediatric studies in depression. sponscr has, as yet, not submitted protocols.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER PAUL DAVID

/S/
Signature

8-17-99
Date

PATENT INFORMATION

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PATENT INFORMATION
US Citalopram Patents

Patent No.	Title	Expiration Date	Type of Patent	Patent Owner	US Agent
5,296,507	Treatment of Cerebrovascular Disorders	August 9, 2011	Method of Use	H. Lundbeck A/S	Forest Labs
34,712	Pharmaceutically Useful (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and Non-toxic Acid Addition Salts thereof	June 8, 2009	Drug Substance	H. Lundbeck A/S	Forest Labs
4,650,884	Novell Intermediate and Method for its Preparation	August 2, 2005	Method of Preparation	H. Lundbeck A/S	

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

PATENT CERTIFICATION

US Patent No. 5,296,507 Patent expiry date: August 9, 2011

Patent title: Treatment of Cerebrovascular Disorders

Patent type: method of use patent

Patent Owner: H. Lundbeck, A/S

US Agent: Forest Laboratories, Inc.

The undersigned declares that Patent No. 5,296,507 relates to the use of a class of 1-[3-(dimethylamino) propyl]-1-phenylphthalanes for the treatment of dementia and cerebrovascular disorders and for the inhibiting platelet aggregation, and to the production of medicaments or pharmaceutical compositions containing the some for such purposes. The drug product, Celexa™ (citalopram hydrobromide) Oral Solution, is the subject of this application for which approval is being sought.

Kathryn Bishburg

Date: 10/25/98

Kathryn Bishburg, Pharm.D.
Director, Regulatory Affairs

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

PATENT CERTIFICATION

US Patent No. 34,712 Patent expiry date: June 8, 2009.

Patent title: Pharmaceutically useful (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile andnon-toxic acid

Patent type: drug substance

Patent Owner: H. Lundbeck, A/S

US Agent: Forest Laboratories, Inc.

The undersigned declares that Patent No. 34,712 relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'fluorophenyl)-1,3-dihydroisobenzofuran-b 5-carbonitrile (citalopram) and to the use of these enantiomers as antidepressant compounds. The drug product, Celexa™ (citalopram hydrobromide) Oral Solution, is the subject of this application for which approval is being sought.

Kathryn Bishburg

Date: 10/29/98

Kathryn Bishburg, Pharm.D.
Director, Regulatory Affairs

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

PATENT CERTIFICATION

US Patent No. 4,650,884 Patent expiry date: August 2, 2005

Patent title: Novell Intermediate and Method for its Preparation

Patent type: method of preparation

Patent Owner: H. Lundbeck, A/S

US Agent: Forest Laboratories, Inc.

The undersigned declares that Patent No. 4,650,884 relates to the preparation and properties of antidepressant substituted 1-dimethylaminopropyl-1-phenylphthalans or 1-(3-dimethyaminopropyl)-1-phenyl-1,3-dihydroisobenzofurans). The drug product, Celexa™ (citalopram hydrobromide) Oral Solution, is the subject of this application for which approval is being sought.

Kathryn B. Bishburg

Kathryn Bishburg, Pharm.D.
Director, Regulatory Affairs

Date: 10/29/98

US005296507A

United States Patent [19]

Tanaka et al.

[11] Patent Number: 5,296,507

[45] Date of Patent: Mar. 22, 1994

[54] TREATMENT OF CERBROVASCULAR DISORDERS

[75] Inventors: Yoshiaki Tanaka; Naomi Kobayashi; Tadashi Kurimoto, all of Saitama; Yugo Ikeda, Tokyo, all of Japan

[73] Assignee: H.Lundbeck A/S, Copenhagen-Valby, Denmark

[21] Appl. No.: 1,571

[22] Filed: Jan. 6, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 742,907, Aug. 9, 1991, abandoned.

[30] Foreign Application Priority Data

Sep. 6, 1990 [DK] Denmark 2132/90

[51] Int. Cl.[5] A61K 31/36

[52] U.S. Cl. 514/465

[58] Field of Search 514/465

[56] References Cited

PUBLICATIONS

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The British Journal of Psychiatry, vol. 157, Dec. 1990, pp. 894–901, The Royal College of Psychiatrists, Nyth, et al., "The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A nordic multicentre study".

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Nyth, A. L. et al., "The effect of citalopram in dementia disorders. A Scandinavian multicentre study", Abstract of the XVIth C.I.N.P. Congress, Munich, Aug. 15–19, 1988.

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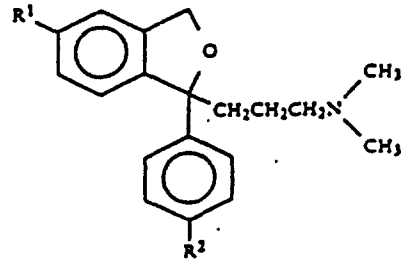
Primary Examiner—S. J. Friedman

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] ABSTRACT

A method for the treatment of dementia and cerebrovascular disorders and for inhibiting platelet aggregation in patients in need thereof comprising the step of administering a therapeutically effective amount of a 1-[3-(dimethylamino)propyl]-1-phenylphthalane of the general formula

Formula I



wherein R^1 and R^2 each are selected from the group consisting of halogen, trifluoromethyl, cyano and R—CO—, wherein R is an alkyl radical, or a pharmaceutically-acceptable acid addition salt thereof, is described.

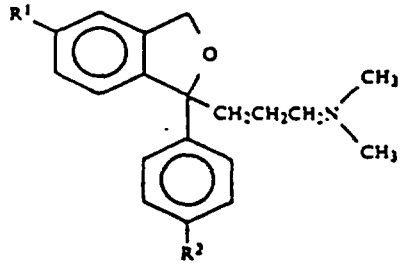
7 Claims, No Drawings

TREATMENT OF CERBROVASCULAR DISORDERS

This is a continuation of application Ser. No. 07/742,907, filed Aug. 9, 1991, now abandoned.

The present invention relates to the use of a class of 1-[3-(dimethylamino)propyl]-1-phenylphthalanes for the treatment of dementia and cerebrovascular disorders and for inhibiting platelet aggregation, and to the production of medicaments or pharmaceutical compositions containing the same for such purposes.

U.S. Pat. No. 4,136,193 relates to 1-[3-(dimethylamino)propyl]-1-phenylphthalanes having the general formula



Formula I

wherein R^1 and R^2 each are selected from the group consisting of halogen, trifluoromethyl, cyano and R—CO—, wherein R is an alkyl radical with 1 to 4 C-atoms inclusive, and acid addition salts thereof with pharmaceutically-acceptable acids.

Said compounds are described to be selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors and accordingly to have antidepressant activities. One of the tests used to show such activities was inhibition of ^{14}C-5-HT uptake in rabbit blood platelets in vitro. The compound of Formula I wherein R^1 is a cyano group and R^2 is a fluorine atom is the known antidepressant citalopram, the antidepressant activity of which has been reported in several publications, e.g. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, 1982, 6, 277–295 and A. Gravem, *Acta Psychiatr. Scand.*, 1987, 75, 478–486. A method for preparation of and intermediates for the preparation of citalopram are described in U.S. Pat. No. 4,650,884 and methods of preparing the individual enantiomers of citalopram are disclosed in U.S. Pat. No. 4,943,590.

Biochemical postmortem investigations of patients with Alzheimer's disease have shown hypofunction of the serotonin nervous system in the brain (D. M. Bowen et al., *J. Neurochem.*, 1983, 41, 266–272). It is also known that depression is one of the major symptoms in Alzheimer's disease, and citalopram has been reported to be effective against depression associated with Alzheimer's disease (C. G. Gottfries, *Psychopharmacology*, 1988, 96, 45 (Suppl.)). A study of a group of patients with moderate dementia of Alzheimer's type (AD/SDAT) or multi-infarct dementia (MID) has shown significant improvements in emotional lability, motivation, confusion, fear-panic, irritation, reduced mood and restlessness, whereas citalopram did not appear to have effect on intellectual functions (Nyth, A. L. et al. "The effect of citalopram in dementia disorders", presentation at CINP, August 1988; subsequently reported in Nyth, A. L. and Gottfries, C. G., "The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A nordic multicentre study." *Br. J. Psychiat.*, 1990, 157, 894–901). Later controlled studies showed that treatment with citalopram caused no significant improvement on emotional disturbances in patients with vascular dementia (VD, incl. MID) (Nyth, A. L. et al. "The efficacy of citalopram in treatment of emotional disturbances in dementia disorders", *ECNP Abstract* 1989, Sweden, 79).

It has also been described that certain 5-HT_{1A} agonists show effect in the treatment of *Apoplexia cerebri* (Danish Patent Application No 4616/89).

Cerebrovascular disorders, such as ischemia which are triggered by cerebral infarction, cerebral hemorrhage, cerebral arteriosclerosis, subarachnoid hemorrhage, cerebral thrombosis, cerebral embolism, and other diseases are of increasing importance among the population and there is a great demand for effective and safe drugs for the treatment of such disorders and the sequelae of such disorders. A particular problem is dementia not only caused by cerebrovascular disorders but also dementia of other genesis.

Surprisingly, it has now been found that the compounds of the above Formula I effect improvement of cerebrovascular disorders, in particular ischemia, and the brain damage and the impairment of memory functions in connection therewith, and that they show inhibiting action on platelet aggregation. Furthermore, the compounds of the general Formula I have been found to have an anti-amnesic effect and to improve cognitive function in elderly depressed patients having concomitant dementia, i.e. not only dementia of cerebrovascular origin, but also dementia as a result of chronic organic reactions, such as neurodegenerative disorders.

Accordingly, the present invention relates to the use of a compound of the above Formula I for the prevention or treatment of senile dementia and of cerebrovascular disorders and for the inhibition of platelet aggregation, and for the manufacture of medicaments or pharmaceutical compositions for such uses.

Senile dementia may be senile dementia of any genesis such as neurodegenerative, traumatic, cerebrovascular, anoxic, etc, i.e., dementia of Alzheimer's type, multi-infarct dementia or vascular dementia, etc.

Cerebrovascular disorders are brain damages caused by cerebral infarction, cerebral hemorrhage, cerebral arteriosclerosis, subarachnoid hemorrhage, cerebral thrombosis, cerebral embolism, or the like, e.g., ischemia, and the psychological and neurological sequelae of such damages.

The use of the optical isomers of the compounds of general Formula I and their mixtures, including racemic mixtures thereof, is embraced by the invention.

The compound of general Formula I may be used as the free base or as a pharmacologically-acceptable acid addition salt thereof. As acid addition salts such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

An appropriate oral dose of the compound of general Formula I is 1-100 mg/day p.o.

Due to the inhibition of platelet aggregation the medicaments obtained and used in accordance with the invention are useful in the treatment and/or prevention of microcirculation disturbances in the brain resulting from the above cerebral conditiolns or from venous or arterial thrombosis, or elsewhere in the body resulting from venous or arterial thrombosis or related conditions.

In view of the beneficial effects on cognitive function and on brain damages and of the platelet aggregation inhibiting effects now found as well as of the known effects on 5-HT uptake, the medicaments obtained and used in accordance with the present invention are useful in the treatment of senile dementia and cerebrovascular disorders, and the sequelae of cerebrovascular disorders such as psychiatric symptoms, e.g., anxiety, depression, loss of memory, hypobulia, restlessness, dementia, hallucinations, delusions, disturbances of conciousness, hypochondriac tendency, insomnia, excitation, garrulity, hyperkinesia, deliriums, and disturbances of orientation, neurological symptoms, e.g., alalia, and hypodynamia, and subjective symptoms, e.g., headache, dizziness, feeling of numbness, feeling of stiffness in the shoulder, feeling of exhaustion and heavy feeling in the head.

Additionally they have the further advantage of a very good safety profile.

A preferred compound of Formula I is citalopram.

The medicaments manufactured and used in accordance with the present invention are particularly useful in the treatment or prevention of ischemia in the brain and especially of dementia caused by ischemia.

Due to the pharmacological profile the medicaments manufactured and used in accordance with the present invention are especially useful in elderly patients.

Citalopram may be prepared by the methods disclosed in U.S. Pat. No. 4,650,884 and the other compounds used in accordance with the invention may be prepared analogueously or by the methods of U.S. Pat. No. 4,136,193. The individual enantiomers of citalopram may be prepared as described in U.S. Pat. No. 4,943,590 and enantiomers of the other compounds of Formula I may be prepared by similar methods.

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling or with an excess of the acid in a water-immiscible solvent, such as ethylether, ethylacetate, or dichloromethane, with the salt separating spontaneously.

The medicaments prepared and used in accordance with the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives, etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

The present compounds and their non-toxic acid addition salts may also be used in combination with other active ingredients, such as neuroleptics, thymoleptics, analgetics, etc.

TOXICITY STUDY

In toxicity studies male and female SD rats ranging in weight from 170 g to 200 g were used one day after fasting. Citalopram was dissolved in water and administered orally. Symptoms were observed for one week after citalopram administration. Even when citalopram was administered at a dose of 350 mg/kg no deaths were observed and accordingly it was obvious that citalopram has a very good safety profile.

PHARMACOLOGICAL TESTS

Ischemia-Induced Hippocampal Death in Gerbils

The overall objective of the study was to investigate the effects of citalopram on hippocampal lesions induced by ischemia in Mongolian gerbils.

Methods

Test compounds were administered intraperitoneally to Male Mongolian gerbils 30 min before carotid occlusion. Carotid occlusion time was 5 min. Seven days after recovery, the animals were killed, brains removed, sectioned and surviving neurons were counted along CA1 in the hippocampus.

Results

As is shown in Table 1, citalopram (20 mg/kg) had a weak but non-significant protective effect against neuronal lesions. The higher dose of this compound (40 mg/kg) showed a significant ($p<0.05$) protective effect against neuronal lesions. Ketamine (100 mg/kg) showed significant ($p<0.01$) protective effect.

TABLE 1

Effects on ischemia induced hippocampal neuronal damage in gerbils					
	Dose		Survival neurons/mm		
Drug	(mg/kg i.p.)	Gerbils used	mean	S.E.	p
Vehicle	—	10	12.8	2.6	
Citalopram	20	12	38.0	18.5	N.S.
Citalopram	40	11	95.8	27.9	<0.05
Ketamine	100	8	174.5	25.7	<0.01

Statistical analysis was carried out according to Dunnett's t-test vs vehicle group.

Passive Avoidance in Ischemic Gerbils

The test employed was step-down passive avoidance in gerbils treated with test compounds prior to occlusion of carotid arteries followed by acquisition trial (training phase).

Methods

Test compounds were administered intraperitoneally to gerbils 30 min prior to carotid occlusion or ketamine was administered intraperitoneally 10 min prior to carotid occlusion. The gerbils were anesthetized with 2% halothane contained in a mixture of 70% nitrogen and

30% oxygen. The right and left common carotid arteries were occluded for 5 min. The gerbils were trained for 5 min in a step-down type passive avoidance chamber (16×16×20 cm) two days after induced ischemia. Each gerbil was placed on a safety platform (6×16×20 cm) in the chamber and received a series of mild foot shocks (0.1 mA for 3 sec every 6 sec), when the gerbil stepped down to a floor made of metal rods. Gerbils were returned to the safety platform for testing 24 hrs later and their step-down latencies to the grid floor were recorded (max. 60 sec).

Results

Ischemia did not alter step-down latency measured during the training phase. Step-down latency during the training phase was not significantly modified in the gerbils treated with test compound.

Step-down latency in the testing phase was significantly decreased between ischemic control and sham operated gerbils. Citalopram (20 mg/kg) and ketamine (120 mg/kg) significantly increased the latency of ischemic gerbils. But the latency in indeloxazine (40 mg/kg) treated gerbils was not significantly different from that in ischemic control gerbils.

TABLE 2

Effect on passive avoidance in ischemic gerbils

Drug	Dose (mg/kg i.p.)	Number of gerbils	Ischemic treatment	Step-down latency [log(sec)] Mean	S.E.
Saline (sham)	—	15	–	1.471	0.075***
Saline (control)	—	20	+	0.953	0.116
Citalopram	20	7	+	1.386	0.083**
Indeloxazine	40	6	+	1.085	0.244
Ketamine	120	9	+	1.348	0.100*

*p < 0.05,
**p < 0.01,
***p < 0.001 (vs Saline control, by Student's t-test)

Brain Ischemia-Induced Death in Mice

Materials

Male ICR MICE (Charles River) weighing 30–40 g were used after they were fasted for 1 day.

Method

Test compounds were administered intraperitoneally to the mice 30 min prior to permanent ligation of bilateral common carotid arteries under conscious condition. Surviving mice were observed over 4 hrs.

Results

Citalopram (30 mg/kg) significantly prevented ischemia-induced death both 2 hrs and 4 hrs after bilateral carotid arterial ligation. Ifenprodil (30 mg/kg), however, did not significantly increase survival rate 4 hrs after ligation, although it showed significantly increased survival rate 2 hrs after the ligation.

TABLE 3

Effect on ischemia-induced death in bilateral carotid arterial ligation (BCAL) in mice

Drug	Dose (mg/kg, p.o.)	Number of mice	Survival rate (%) 2 hr after BCAL	4 hr after BCAL
Saline	—	30	23	17
Citalopram	30	30	50*	43*
Saline	—	30	13	7
Ifenprodil	30	30	47**	20

*p < 0.05,
**p < 0.01 (Chi-square test vs each Saline)

KCN-Induced Coma in Mice

Methods

Male mice (Crj:ICR) weighing 20–30 g were used. The mice were fasted for one day. The drugs, dissolved in saline, were injected intraperitoneally. 30 min after the injection, KCN, dissolved in saline, was injected intravenously at a dose of 1.3 mg/kg. The duration of disappearance of righting reflex was measured as coma time.

Results

Intraperitonal injection of citalopram significantly reduced coma time at a dose of 10 mg/kg. Indeloxazine at a dose of 20 mg/kg also significantly reduced the coma time.

TABLE 4

Effects of intraperitoneal injection of citalopram on KCN-induced coma in mice

Drug	Dose (mg/kg, i.p.)	Number of mice	Coma time (sec) Mean	S.E.
Vehicle	—	16	55.9	8.8
Citalopram	1.25	15	38.5	4.2
Citalopram	2.5	15	33.2	10.0
Citalopram	5	16	35.0	8.2
Citalopram	10	16	27.4	6.9*
Indeloxazine	20	17	13.8	3.7**

*P < 0.05,
**P < 0.01, Significantly different from values of vehicle control (Dunnett's t-test).

Carbon Dioxide-Induced Amnesia in Rats (Passive Avoidance Test)

The test employed was a one-trial passive avoidance test in rats, using carbon dioxide asphyxiation to induce amnesia.

Methods

Female Sprague-Dawley (CD) rats (A. Tick & Son Ltd.) in the body weight range 160–180 g were used for the study.

The one-trial passive avoidance apparatus consisted of a 32×32×32 cm chamber with opaque walls and a metal grid floor. A 6 cm wide, 25 cm long runway protruded from the front wall of the chamber. The runway was illuminated while the chamber was dark. When placed on the runway, a rat could enter the chamber through a 6×6 cm opening. A scrambled footshock could be delivered through the metal grid floor of the chamber.

On the first day of the experiment, the rats received three pre-treatment training trials, during which each animal was placed on the end of the runway and the time taken to enter the chamber (the 'step-through' latency) was determined.

On the second day of the experiment, groups of 10 animals were treated p.o. with test compound dissolved in saline or with saline.

One hour after administration, an acquisition trial was performed. This was similar to a training trial, except that the rats received a footshock of 1.0 mA for 10 sec, commencing 10 sec after entering the chamber. Immediately after the application of the footshock the animals were subjected to amnesic treatment.

Amnesic treatment consisted of placing the rats in a box filled with carbon dioxide until respiratory arrest occurred; the rats were then revived by artificial respiration. 24 Hours after the acquisition trial, a single retrieval trial was given to each rat and the time taken to

enter the chamber ('step-through' latency) was recorded for each animal.

If a rat did not enter the chamber within 180 seconds it was taken from the runway.

Results

There were no significant differences between the time of entry ('step-through' latency) of rats dosed with either vehicle, citalopram or piracetam, thus indicating that at oral doses of 40 or 1000 mg/kg, these compounds did not induce marked muscle incoordination of CNS effects of sufficient magnitude to modify entry times. The amnesic effect of carbon dioxide has been clearly demonstrated in this study. In those rats receiving footshock, but no drug treatment, treatment with carbon dioxide asphyxiation caused a decrease in 'step-through' latency.

Oral administration of citalopram at all dos. tested caused dose-related increases in the group mean 'step-through' times, which in most cases were statistically significant when compared to the saline-treated control group using Student's t-test. At the 2 highest doses tested (i.e., 20 and 40 mg/kg), a marked and highly significant increase in time was observed.

As expected, piracetam treatment gave statistically significantly longer 'step-through' latencies.

TABLE 5

Effects of oral administration of citalopram on carbon dioxide-induced amnesia in rats.

Drug	Dose (mg/kg; p.o.)	CO2 Treatment	Number of animals	Latency (sec)
Saline		–	10	119.6***
Saline		+	10	0.8
Citalopram	5	+	10	31.2
Citalopram	10	+	10	77.2**
Citalopram	20	+	10	114.3***
Piracetam	300	+	10	108.6***

**p < 0.01.
***p < 0.001, significantly different from values of relevant control group (Students t-test).

In Vitro Platelet Aggregation

Methods

The test was performed with fresh human platelets. The drugs were diluted in physiological saline to give a solution at a concentration ten times that of the final concentration. The drug was added to the platelets and incubated at 37° C. for 15 min. and then platelet aggregation was induced by the addition of collagen (10 microgram/ml).

Results

Citalopram at a final concentration of 100 microgram/ml inhibited the aggregation of human platelet induced by collagen by 58%. The same concentration of indeloxazine revealed weaker inhibitory effect (8%) than citalopram did on the aggregation by collagen.

Ex Vivo Platelet Aggregation

Effect on collagen-induced platelet aggregation using blood of rats administered orally with citalopram was investigated.

Materials

Male Wistar rats (Charles River) in the body weight range 350–400 g were used.

Methods

One hour after oral dosing the rats were lightly anesthetized with ether and blood was collected by cardiac puncture. Nine ml of the blood was mixed with 1 ml of 3.8% sodium citrate and platelet rich plasma (300000 platelets/cmm) was prepared. At the end of the incubation period at 37° C. for 2 min. effects of addition of 10 microgram/ml collagen on platelet aggregation were determined.

Results

A moderate inhibition of collagen-induced aggregation was noted following citalopram at 30 mg/kg (60.4%). At doses of 10 mg/kg only slight inhibition of collagen-induced aggreagation was noticed (16.7%).

TABLE 6

Effect on platelet aggregation ex vivo in rats.

Drug	Dose (mg/kg, p.o.)	Number of rats	Mean (%)	S.D. (%)	[% Change from control]
Vehicle	—	12	54.6	27.3	[—]
Citalopram	10	8	45.5	16.0	[–16.7]
Citalopram	30	8	21.6	21.6**	[–60.4]

S.D.: Standard deviation.
Statistical significance using analysis of variance of treatment groups as compared to vehicle treated groups.
**P < 0.01.

It appears from the foregoing Ischemia Induced Hippocampal Death Test that the compound according to the invention tested shows improving effect on neuronal lesion. The Passive Avoidance Test is Ischemic gerbils indicates improving effect on memory following ischemic attack, the Brain Ischemia-Induced Death Test in mice indicate effect on survival rate following ischemic attack, the KCN-induced Coma test in mice indicates improving effect following anoxia, and the Carbondioxide-Induced Amnesia Test in rats show positive effect on amnesia.

The results of the in vitro and the in vivo Platelet Aggregation Tests show inhibiting effects on platelet aggregation.

Clinical Test

In a group of depressed patients having concomitant dementia, it was observed that cognitive functions improved after treatment with compounds of the general Formula I but not after treatment with placebo. Accordingly, compounds of general Formula I clinically have memory improving effect in patients having dementia which may not only be of cerebrovascular origin but also may result from chronic organic reactions such as neurodegenerative disorders. This is in contradiction to the earlier study of Nyth et al. mentioned above (Nyth, A. L. et al. "The effect of citalopram in dementia disorders", presentation at CINP, August 1988).

FORMULATION EXAMPLES

The following examples show typical formulations of the medicaments manufactured in accordance with the invention.

1) Tablets containing 0.5 milligram of citalopram calculated as the free base:

Citalopram	100 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 1 milligram of citalopram calculated as the free base:

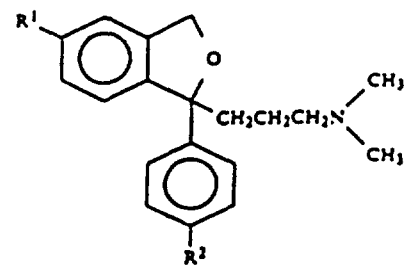
Citalopram	50 mg

-continued

Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg
3) Syrup containing per milliliter:	
Citalopram	5.0 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml
4) Solution for injection containing per milliliter:	
Citalopram	50 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml
5) Solution for injection containing per milliliter:	
Citalopram	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

We claim:

1. A method for the treatment of dementia cognitive disorders, or amnesia associated with and cerebrovascular disorders in a patient in need thereof comprising the step of administering an amount of a 1-[3-(dimethylamino)propyl]-1-phenylphthalane of the formula



Formula I

wherein R^1 and R^2 each are selected from the group consisting of halogen, trifluoromethyl, cyano and R—CO—, wherein R is an alkyl radical with 1 to 4 C-atoms inclusive a, or a pharmaceutically-acceptable acid addition salt thereof which is effective for such purpose to the said patient.

2. A method according to claim 1 wherein the cerebrovascular disorder is caused by cerebral infarction, cerebral hemorrhage, cerebral arteriosclerosis, subarachnoid hemorrhage, cerebral thrombosis, or cerebral embolism.

3. A method according to claim 2 wherein the disorder is ischemia.

4. A method according to claim 2 wherein the disorder is amnesia associated with ischemia.

5. A method according to claim 2 wherein the disorder is Vascular or Multiinfarct dementia.

6. A method according to claim 1 wherein the disorder is dementia of the Alzheimer's type.

7. A method according to claim 1 wherein the compound of Formula I is citalopram or a pharmaceutically-acceptable acid addition salt thereof.

* * * * *

US00RE34712E

United States Patent [19]

Boegesoe et al.

[11] E Patent Number: Re. 34,712

[45] Reissued Date of Patent: Aug. 30, 1994

[54] **PHARMACEUTICALLY USEFUL (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-FLUOROPHENYL)-1,3-DIHYDROISO BENZOFURAN-5-CARBONITRILE AND NON-TOXIC ACID ADDITION SALTS THEREOF**

[75] Inventors: Klaus P. Bocgesoe, Horsholm; Jens K. Perregaard, J gerspris, both of Denmark

[73] Assignee: H. Lundbeck A/S, Copenhagen-Valby, Denmark

[21] Appl. No.: 122,009

[22] Filed: Sep. 14, 1993

Related U.S. Patent Documents

Reissue of:

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Issued: Jul. 24, 1990
Appl. No.: 363,589
Filed: Jun. 8, 1989

[30] Foreign Application Priority Data

Jun. 14, 1988 [GB] United Kingdom 8814057

[51] Int. Cl.[5] A61K 31/34; C07D 307/87; C07C 255/59

[52] U.S. Cl. 514/469; 549/467; 558/422

[58] Field of Search 549/467; 558/422; 514/469

[56] References Cited

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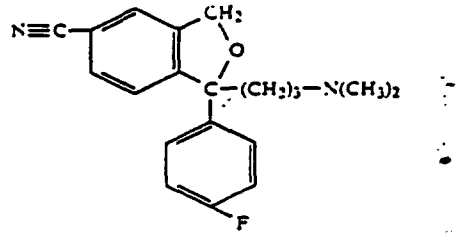
Primary Examiner—Bernard Dentz
Attorney, Agent, or Firm—Gordon W. Hueschen

[57] ABSTRACT

The two enantiomers of the anti-depressant drug of the formula I



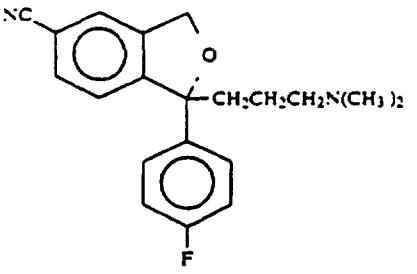
are disclosed. Methods for resolving intermediates and their [steroselective] *stereoselective* conversion to a corresponding [enatiomer] *enantiomer* of I are also disclosed.

12 Claims, No Drawings

PHARMACEUTICALLY USEFUL (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-FLUOROPHENYL)-1,3-DIHYDROISO BENZOFURAN-5-CARBONITRILE AND NON-TOXIC ACID ADDITION SALTS THEREOF

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

The present invention relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-[dihydroisobenzofuran] *dihydroisobenzofuran*-b 5-carbonitrile (citalopram) of the following formula I:



I

and to the use of these enantiomers as antidepressant compounds as well as the possible use as geriatrics or in the cure of obesity or alcoholism.

This invention also includes pharmaceutically acceptable salts of the enantiomers of compound I formed with non-toxic organic or inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqeuous immiscible solvent, such as ethyl ether, ethyl acetate or [dicloromethane] *dichloromethane*, with the desired salt separating directly. Exemplary of such organic]salt] *salts* are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, oxalic, salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acid, as well as the 8-halotheophyllines, for example 8-bromotheophylline.

Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

Furthermore it was found that non-hygroscopic acid addition salts might be obtained by [conventinal] *conventional* freeze drying techniques from water solutions of appropriate salts of the above mentioned kinds.

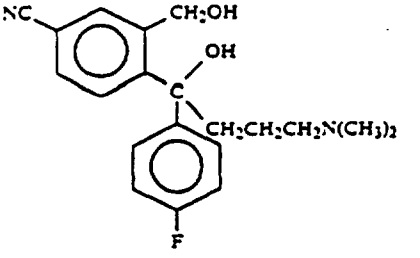
The invention is also concerned with a method to resolve the intermediate racemate and to produce the individual isomers of I therefrom.

BACKGROUND OF THE INVENTION

Citalopram, which has been disclosed in e.g. U.S. Pat. No. 4,136,193, has proven to be an efficient antidepressant compound in man (Ref.: A. Gravem et. al., Acta pysychiat. Scan., No. 75, p. 478–486 (1987). All work in the development of this compound has been made with the racemate. Citalopram has been shown pharmacologically to be a very selective inhibitor of 5-HT reuptake. Previous attempts to crystallize diastereomeric salts of citalopram enantiomers have failed.

SUMMARY OF THE INVENTION

Surprisingly, it has now proven possible to resolve the intermediate [4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile] *4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, II, into its enantiomers and finally in a stereoselective way to convert these enantiomers to the corresponding citalopram enantiomers. Likewise, monoesters of II formed by optically active carboxylic acids could be separated into the corresponding diastereomers and subsequently converted directly into citalopram enantiomers in a steroselective ringclosure reaction. The intermediate diol, II, has been disclosed in e.g. U.S. Pat. No. 4,650,884 as a racemic mixture.



II

The enantiomers of the intermediate of formula II as well as monoesters fall likewise within the scope of the present invention.

Furthermore, it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer.

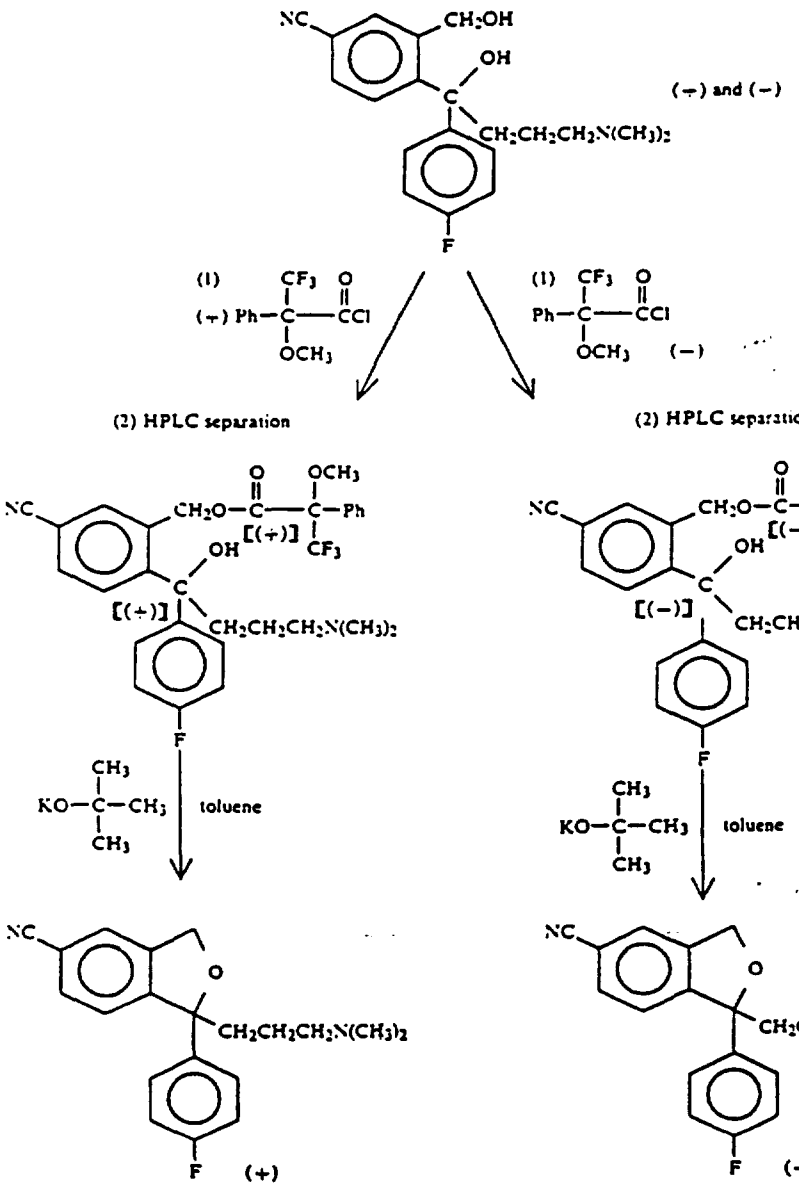
The present invention also includes a new method of synthesizing I from the diol compound II by esterification of the primary alcohol group into a labile ester, which in the presence of a base undergoes spontaneous ringclosure to citalopram or, if enantiomerically pure II is esterified, the corresponding citalopram enantiomer is produced with fully conservation of stereoconfiguration.

According to the invention, II is reacted with:

(a) an enantiomerically pure acid derivative as an acid chloride, anhydride or [libile] *labile* ester as e.g. [examplified] *exemplified* in reaction scheme I by (+)- or (−) -α-methoxy-α-trifluoromethylphenylacetyl chloride. The reaction is preferably performed in an inert organic solvent as e.g. toluene, dichloromethane or tetrahydrofuran. A base (triethylamine, N,N-dimethylaniline, pyridin or the like) is added to neutralize liberated HCl. The diastereoisomers are subsquently separated by HPLC or fractional crystallization. The thus purified [disatereoisomers] *diastereoisomers*are [finnaly] *finally* separately treated with strong base (e.g. alkoxide) in an inert organic solvent as e.g. toluene, tetrahydrofuran, or dimethoxyethane yielding the pure citalopram enantiomers respectively. The ringclosure reaction is preferably performed at

relatively low temperatures (−20° C.) to room temperature).

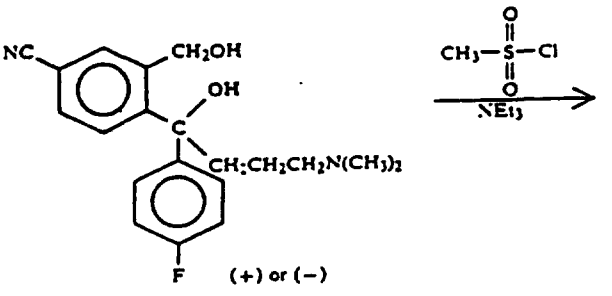
REACTION SCHEME I



(b) the enantiomers of an optically active acid successively affording the pure diastereomeric salts. Optically antipodes of tartaric acid, di-benzoyltartaric acid, di-(p-[toloyl] *toluoyl*)tartaric acid, bisnaphthylphosphoric acid, 10-camphorsulphonic acid and the like are conveniently used.

(c) Stereoselective ringclosure of the pure enantiomers of II prepared as in (b) is performed via a labile ester as e.g. methansulfonyl, p-toluenesulfonyl, 10-camphorsulfonyl, trifuoracetyl or trifluoromethansulfonyl with simultaneous addition of a base (triethylamine, dimethylaniline or pyridin) in an inert organic solvent at 0° C. The ringclosure reaction is [examplified] *exemplified* in reaction scheme II:

REACTION SCHEME II



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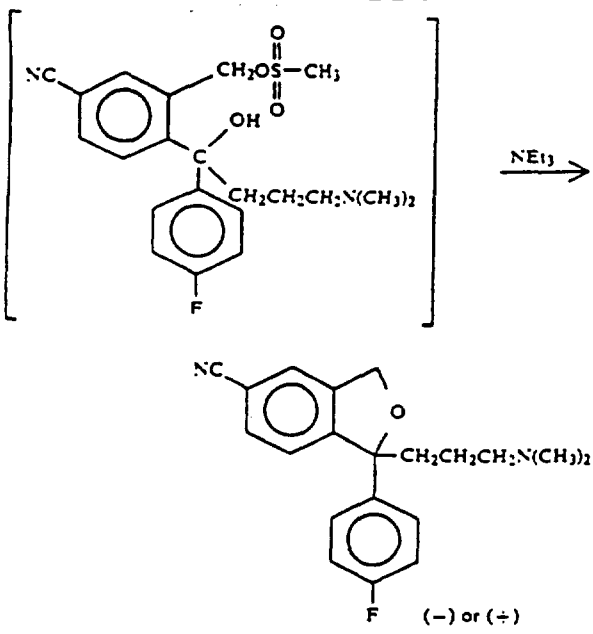
REACTION SCHEME II



EXAMPLE 1

Resolution by method (a)

To 11 g of (+)-α-methoxy-α-trifluoromethylacetic acid dissolved in 25 ml of chloroform were added 50 ml of thionylchloride and a few drops of dimethylformamide. The reaction mixture was refluxed for 2 hours. Excess of thionylchloride was evaporated with toluene leaving the (+)-α-methoxy-α-trifluoromethylacetyl chloride as a liquid. This liquid diluted with 50 ml of dichloromethane was added dropwise to an ice cooled solution of 17 gr of [4-(4-dimethylamino-1-(4'-fluorophenyl)-1-hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] *4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, II, and 8 ml of triethylamine in 150 ml of dichloromethane. The reaction mixture was further stirred for another hour at room temperature, subsequently washed with brine, dried ($MgSO_4$) and the solvent evaporated below 30° C. in vacuo affording 29 gr of the ester as a diastereomeric mixture. By repeated HPLC purification (eluted with ethyl acetate/tetrahydrofuran 9:1 containing 4% of triethylamine) and by collecting only the 5–10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0° C. The toluene solution was washed with water, dried ($MgSO_4$) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D = +11.81°$ (c=1, CH_3OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ^1H NMR spectroscopy ($CDCL_3$ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (−)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D = -12.34°$ (c=1, CH_3OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.0%.

EXAMPLE 2

Resolution by methods (b) and (c)

To a solution of 85 gr of [4-(4-dimethylamino)-1-4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] *4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, hydrobromide in 500 ml of water were added 200 ml of ice cooled 2M NaOH solution and 500 ml of ether. The mixture was stirred for ½ hour, the ether phase separated, dried ($MgSO_4$) and the ether evaporated. The remaining oil was dissolved in 400 ml of 2-propanol at 40° C., and 40 gr of (+)-di-p-[toloyltartaric] *toluoyltartaric* acid (as hydrate) were added under vigorous stirring. After a short while crystallization began. After 3 hours of stirring the precipatated salt was filtered off and dried yielding 29.2 gr (55.1%) of [(−)-4-(4-dimethylamino)-1-(4'fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile] (−)-*4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)benzonitrile*, hemi (+)-di-p-[toloyltartaric] *toluoyltartaric* acid salt. MP: 134°–135° C., $[\alpha]_D = +10.0°$ (c=1, CH_3OH). The filtrate is used below.

To an ice cooled solution of 14 gr of the (−)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methansulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for ½ hour, washed with brine, dried ($MgSO_4$) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4'-[flurophenyl] *fluorophenyl*-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = +12.33°$ (c=1, CH_3OH). The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147°–148° C., $[\alpha]_D = +12.31°$ (c=1, CH_3OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently colled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt. MP: 264°–266° C., $[\alpha]_D = +13.88°$ C. (c=1, dimethylformamide).

A 2:1 addition compound of the (+)-isomer with L(+)-tartaric acid was prepared in the following manner: 4 g of the (+)-isomer as base were dissolved in 100 ml of diethyl ether and extracted into 100 ml of water containing 0.8 g of L(+)-tartaric acid by stirring. The organic phase was separated and discarded. The water-phase was freeze-dried in vacuo (<0.1 mm Hg) for 18 hours leaving 3.8 g of a white powder of the title compound. This addition compound was stable and not hygroscopic.

In a corresponding manner as above via the [(+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benezonitrile] (+)-*4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile*, hemi (−)-di-(p-toloyl)-tartaric acid salt ($[\alpha]_D = -8.9°$ (c=1, CH_3OH)) which was converted to the corresponding diol base ($[\alpha]_D = +61.1°$ (c=1, CH_3OH)) and finally ringclosure

reaction yielded 10 gr of (−)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = -12.1°$ (c = 1, CH_3OH).

The oxalic acid salt of the (−)-isomer crystallized from acetone, MP: 147°-148° C., $[\alpha]_D = -12.08°$ (c = 1, CH_3OH).

EXAMPLE 3

Preparation of citalopram by method (c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methansulfonyl chloride in 30 ml of dichloromethane were added dropwise during a half hour. The reaction mixture was washed with 0.1M NaOH solution twice, the organic phase separated, dried ($MgSO_4$) and the solvent evaporated, leaving 21.5 gr of the title (±)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP 184°-186° C.

The enantiomers from Example 1 were tested for their ability to block 5-HT reuptake in standard and reliable test method. Results are shown in Table I in comparison with the racemic mixture of citalopram.

5-HTP-POTENTIATION

The test evaluates the ability of the substance to potentiate the effect of 5-HTP, which results in development of 5-HT syndrome (Christensen, Fjalland, Pedersen, Danneskiold-Samsoe and Svendsen; European J. Pharmacol. 41, 153-162, 1977).

Procedure

Each treatment group consists of 3 mice, and two groups are treated with the highest test dose. A control group only treated with 5-HTP is included and a group treated with citalopram 10 mg/kg and 5-HTP is used as reference for full 5-HT syndrome.

The Route of Administration

30 minutes after the administration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5-10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HTP syndrome will occur. The symptoms are the same as previously described: (1) excitation, (2) tremor, and (3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, . . . 9/9, where 0, 1, . . . , 9 are the number of points per group after the dose in question. The ED_{50} value is calculated by log-probit analysis.

INHIBITION OF ^{3}H-SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSOMES

By this method the inhibition by drugs of the uptake of [$_3$H-serotonin] *^{3}H-serotonin* (^{3}H-5-HT)(10 nm) in rat brain synaptosomes is determined in vitro. Method and results in Hyttel, Psychopharmacology 1978, 60, 13-18; Hyttel, Prog. Neuro-Psychopharmacol. & Biol. [Psychait.] *Psychiat.* 1982, 6,277-295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suppl. 1, 146-153. [Procedure p]

Procedure

Male Wistar (Mol: Wist) rats (125-250 g) are sacrified by decapitation and [exanguinated] *exsanguinated* Brain tissue (minus cerebellum) is gently homogenized (glass teflon homogenizer) in 40 vol (w/v) of ice cold 0.32M of sucrose containing 1 mM of nialamide. The P_2 fraction (synaptosomal fraction) is obtained by centrifugation (600 g. 10 min and 25000 g. 55 min, 4° C.) and suspended in 800 volumes of a modified Krebs-Ringer-phosphate buffer, pH 7.4.

To 4000 µl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 µl test substance in water. After preincubation at 37° C. for 5 min, 100 µl of ^{3}H-1-NA (final [concnetration] *concentration* 10 nM) are added and the samples are incubated for 10 min at 37° C. The incubation is terminated by filtering the samples under vacuum through [Whatmam] *Whatman* GF/F filters with a wash of 5 ml buffer containing 10 µM of unlabeled 5-HT. The filters are placed in counting vitals and 4 ml of appropriate scintillation fluid (e.g. Picofluor ®15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 µM citalopram (Lu 10-171-B).

For determination of the inhibition of uptake five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve is drawn. The IC_{50}-value is determined as the concentration, at which the uptake is 50% of the total uptake in control samples minus the nonspecific binding and uptake in the presence of 10 µM of citalopram.

TABLE 1

PHARMACOLOGICAL TEST RESULTS

Compound	5-HTP pot. ED_{50} µmol/kg	5-HT uptake inhibition IC_{50} (nM)
(+)-citalopram	2.0	1.1
(−)-citalopram	120	150
(±)-citalopram	3.3	1 8

(+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ((+)-citalopram) and the non-toxic acid addition salts thereof may be administered to animals such as dogs, cats, horses, sheeps or the like, including human beings, both orally and parenterally, and may be used for example in the form of tablets, [capsles] *capsules*, powders, syrups or in the form of the usual [sterial] *sterile* solutions for injection. [Results upon administration to human being have been very gratifying.]

Most conveniently the compounds of Formula I are administered orally in unit dosage form such as tablets or capsules, each dosage unit containing the free amine or a non-toxic acid addition salt of one of the said compounds in [a] *an* amount of from about 0.10 to about 100 mg; most preferably, however, from about b 5 to 50 mg, calculated as the free amine, the total daily dosage usually ranging from about 1.0 to about 500 mg. The exact individual dosages as well as daily dosages in a particular case will, of course, be determined according to established medical principles under the direction of a physician.

When preparing tablets, the [acitve] *active* ingredient is for the most part mixed with ordinary tablet adjuvants such as corn starch, potato starch, talcum, magnesium stearate, gelative, lactose, gums, or the like.

Typical examples of formulas for [composition] *compositions* containing (+)-citalopram in the form of an acid addition salt as the active ingredient, are as follows:

(1) Tablets containing 5 milligrams of (+)-citalopram calculated as the free base:	
Compound 20	5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg
(2) Tablets containing 50 milligrams of (+)-citalopram calculated as the free base:	
(+)-citalopram	50 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg
(3) Syrup containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water ad	1 ml
(4) Solution for injection containing per milliliter:	
(+)-citalopram	50 mg
Acetic acid	17.9 mg
Sterile water ad	1 ml
(5) Solution for injection containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water ad	1 ml

Any other pharmaceutical tableting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, analgesics or antidepressants.

Also combinations of (+)-citalopram as well as its non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgetics or the like, fall within the scope of the present invention.

As previously stated, when isolating the enantiomers of citalopram in the form of an acid addition salt the acid is preferably selected so as to contain an anion which is non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates, phosphates, nitrates, methanesulphonates, ethane-sulphonates, lactates, citrates, tartrates or bitartrates, pamoates and maleates of the amines of Formula I. Other acids are likewise suitable and may be employed if desired. For example: fumaric, benzoic, ascorbic, succinic, salicylic, bismethylenesalicylic, propionic, gluconic, malic, malonic, mandelic, [cannamic] *cinnamic*, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphonic, and sulphamic acids may [be] also be employed as acid addition salt-forming acids.

When it is desired to isolate a compound of the invention in the form of the free base, this may be done according to conventional procedure as by dissolving the isolated or unisolated salt in water, treating with a suitable alkaline material, extracting the liberated free base with a suitable organic [solvent] *solvent*, drying the extract and evaporating to dryness or fractionally distilling to effect isolation of the free basic amine.

The invention also comprises a method for the alleviation, palliation, mitigation or inhibition of the manifestations of certain physiological-psychological [abnormalies] *abnormalities* of animals, especially depressions, by administering to a living animal body, including human beings, an adequate quantity of (+)-citalopram or a non-toxic acid addition salt thereof. An adequate quantity would be from about 0.001 mg to about 10 mg per kg of body weight in each unit dosage, and from about 0.003 milligrams to about 7 milligrams/kg of body weight per day.

It is to be understood that the invention is not limited to the exact details of operation or exact [compound] *compounds* or compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

We claim:

1. A compound selected from substantially pure (+)-1-(3-Dimethylaminopropyl)-1-(4'- fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof.

2. A compound of claim 1 being *the* pamoic acid salt of substantially pure (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

3. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, a compound as defined in claim 1.

4. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, the compound of claim 2.

5. A pharmaceutical composition in unit dosage form, according to claim 3, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

6. A pharmaceutical composition in unit dosage form, according to claim 4, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

7. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 1 which is effective for said purpose.

8. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 2 which is effective for said purpose.

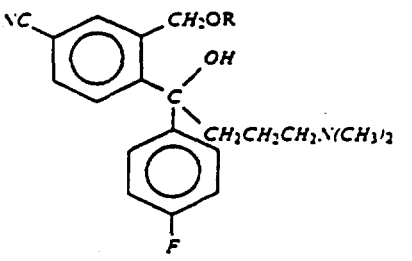
9. Method of claim [10] *7* wherein the compound is administered in the form of a pharmaceutical composition thereof.

10. Method of claim 8 wherein the compound is administered in the form of a pharmaceutical composition thereof.

11. A method for the preparation of a compound as defined in claim 1, which comprises, converting substantially, pure [(+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile] (−)-*4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-*hydroxy-*1-butyl]-3-(hydroxymethyl)-benzonitrile* or a [monomester] *monoester* thereof in a stereoselective way to substantially pure (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof.

12. A compound of the formula *(31)-Enantiomer of the compound 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-*

1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile or an ester of said (−)enantiomer, which has the formula



wherein R is hydrogen or represents a group completing a labile ester.

* * * * *

United States Patent [19]

Bogeso

[11] **Patent Number: 4,650,884**

[45] **Date of Patent: Mar. 17, 1987**

[54] **NOVEL INTERMEDIATE AND METHOD FOR ITS PREPARATION**

[75] Inventor: **Klaus P. Bogeso, Lyngby, Denmark**

[73] Assignee: **H. Lundbeck A/S, Copenhagen-Valby, Denmark**

[21] Appl. No.: **761,774**

[22] Filed: **Aug. 2, 1985**

[30] **Foreign Application Priority Data**

Aug. 6, 1984 [GB] United Kingdom 8419963

[51] Int. Cl.[4] C07D 307/87; C07C 121/80

[52] U.S. Cl. 549/467; 558/422

[58] Field of Search ..... 260/465 E; 549/467; 558/422

[56] **References Cited**

U.S. PATENT DOCUMENTS

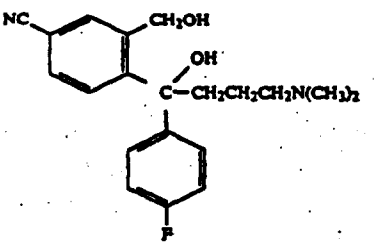
4,136,193 1/1979 Bogeso et al. 549/467

Primary Examiner—Dolph H. Torrence

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

The present invention relates to the novel compound of the following formula:



I

as well as acid addition salts thereof, a method for the preparation of the compound of Formula I, and to the use of said novel compound in the preparation of the known antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, or a pharmaceutically acceptable acid addition salt thereof.

3 Claims, No Drawings

NOVEL INTERMEDIATE AND METHOD FOR ITS PREPARATION

BACKGROUND OF THE INVENTION

The preparation and properties of antidepressant substituted 1-dimethylaminopropyl-1-phenylphthalans (or 1-(3-dimethylaminopropyl)-1-phenyl-1,3-dihydroisobenzofurans) have been described in U.S. Pat. No. 4,136,193. The most interesting of these compounds contain a cyano-group, and one of these, 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, has shown great promise as a valuable antidepressant drug with few side effects.

It has been found, however, that the methods described in U.S. Pat. No. 4,136,193 for the preparation of this compound possess some problems in the scale-up to commercial production, and this has necessitated further research in an attempt to discover a shorter route to this compound and to avoid the risk involved in the metalation step used previously.

SUMMARY OF THE INVENTION

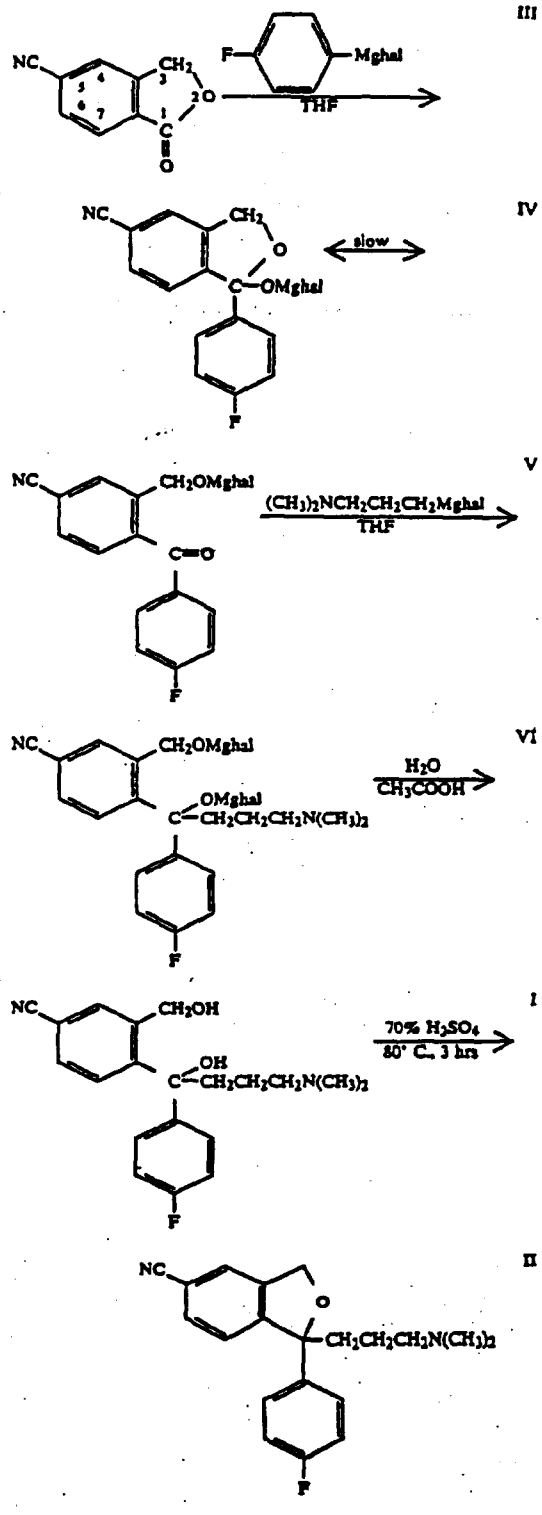
It is an established fact that the cyano-group of aromatic nitriles is very sensitive to attack by a number of organic as well as inorganic compounds (see for example "Methoden der Organischen Chemie", Houben-Weyl, Vol. 8, 345–51, 429, Georg-Thieme Verlag, Stuttgart (1952)).

For example, nitriles may be attacked by Grignard reagents to give ketimines which can be hydrolyzed to ketones. This method is a recommended standard method for preparation of ketones ("Methoden der Organischen Chemie", Houben-Weyl, Vol. 13/2a, 353–366, Georg-Thieme Verlag, Stuttgart (1973)). Actually, advantage of this invention has already been taken (as mentioned in U.S. Pat. No. 4,136,193) with molecules closely related to those of the present invention.

It is also wellknown that treatment of nitriles with strong acids such as high-percentage sulfuric acid normally will hydrolyze the nitrile-group to a carboxylic acid amide or a carboxylic acid.

The most useful method of preparation described in U.S. Pat. No. 4,136,193 involves Grignard reactions as well as treatment with strong acid, but the nitrile group was always introduced subsequent to such steps because of the known reactivity of the nitrile group described above. Typically, the cyano-group was introduced by reaction of a halogen substituted phthalane (as for example 1-(4'-fluorophenyl)-5-bromophthalane) with cuprous cyanide in DMF to yield a cyano-phthalane (as for example 1-(4'-fluorophenyl)-5-phthalanecarbonitrile) which was metalated and then alkylated through reaction with 3-dimethylaminopropyl chloride to yield the desired 1-(3-dimethylaminopropyl)-1-phenylphthalan, especially 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-5-phthalancarbonitrile.

According to the method of the present invention it has now surprisingly been found that cyano-substituted compounds can be prepared in good yields by the following route:



The compound of Formula II is the wellknown antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

The 5-cyanophthalide (Formula III) used as a starting material is a known compound (Tirouflet, J.; Bull.Soc.-Sci.Bretagne 26, 35, (1951).

In the formulas IV, V and VI "hal" means halogen, preferably chlorine or bromine. It is, indeed, surprising that only modest amounts of biproducts are formed by reaction of the cyano-group with the two Grignard-reagents involved. Of similar great importance to the success of this scheme is the surprisingly low rate of ring opening of the addition product formed in the first Grignard step (Formula IV). Actually, it is very convenient from a practical point of view to be able to run these two Grignard reactions in succession in the same vessel.

The novel intermediate (of Formula I) produced in the combined Grignard steps may be isolated and purified as described below. However, it is far more convenient to proceed with the ring closure of the crude material.

The cyano-group also shows a surprising resistance to the rather drastic and prolonged treatment with strong acid in the step of ring closure.

With careful control of the reaction conditions involved this process has already been shown to be very reliable on a technical scale as evidenced by smooth performance, stable yields and high purity of the final product (Formula II) produced.

The following examples are given by way of illustration only and are not to be construed as limiting:

EXAMPLE 1

4-[4-(Dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile

A Grignard solution is prepared by addition of 1-bromo-4-fluorobenzene (594 g, 3.4 mole) in dry tetrahydrofuran (1.6 liters) to a suspension of magnesium turnings (101 g, 4.15 mole) in dry tetrahydrofuran (250 ml) at reflux. When all has been added the solution is left stirring for 30 minutes without cooling or heating, and is then filtered to remove excess magnesium turnings. The Grignard solution is added to a nitrogen purged slurry of 5-cyanophthalide (450 g, 2.83 mole) in dry tetrahydrofuran (2.9 liters) in the course of 3 hours. The temperature is kept at 0°–3° C. during the addition after which the reaction mixture is stirred for 30 min. without cooling and then left standing overnight.

The same day a second Grignard solution is prepared from 3-dimethylaminopropyl chloride (342 g, 2.81 mol) and magnesium turnings (81 g, 3.3 mol) in dry tetrahydrofuran (1.15 liters). Next day the filtered solution of 3-dimethylaminopropylmagnesium chloride is added in the course of 6 hours to the reaction mixture obtained in the first Grignard reaction. The temperature is kept at 10°–12° C. during the addition whereupon the mixture is stirred for 30 minutes without cooling, and is then left overnight at room temperature without stirring. The reaction mixture is poured into icewater (2 kg ice, 3 liters water) whereupon acetic acid (700 ml, 80% by weight) is added, resulting in a final pH of 6.5–7.0 in the solution. Tetrahydrofuran is then distilled until a maximum pot temperature of 50° C. at 60 mm Hg is reached, whereupon toluene (4.5 liters) is added to the mixture. Aqueous ammonia (300 ml, 25% by weight) is then added to give a final pH of 9 in the water layer, the temperature is adjusted to 45°–50° C., and the mixture is stirred for 15 minutes. The toluene layer is separated, and the aqueous layer is extracted once with toluene (600 ml). The combined toluene extracts are washed with warm (50° C.) water (600 ml) and are then extracted with dilute acetic acid (2.5 liters water and 800 ml acetic acid, 80% by weight). The acetic extract is separated and combined with toluene (3.8 liters), whereupon aqueous ammonia (900 ml, 25% by weight) is added to give a final pH of 9 or higher in the water layer. The toluene phase is separated, and the water layer is extracted once with toluene (600 ml), whereupon the combined toluene extracts are washed four times with warm (50° C.) water (4×1 liter). This toluene solution is normally used directly in the next step.

If desired, the title compound can be isolated and purified in the following manner:

The warm toluene solution from above is stirred for 30 min. at 60° C. with charcoal (50 g) and silica gel (150 g, Merck Darmstadt No. 7734) and then filtered by suction on a filter pretreated with filter aid. This treatment is repeated with charcoal (25 g) and silica gel (90 g). After filtration the toluene is removed at reduced pressure (20 mm Hg) to a maximum of 60° C. The resulting oil (640 g) is dissolved in boiling diethyl ether (1500 ml) and this solution is stirred vigorously with water (1500 ml) while adding 47% aqueous hydrogen bromide (190 ml) during 10 min. at 27°–34° C. Diethyl ether is then distilled at reduced pressure at 33°–35° C. Additional water (500 ml) is added, and the mixture is cooled to 11° C. After 18 hours the crystals are collected on a suction filter. The wet cake is recrystallized from water (1500 ml) with the use of charcoal (37 g) and then dried for 23 hours in a vacuum oven at 50° C. and 220 mm Hg. Yield: 525 g of solid material which is purified further from a hot mixture of 2-propanol (9.5 liters) and ethanol (2.73 liters) with the use of charcoal (82 g) and silica gel (191 g) after which the filtrate is mixed with hexane (2 liters) and then cooled to 12° C. The crystals are isolated by suction and then dried in vacuum (200 mm Hg) at room temperature.

Yield of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile, hydrobromide: 425 g. MP 205°–206° C.

Elemental analysis ($C_{20}H_{23}FN_2O_2HBr$):

	Found	Calculated
% C	56.21	56.74
% H	5.69	5.73
% N	6.33	6.61
% Br	18.86	18.87

^{1}H-NMR (DMSO-d_6, Me_4Si as internal reference standard): 1.1–1.9 ppm (m, 2H, —CH_2—CH_2—$CH_2N<$), 2.1–2,45 ppm (broad t, 2H, >$\overline{CO}$H—CH_2—CH_2—), 2.6–2.8 ppm (s, 6H, —$N(CH_3)_2$), 2.85–3.2 ppm (broad t, 2H, —$CH_2N<$), 3.85–4.75 ppm (broad q, 2H, —CH_2OH), 5.0–5.4 ppm (broad s, 1H, —OH), 5.8–6.2 ppm (broad s, 1H, —OH), 6.95–7.5 ppm (m, 4H, aromatic), 7.7–8.0 ppm (m, 3H, aromatic), 9.0–9.75 (broad s, 1H,

HPLC-analysis (Spherisorb S 5 W; Mobile phase: Heptane-propanol-2-aqueous ammonia-H_2O,

85:15:0.4:0.2, UV_{254} detector) showed a content of 99.6% of the title compound.

EXAMPLE 2

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide

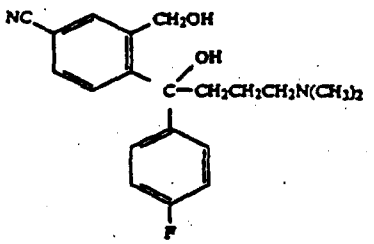
The toluene solution containing the crude product mentioned in Example 1 is heated to 50° C., and 70% sulfuric acid (made from 321 g of 96% sulfuric acid and 119 g ice) is added while stirring. The mixture is heated to 80° C. and kept at this temperature for 3 hours, whereupon it is cooled to about 30° C. Cold water (600 ml) and aqueous ammonia (600 ml, 25% by weight) are then added, and the mixture (pH 10) is stirred at 50°–60° C. for 15 minutes. The water phase is discarded, and the toluene layer is washed 5 times with warm water (5×1 liter). The organic phase is dried over anhydrous sodium sulfate, filtered and stirred for 1 hour with silica gel (375 g). The mixture is filtered by gravity on a filter precharged with silica gel (188 g). The filter is rinsed with toluene (3.4 liters) and the combined filtrates are evaporated under reduced pressure (30 mm Hg) until a maximum temperature of 50° C. is reached. The residue is then dissolved in acetone (2 liters) and filtered with charcoal. The filtrate is cooled to 20° C. Gaseous hydrogen bromide (130–140 g) is then introduced during 2 hours at 20°–25° C. until pH is 3, and pH is then adjusted to 7 by adding some of the acetone solution of the title compound. The mixture is left crystallizing overnight whereupon the crystals are filtered and washed with hexane (750 ml) and then with acetone (750 ml). After drying at 45° C. a yield of 610–650 g crude title compound is obtained. This material is dissolved in water (1.8 liters) at about 55° C. and is then filtered with charcoal, cooled to 20° C. and left overnight for crystallization after addition of seed crystals. The crystals are filtered, washed with water (350 ml) and dried. Yield: 560–570 g.

The crystals from the 1st recrystallization are dissolved in a mixture of methanol (1.7 liters) and 2-propanol (3.4 liters) at 70° C., and are then filtered with charcoal, cooled to 20° C. and left for crystallization overnight. The crystals are filtered and washed with a mixture of methanol (150 ml) and 2-propanol (300 ml). After drying there is obtained 510–520 g of purified material.

The material from the 2nd recrystallization is dissolved in a mixture of methanol (510 ml) and acetone (2.04 liters) at 55° C. and is then filtered with charcoal. The filtrate is cooled to 20° C., and after addition of seed crystals hexane (4.1 liters) is slowly added during 1 hour. After crystallization overnight the crystals are filtered and washed first with a mixture of acetone (150 ml) and hexane (300 ml), and then washed two times with hexane (2×300 ml). After drying there is obtained 470–480 g of pure (1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, hydrobromide, MP 185°–186° C.

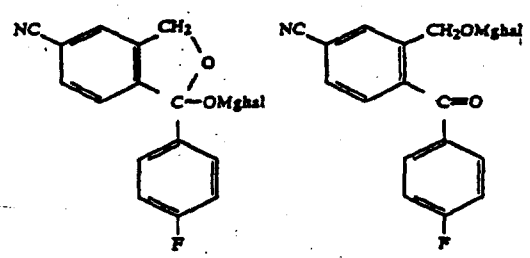
I claim:

1. A compound of the following formula:



or an acid addition salt thereof.

2. A method for the preparation of a compound of claim 1, characterized thereby that 5-cyanophthalide is reacted with a Grignard solution containing a 4-fluorophenyl magnesium halide, whereupon the resulting mixture containing the compounds of the following structures in equilibrium



is reacted with a Grignard solution containing a 3-dimethylaminopropyl magnesium halide, the reaction mixture hydrolyzed and the resulting 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile isolated as the free base, or an acid addition salt thereof.

3. In a method for the preparation of the compound 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, or a pharmaceutically-acceptable acid addition salt thereof, the step of effecting ring-closure by dehydration of a compound of claim 1 by reacting the same with strong sulfuric acid.

* * * * *

EXCLUSIVITY SUMMARY for NDA # 21-046 SUPPL # _____

Trade Name Celexa Generic Name citalopram HBr 10 mg/5 ml oral solution
Applicant Name Forest Pharmaceuticals HFD-120
Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /__/ NO /_X__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   Bioavailability study to establish bioequivalence between the oral solution to the approved immediate release tablet formulation.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X__/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

THREE YEARS

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-822 Celexa (citalopram HBr) 20, and 40 mg Tablets

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An

active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /X___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

Efficacy has already been established using the immediate release formulation. This NDA is a vehicle to solely obtain a liquid formulation on the market place.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug

product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

© If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #_____

Investigation #2, Study #_____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of

a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study #_____

Investigation #_, Study #_____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily,

substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #_____ YES /__/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # ___ YES /__/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
N/A

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____ _____

Signature of preparer Date

Title:_____

_____ _____

Signature of Division Director Date

cc:
Archival NDA 21-046
HFD-120/Division File
HFD-120/PDavid
HFD-92/Mary Ann Holovac

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98

DEBARMENT CERTIFICATION

DEBARMENT CERTIFICATION

In compliance with Section 306(k) of the Federal Food, Drug and Cosmetic Act, we hereby certify that Forest Laboratories, Inc. did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act in connection with this application (NDA #21-046) for Celexa™ (citalopram hydrobromide) Oral Solution.

FOREST LABORATORIES, INC.

Kathryn Bishburg

Kathryn Bishburg, Pharm.D.
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 021046

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter	X			
Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)				X
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative/ Correspondence Document(s)	X			

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DAVID

Food and Drug Administration
Rockville MD 20857

NDA 21-046

Forest Laboratories, Inc.
Attention: Keith Rotenberg, Ph.D.
Executive Director, Regulatory Affairs
909 Third Avenue
New York, New York 10022-4731

NOV 13 1998

Dear Dr. Rotenberg:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Celexa (citalopram Hydrobromide) 10 mg/5 ml Oral Solution

Therapeutic Classification: Standard

Date of Application: October 30, 1998

Date of Receipt: November 2, 1998

Our Reference Number: 21-046

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 1, 1999, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

/S/

11/12/98

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DAVID

Food and Drug Administration
Rockville MD 20857

NDA 21-046

Forest Laboratories Inc.
Attention: Keith S. Rotenberg, Ph.D.
Executive Director, Regulatory Affairs and Quality Operations
909 Third Avenue
New York, New York 10022-4731

MAR 22 1999

Dear Dr. Rotenberg:

Please refer to your pending October 30, 1999 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celexa (citalopram hydrobromide) 10mg/5mL oral solution.

We have completed our review of the microbiology sections of your submission and have the following comments and information requests:

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Paul David, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/ 3/22/99

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-046
HFD-120/Div. Files
HFD-120/P.David
HFD-120/L.Rocca
HFD-120/R.Seevers
HFD-805/B.Uratani

DISTRICT OFFICE

Drafted by: LR/March 22, 1999
Initialed by:
final:
filename: c:\LR\Nda\Nda21046\MICRO2.WPD

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-046

NOV - 8 1999

DAVID

Forest Laboratories Inc.
Attention: Keith Rotenberg, Ph.D.
Director, Drug Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 073115

Dear Dr. Rotenberg:

We acknowledge receipt on November 1, 1999 of your October 29, 1999 resubmission to your new drug application (NDA) for Celexa (citalopram hydrobromide) 10 mg/5 ml oral solution.

This resubmission contains additional chemistry, manufacturing, and controls (CMC) and labeling information submitted in response to our September 2, 1999 action letter.

We consider this a complete, class 1 response to our September 2, 1999 action letter. Therefore, the primary user fee goal date is January 1, 2000 and the secondary user fee goal date is March 1, 2000.

If you have any questions, please contact Mr. Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

/S/ 11/8/99

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