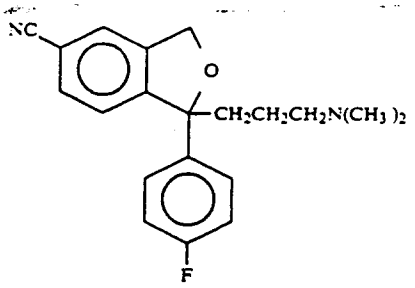
PHARMACEUTICALLY USEFUL (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-FLUOROPHENYL)-1,3-DIHYDROISO BENZOFURAN-5-CARBONITRILE AND NON-TOXIC ACID ADDITION SALTS THEREOF

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.

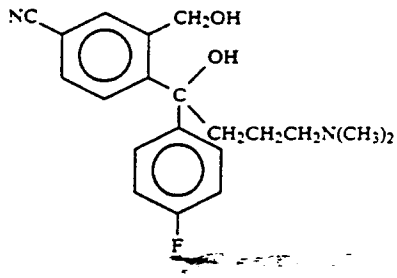
The invention is also concerned with a method to resolve the intermediate racemate and to produce the individual isomers of I therefrom.

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.

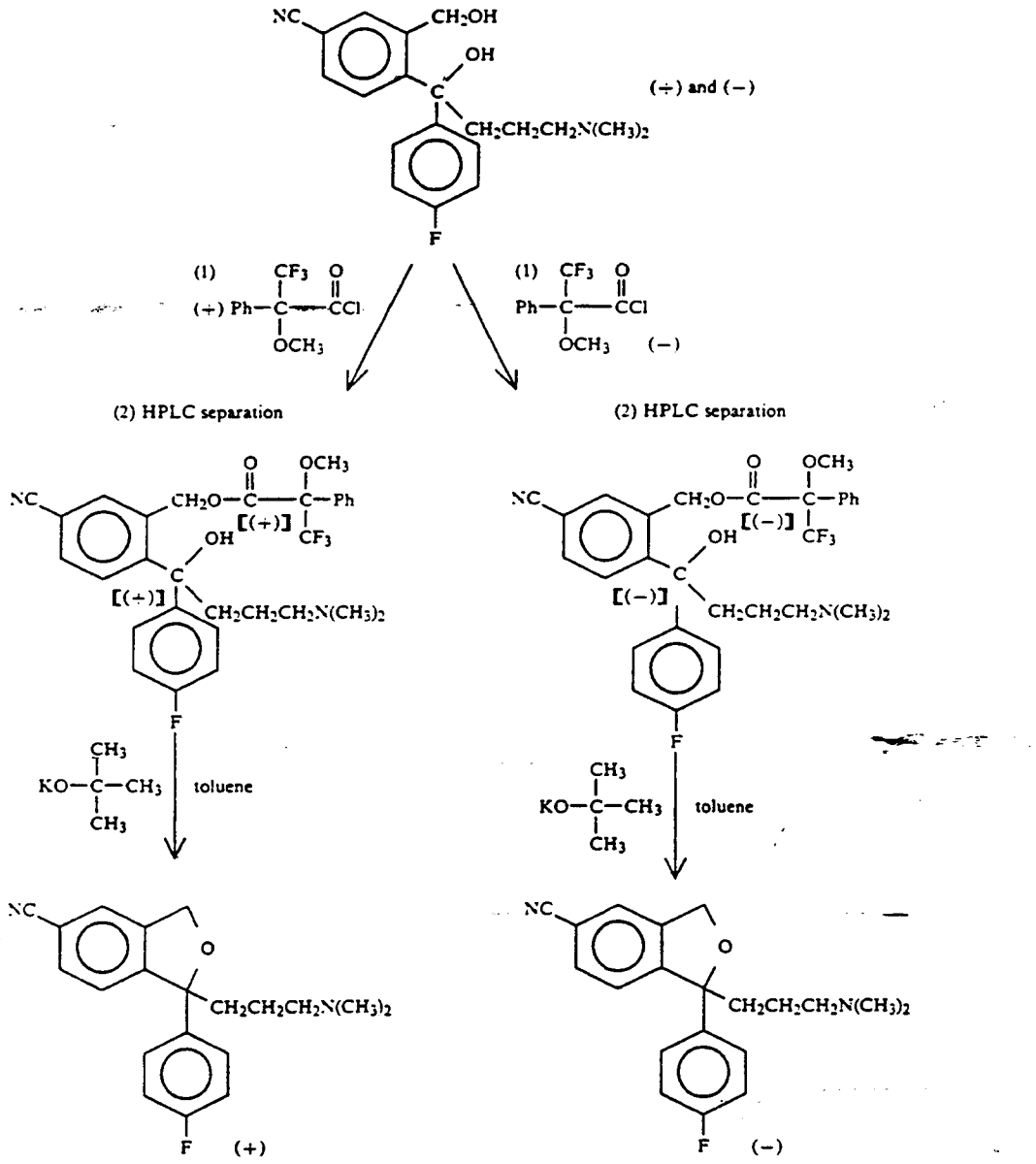
According to the invention, II is reacted with:

(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).

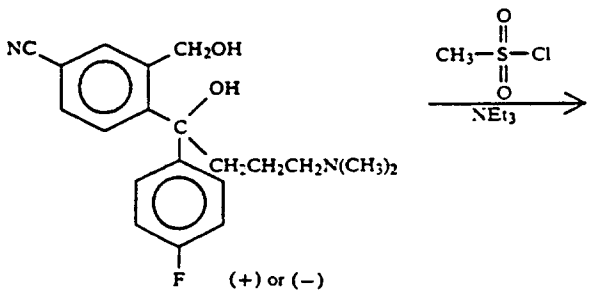
REACTION SCHEME II

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:



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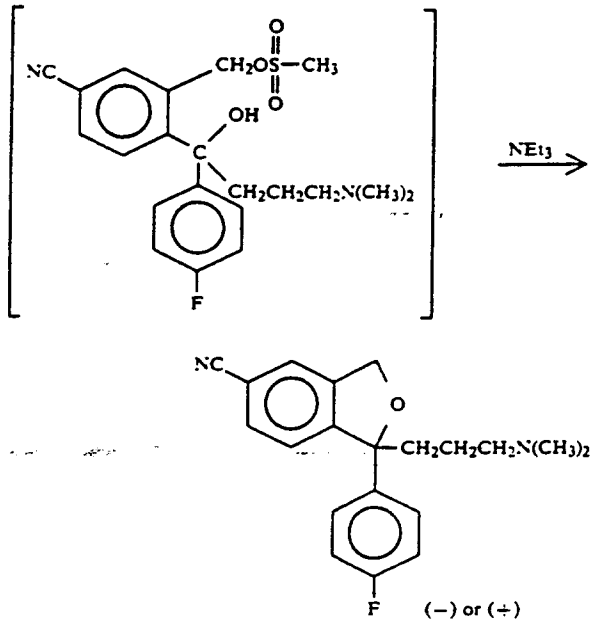
REACTION SCHEME II



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.

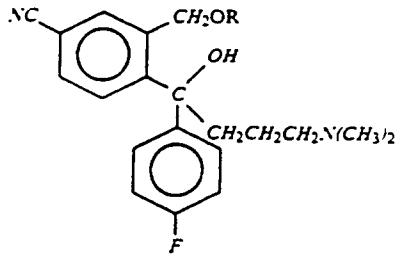
9. Method of claim [10] 7 wherein the compound is administered in the form of a pharmaceutical composition thereof.

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.

* * * * *

EXCLUSIVITY STATEMENT

Forest Laboratories, Inc. is claiming five (5) year period of marketing exclusivity for Citalopram Hydrobromide Tablets in accord with 21 CFR § 314.108(b)(2). To the best of our knowledge the active ingredient, Citalopram Hydrobromide (including any ester, salt or other noncovalent derivative of the molecule, responsible for the physiological or pharmacological action of the drug substance)has not been approved in any other New Drug Application in the United States.

Foma Rashkovsky
Acting Director, Regulatory Affairs
Forest Laboratories, Inc.

Date: May 7, 1997

FAX: (212) 750-9152
DIRECT LINE:

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 #20-822) for Citalpram Hydrobromide Tablets.

FOREST LABORATORIES, INC.

Executive Director Clinical Research
Warren Stern, Ph.D.

Consult #923
A
B

MEMORANDUM

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

DELIVERED JAN 14 1998

DATE: January 12, 1998

FROM: Paul Leber, M.D. /S/ 1/13/98
Director, Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Mr. John Grace, R.Ph.
Chair, Labeling and Nomenclature Committee, (HFD-600) MPN II

Proposed Trademark: Celexa™ (primary choice)
Selectin™ (secondary choice); NDA 20-822

Established name: citalopram HBr 10 mg, 20 mg, 40 mg, and 60 mg tablets

Indication and Use: Treatment of depression

Pharmacological Class: Selective Serotonin Reuptake Inhibitor

Initial comments from the submitter: The Division believes that the proposed tradenames are acceptable. Please note that the sponsor submitted the tradename Anspire™ in correspondence dated December 1, 1997 (consult to LNC dated December 5, 1997). The sponsor is now formally withdrawing the tradeneme of Anspire™. Please attempt to review the sponsor's proposed tradenames at your next LNC meeting (scheduled for January 27, 1998).

PM Contact: Paul David, R.Ph.; 594-5530

cc:
NDA 20-822 /S/ 1-13-98
HFD-120/Div File /S/ 1/14/98
HFD-120/PLeber/TLaughren/SMalchan/GDubitsky
HFD-120/MGuzewska/WRzeszotarski/PDavid /S/ 1/12/98
Doc #CITALOPR\NOMEN3.REQ

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

January 7, 1998

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

APPEARS THIS WAY
ON ORIGINAL

Re: **NDA#20-822 - Request for Tradename**
Product: **Citalopram Hydrobromide Tablets (10mg, 20mg, 40mg and 60 mg)**

Dear Dr. Leber:

Reference is made to the December 1, 1997 submission proposing Anspire™ as the proprietary name for Citalopram HBr.

Forest hereby withdraws the name We propose Celexa™ as the first choice and Selectin™ as the second choice for proposed proprietary names for Citalopram HBr. We request these names be sent to the Labeling and Nomenclature Committee for evaluation at their January meeting to replace Anspire.

Thank you for your consideration of this matter.

Sincerely,

Kathryn Bishburg

APPEARS THIS WAY
ON ORIGINAL

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

CONSULT # 923

LNC TRADEMARK REVIEW

TO: HFD-120

ATTN: Paul Leber, MD
Paul David, R.Ph.

PROPOSED NAME(S): CELEXA
SELECTIN

ESTABLISHED NAME: citalopram hydrobromide tablets

COMMITTEE'S COMMENTS:

A review revealed one name which significantly sounds like or looks like the proposed names: Skelaxin (metaxalone tablets by Carnick). Therefore, the Committee finds the proposed name misleading as defined in 21 CFR 201.10(c)(5).

For the reason stated, the Committee finds the proposed name unacceptable.

/S/ 3/1/98
Dán Boring, Ph.D., Chairman
Labeling and Nomenclature Committee

(876)

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

SEP 15 1997

DATE: September 16, 1997

FROM: Paul Leber, M.D. 9/15/97
Director, Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Mr. Dan Boring, R.Ph., PH.D.
Chair, Labeling and Nomenclature Committee, (HFD-600) MPN II

Proposed Trademark: Sertin™; NDA 20-822

Established name: citalopram HBr 10 mg, 20 mg, 40 mg, and 60 mg tablets

Indication and Use: Treatment of depression

Pharmacological Class: Selective Serotonin Reuptake Inhibitor

Initial comments from the submitter: The Division does not have any concerns or observations with the proposed Trademark.

PM Contact: Paul David, R.Ph.; 594-5530

cc:
NDA 20-822
HFD-120/Div File /S/ 9-15-97
HFD-120/PLeber/TLaughren/SMolchan/GDubitsky
HFD-120/MGuzewska/WRzeszotarski/PDavid
Doc #CITALOPR\NOMEN.REQ /S/ 9-15-97

Consult #876 (HFD-120)

SERTIN citalopram HBr tablets

There were two look-alike/sound-alike conflicts noted with the proposed proprietary name: SERTINA and SERUTAN. SERTINA is a antihypertensive and SERUTAN is an OTC laxative. The committee believes there is high potential for confusion with SERTINA. Additionally, the Committee feels the name is misleadingly promotional in conveying the impression of a "certain" cure when using this medication.

Overall, the committee finds the proposed name unacceptable.

/S/ 1/28/98, Chair
CDER Labeling and Nomenclature Committee

David

NDA 20-822

MAY 20 1997

Forest Laboratories, Inc.
Attention: Kathryn Bishburg, Pharm.D.
Associate Director, Regulatory Affairs
909 Third Avenue
New York, New York 10022-4731

Dear Dr. Bishburg:

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: Citalopram Hydrobromide 10 mg, 20 mg, 40 mg, and 60 mg Tablets

Therapeutic Classification: Standard

Date of Application: May 7, 1997

Date of Receipt: May 12, 1997

Our Reference Number: 20-822

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 July 12, 1997 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Paul David, R.Ph., 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,

APPEARS THIS WAY ON ORIGINAL

/S/ 5/19/97

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

cc:
Original NDA 20-822
HFD-120/Div. Files /S/ 5-16-97 /S/ 5-16-97
HFD-120/P.David
HFD-120/PLeber/TLaughren/GDubitsky/SMolchan
DISTRICT OFFICE

May 16, 1997/

ACKNOWLEDGMENT (AC)

MEMORANDUM OF TELECON

NDA/IND:	N 20-822
DATE:	08-DEC-97
PRODUCT NAME:	Citalopram Hydrobromide Tablets
FIRM NAME:	Forest Laboratories
Conversation with:	Ms Kathryn Bishburg
Telephone #:	(212) 224-6820

(BACKGROUND):

. The sponsor committed themselves to amend the application by providing the additional 12 and 18 month stability data before the end of the review process.

****

I have called Ms Bishburg to remind her that I am about to complete my review of the NDA and that the only thing missing is the promised additional stability data. Ms Bishburg said that she just received the package of 12 months real time stability and will send it to me bu the end of the week.

****

/S/
/S/
W. Janusz Rzeszotarski, Ph.D

Init: MEG
cc: MEGuzewska 12.8.97
PDavid

filename: N020822.T01

David

COPY

FILED NOV 07 1997

MEMORANDUM

DATE: November 6, 1997

NDA #: 20-822

APPEARS THIS WAY
ON ORIGINAL

DRUG NAME: Citalopram

SPONSOR: Forest Laboratories

SUBJECT: Internal consult from HFD-730 (Division of Pharmacovigilance and Epidemiology) on adverse events following citalopram use reported to the WHO Center for International Drug Monitoring

A memo dated October 27, 1997 was sent from Harold Davis, M.D., Medical Officer, Epidemiology Branch through Robert O'Neill, Ph.D., Acting Director, Division of Pharmacovigilance and Epidemiology, responding to Dr. Dubitsky's request for adverse event information from the WHO Center for International Drug Monitoring.

The information was reviewed and incorporated into the appropriate sections of the safety review for the NDA. The information was similar to that from the sponsor's post-marketing spontaneous reporting system. The only additional information added to the review were 3 birth defect cases (to section 8.1.11 in the safety review). These were single cases, and the defects were different from those reported previously.

/S/

APPEARS THIS WAY
ON ORIGINAL

Susan Molchan, M.D.

11-7-97

/S/

cc:
HFD-120/S. Molchan
G. Dubitsky
T. Laughren
P. David

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: October 28, 1997

APPLICATION NUMBER: NDA 20-822

DRUG NAME: Sertin (citalopram HBr)

BETWEEN:

Name: Kathryn Bishburg, Pharm.D.
Phone: (212) 224-6820
Representing: Forest Pharmaceuticals

AND /S/

Name: Paul David
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Results of the Labeling and Nomenclature Committee (LNC) review of proposed tradename

At the request of Dr. Laughren, I contacted Dr. Bishburg and informed her that the LNC found their proposed tradename of Sertin unacceptable for the following reasons:

> The LNC noted two look-alike/sound-alike conflicts with the proposed proprietary name: SERTINA and SERUTAN. SERUTAN is an OTC laxative and ~~is~~ ~~not~~ likely to be confused, however, SERTINA is a Rx product containing reserpine and has some potential for confusion. The name has a significant potential for promotional misuse since it is a homonym for "certain". The LNC understands that citalopram HBr is a serotonin re-uptake inhibitor and the name is derived from serotonin. However the Committee feels it is misleadingly close to "certain" and will be used inappropriately in advertising.

Dr. Bishburg acknowledged understanding of the above, and stated that she would take the message back to their marketing group.

cc:
NDA 20-822
HFD-120/Div file
HFD-120/PLeber/TLaughren/GDubitsky/SMolchan
HFD-120/PDavid

TELECON

Dubitsky HFD-120

ANSWERED OCT 3 1 1997

MEMORANDUM

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

Date: October 27, 1997

From: Harold Davis, M.D., Medical Officer, Epidemiology Branch, HFD-733

Through: Robert O'Neill, Ph.D., Acting Director, Division of Pharmacovigilance and Epidemiology, HFD-730 for RONeill 10/27/97

Subject: Adverse events following use of citalopram reported to the World Health Organization Center for International Drug Monitoring

To: Paul Leber, M.D., Director, Division of Neuropharmacologic Drug Products, HFD-120

This is to respond to your request for data from the World Health Organization Collaborating Center for International Drug Monitoring on adverse events following use of citalopram. Citalopram is the subject of NDA 20-822.

Colleagues at the World Health Organization Center for International Drug Monitoring in Upsaala, Sweden were contacted and asked to search their data base for all adverse reactions reported following use of citalopram.

The results of the database search are presented in Tables 1 and 2. Table 1 presents the data sorted by number of reports. Table 2 presents the data sorted alphabetically.

There were 1,986 reactions reported following use of citalopram. The ten most common adverse reactions reported were nausea, diarrhoea, headache, dizziness, tremor, urticaria, anxiety, sweating increased, fatigue, and rash erythematous. Of note, there were 17 reports of "convulsions" and 15 reports of "convulsions grand mal".

If there are certain reactions for which you want to obtain individual case reports, it might be possible to do so.

/S/

Harold Davis, M.D.

Table 1. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, in descending frequency.

Rank	Adverse Reaction	No.
1	Nausea	115
2	Diarrhoea	68
3	Headache	52
4	Dizziness	47
5	Tremor	46
6	Urticaria	44
7	Anxiety	42
8	Sweating Increased	41
9	Fatigue	35
10	Rash Erythematous	35
11	Vomiting	35
12	Confusion	33
13	Paraesthesia	33
14	Pruritus	31
15	Hallucination	29
16	Hyponatraemia	28
17	Rash	27
18	Libido Decreased	26
19	Agitation	25
20	Abdominal Pain	24
21	Malaise	23
22	Mouth Dry	22
23	Muscle Contractions Involu	22
24	Depersonalization	20
25	Impotence	20
26	Convulsions	17
27	Dystonia	16
28	Extrapyramidal Disorder	16
29	Convulsions Grand Mal	15
30	Ejaculation Failure	15
31	Hepatic Enzymes Increased	15
32	Palpitation	15
33	Dyspepsia	14
34	Hypertonia	14
35	Oedema	14
36	Rash Maculo-papular	14
37	Somnolence	14
38	Suicide Attempt	14
39	Syncope	14
40	Fever	13
41	Insomnia	13
42	Micturition Disorder	13
43	Nervousness	13
44	Urinary Retention	13
45	Amnesia	12
46	Chest Pain	12
47	Manic Reaction	12
48	Paroniria	12
49	Aggressive Reaction	11
50	Arthralgia	11
51	Concentration Impaired	11
52	Hepatic Function Abnormal	11

Table 1, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, in descending frequency.

Rank	Adverse Reaction	No.
53	Tinnitus	11
54	Vision Abnormal	11
55	Dyspnoea	10
56	Lactation Nonpuerperal	10
57	Migraine	10
58	Myalgia	10
59	Sleep Disorder	10
60	Withdrawal Syndrome	10
61	Coughing	9
62	Death	9
63	Dysaesthesia	9
64	Hyperkinesia	9
65	Angioedema	8
66	Taste Perversion	8
67	Thrombocytopenia	8
68	Urinary Incontinence	8
69	Alopecia	7
70	Bilirubinaemia	7
71	Bradycardia	7
72	Dyskinesia	7
73	Euphoria	7
74	Hepatitis	7
75	Hypotension	7
76	Pain	7
77	Psychosis	7
78	Weight Increase	7
79	Ataxia	6
80	Coma	6
81	Depression	6
82	Ejaculation Disorder	6
83	Gamma-gt Increased	6
84	Haematoma	6
85	Hypertension	6
86	Hypoglycaemia	6
87	Prothrombin Increased	6
88	Purpura	6
89	Speech Disorder	6
90	Temperature Changed Sensat	6
91	Vertigo	6
92	Abortion	5
93	Anorgasmia	5
94	Aphasia	5
95	Asthenia	5
96	Conjunctivitis	5
97	Constipation	5
98	Convulsions Aggravated	5
99	Extrasystoles	5
100	Fall	5
101	Muscle Weakness	5
102	Phosphatase Alkaline Incre	5
103	Tachycardia	5
104	Accommodation Abnormal	4

Table 1, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, in descending frequency.

Rank	Adverse Reaction	No.
105	Anorexia	4
106	Choreoathetosis	4
107	Coordination Abnormal	4
108	Diplopia	4
109	Flushing	4
110	Hyperprolactinaemia	4
111	Leucopenia	4
112	Mydriasis	4
113	Myocardial Infarction	4
114	Photosensitivity Reaction	4
115	Sensory Disturbance	4
116	Siadh	4
117	Stomatitis	4
118	Sudden Death	4
119	Therapeutic Response Incre	4
120	Acne	3
121	Allergic Reaction	3
122	Amenorrhoea	3
123	Apathy	3
124	Appetite Increased	3
125	Dysphagia	3
126	Emotional Lability	3
127	Eosinophilia	3
128	Erythema Multiforme	3
129	Face Oedema	3
130	Flatulence	3
131	Granulocytopenia	3
132	Jaundice	3
133	Micturition Frequency	3
134	Neuroleptic Malignant Synd	3
135	Neuropathy	3
136	Oedema Peripheral	3
137	Rigors	3
138	Serotonin Syndrome	3
139	Sialoadenitis	3
140	Stupor	3
141	Thrombosis Cerebral	3
142	Torsade De Pointes	3
143	Weight Decrease	3
144	Alcohol Intolerance	2
145	Anaemia Aplastic	2
146	Back Pain	2
147	Cardiac Failure	2
148	Cerebral Haemorrhage	2
149	Cerebrovascular Disorder	2
150	Circulatory Failure	2
151	Condition Aggravated	2
152	Delirium	2
153	Diabetes Mellitus	2
154	Diabetes Mellitus Aggravat	2
155	Drug Level Increased	2
156	Dysuria	2

Table 1, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, in descending frequency.

Rank	Adverse Reaction	No.
157	Ecg Abnormal	2
158	Epidermal Necrolysis	2
159	Faecal Incontinence	2
160	Gait Abnormal	2
161	Glossitis	2
162	Gynaecomastia	2
163	Haemorrhage Nos	2
164	Hyperkalaemia	2
165	Hyperventilation	2
166	Hypoaesthesia	2
167	Hypotension Postural	2
168	Intermenstrual Bleeding	2
169	Menstrual Disorder	2
170	Migraine Aggravated	2
171	NPN Increased	2
172	Oedema Cerebral	2
173	Pancreatitis	2
174	Parosmia	2
175	Priapism	2
176	Prothrombin Decreased	2
177	Respiratory Depression Neo	2
178	Rhabdomyolysis	2
179	Rhinitis	2
180	Saliva Increased	2
181	Sexual Function Abnormal	2
182	Stomatitis Ulcerative	2
183	Taste Loss	2
184	Teeth-grinding	2
185	Therapeutic Response Decre	2
186	Throat Tightness	2
187	Thrombophlebitis Deep	2
188	Thrombosis	2
189	Vasculitis	2
190	Xerophthalmia	2
191	Yawning	2
192	Abscences	1
193	Agranulocytosis	1
194	Anaemia	1
195	Angina Pectoris	1
196	Antidiuretic Hormone Disorder	1
197	Anuria	1
198	Appendicitis	1
199	Arthrosis	1
200	Aspiration	1
201	Asthma	1
202	AV Block	1
203	Birth Premature	1
204	Breast Enlargement	1
205	Bronchitis	1
206	Bullous Eruption	1
207	Cardiac Arrest	1

Table 1, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, in descending frequency.

Rank	Adverse Reaction	No.
208	Cataract	1
209	Cleft Palate	1
210	Convulsions Local	1
211	Corneal Ulceration	1
212	Coronary Artery Disorder	1
213	Cranial Nerve Lesion	1
214	Creatine Phosphokinase Inc	1
215	Dehydration	1
216	Dreaming Abnormal	1
217	Drug - Food Interaction	1
218	Dyskinesia Tardive	1
219	Eczema	1
220	Embolism Pulmonary	1
221	Encephalopathy	1
222	Epididymitis	1
223	Epistaxis	1
224	Erythema Nodosum	1
225	Exophthalmos	1
226	Fibrillation Atrial	1
227	Fibrillation Ventricular	1
228	Gastroesophageal Reflux	1
229	Gi Haemorrhage	1
230	Glaucoma	1
231	Haematemesis	1
232	Haemoptysis	1
233	Hair Disorder Nos	1
234	Halitosis	1
235	Heart Malformation	1
236	Heat Rash	1
237	Hepatitis Cholestatic	1
238	Hernia Congenital	1
239	Hypercholesterolaemia	1
240	Hypernatraemia	1
241	Hypokalaemia	1
242	Hypokinesia	1
243	Hypothyroidism	1
244	Ileus	1
245	Influenza-like Symptoms	1
246	Ketosis	1
247	Libido Increased	1
248	Liver Fatty	1
249	Lymphadenopathy	1
250	Lymphocytosis	1
251	Lymphoma-like Disorder	1
252	Malformation Foot	1
253	Malformation Hand	1
254	Marrow Depression	1
255	Mastitis	1
256	Melaena	1
257	Meningomyelocele	1
258	Micturition Urgency	1
259	Myasthenia Gravis-like Syn	1

Table 1, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, in descending frequency.

Rank	Adverse Reaction	No.
260	Nephritis Interstitial	1
261	Nocturia	1
262	Nystagmus	1
263	Oedema Mouth	1
264	Oedema Periorbital	1
265	Oedema Pharynx	1
266	Pancytopenia	1
267	Parkinsonism Aggravated	1
268	Personality Disorder	1
269	Phlebitis Superficial	1
270	Photophobia	1
271	Pneumonia	1
272	Polydipsia	1
273	Polymyalgia Rheumatica	1
274	Polymyositis	1
275	Polyuria	1
276	Psoriasis	1
277	Pulmonary Eosinophilia	1
278	Pulmonary Infiltration	1
279	Pulmonary Oedema	1
280	Qt Prolonged	1
281	Rash Psoriaform	1
282	Renal Failure Acute	1
283	Renal Function Abnormal	1
284	Salivary Gland Enlargement	1
285	Sex Chromosome Disorder	1
286	Sgpt Increased	1
287	Spasm Generalized	1
288	Stevens Johnson Syndrome	1
289	Tenesmus	1
290	Thinking Abnormal	1
291	Thrombophlebitis	1
292	Tongue Oedema	1
293	Tooth Disorder	1
294	Transposition of Great Ves	1
295	Unexpected Therapeutic Eff	1
296	Urine Abnormal	1
297	Urticaria Acute	1
298	Vein Varicose	1
299	Ventricular Septal Defect	1
300	Visual Field Defect	1
Total Number Reported		1986

Table 2. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, alphabetically sorted.

Adverse Reaction	No.
Abdominal Pain	24
Abortion	5
Abscences	1
Accommodation Abnormal	4
Acne	3
Aggressive Reaction	11
Agitation	25
Agranulocytosis	1
Alcohol Intolerance	2
Allergic Reaction	3
Alopecia	7
Amenorrhoea	3
Amnesia	12
Anaemia	1
Anaemia Aplastic	2
Angina Pectoris	1
Angioedema	8
Anorexia	4
Anorgasmia	5
Antidiuretic Hormone Disorder	1
Anuria	1
Anxiety	42
Apathy	3
Aphasia	5
Appendicitis	1
Appetite Increased	3
Arthralgia	11
Arthrosis	1
Aspiration	1
Asthenia	5
Asthma	1
Ataxia	6
AV Block	1
Back Pain	2
Bilirubinaemia	7
Birth Premature	1
Bradycardia	7
Breast Enlargement	1
Bronchitis	1
Bullous Eruption	1
Cardiac Arrest	1
Cardiac Failure	2
Cataract	1
Cerebral Haemorrhage	2
Cerebrovascular Disorder	2
Chest Pain	12
Choreoathetosis	4
Circulatory Failure	2
Cleft Palate	1
Coma	6
Concentration Impaired	11

Table 2, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, alphabetically sorted.

Adverse Reaction	No.
Condition Aggravated	2
Confusion	33
Conjunctivitis	5
Constipation	5
Convulsions	17
Convulsions Aggravated	5
Convulsions Grand Mal	15
Convulsions Local	1
Coordination Abnormal	4
Corneal Ulceration	1
Coronary Artery Disorder	1
Coughing	9
Cranial Nerve Lesion	1
Creatine Phosphokinase Inc	1
Death	9
Dehydration	1
Delirium	2
Depersonalization	20
Depression	6
Diabetes Mellitus	2
Diabetes Mellitus Aggravat	2
Diarrhoea	68
Diplopia	4
Dizziness	47
Dreaming Abnormal	1
Drug - Food Interaction	1
Drug Level Increased	2
Dysaesthesia	9
Dyskinesia	7
Dyskinesia Tardive	1
Dyspepsia	14
Dysphagia	3
Dyspnoea	10
Dystonia	16
Dysuria	2
Ecg Abnormal	2
Eczema	1
Ejaculation Disorder	6
Ejaculation Failure	15
Embolism Pulmonary	1
Emotional Lability	3
Encephalopathy	1
Eosinophilia	3
Epidermal Necrolysis	2
Epididymitis	1
Epistaxis	1
Erythema Multiforme	3
Erythema Nodosum	1
Euphoria	7
Exophthalmos	1
Extrapyramidal Disorder	16

Table 2, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, alphabetically sorted.

Adverse Reaction	No.
Extrasystoles	5
Face Oedema	3
Faecal Incontinence	2
Fall	5
Fatigue	35
Fever	13
Fibrillation Atrial	1
Fibrillation Ventricular	1
Flatulence	3
Flushing	4
Gait Abnormal	2
Gamma-gt Increased	6
Gastroesophageal Reflux	1
Gi Haemorrhage	1
Glaucoma	1
Glossitis	2
Granulocytopenia	3
Gynaecomastia	2
Haematemesis	1
Haematoma	6
Haemoptysis	1
Haemorrhage Nos	2
Hair Disorder Nos	1
Halitosis	1
Hallucination	29
Headache	52
Heart Malformation	1
Heat Rash	1
Hepatic Enzymes Increased	15
Hepatic Function Abnormal	11
Hepatitis	7
Hepatitis Cholestatic	1
Hernia Congenital	1
Hypercholesterolaemia	1
Hyperkalaemia	2
Hyperkinesia	9
Hypernatraemia	1
Hyperprolactinaemia	4
Hypertension	6
Hypertonia	14
Hyperventilation	2
Hypoaesthesia	2
Hypoglycaemia	6
Hypokalaemia	1
Hypokinesia	1
Hyponatraemia	28
Hypotension	7
Hypotension Postural	2
Hypothyroidism	1
Ileus	1
Impotence	20
Influenza-like Symptoms	1

Table 2, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, alphabetically sorted.

Adverse Reaction	No.
Insomnia	13
Intermenstrual Bleeding	2
Jaundice	3
Ketosis	1
Lactation Nonpuerperal	10
Leucopenia	4
Libido Decreased	26
Libido Increased	1
Liver Fatty	1
Lymphadenopathy	1
Lymphocytosis	1
Lymphoma-like Disorder	1
Malaise	23
Malformation Foot	1
Malformation Hand	1
Manic Reaction	12
Marrow Depression	1
Mastitis	1
Melaena	1
Meningomyelocele	1
Menstrual Disorder	2
Micturition Disorder	13
Micturition Frequency	3
Micturition Urgency	1
Migraine	10
Migraine Aggravated	2
Mouth Dry	22
Muscle Contractions Involu	22
Muscle Weakness	5
Myalgia	10
Myasthenia Gravis-like Syn	1
Mydriasis	4
Myocardial Infarction	4
Nausea	115
Nephritis Interstitial	1
Nervousness	13
Neuroleptic Malignant Synd	3
Neuropathy	3
Nocturia	1
Npn Increased	2
Nystagmus	1
Oedema	14
Oedema Cerebral	2
Oedema Mouth	1
Oedema Periorbital	1
Oedema Peripheral	3
Oedema Pharynx	1
Pain	7
Palpitation	15
Pancreatitis	2
Pancytopenia	1
Paraesthesia	33

Table 2, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, alphabetically sorted.

Adverse Reaction	No.
Parkinsonism Aggravated	1
Paroniria	12
Parosmia	2
Personality Disorder	1
Phlebitis Superficial	1
Phosphatase Alkaline Incre	5
Photophobia	1
Photosensitivity Reaction	4
Pneumonia	1
Polydipsia	1
Polymyalgia Rheumatica	1
Polymyositis	1
Polyuria	1
Priapism	2
Prothrombin Decreased	2
Prothrombin Increased	6
Pruritus	31
Psoriasis	1
Psychosis	7
Pulmonary Eosinophilia	1
Pulmonary Infiltration	1
Pulmonary Oedema	1
Purpura	6
Qt Prolonged	1
Rash	27
Rash Erythematous	35
Rash Maculo-papular	14
Rash Psoriaform	1
Renal Failure Acute	1
Renal Function Abnormal	1
Respiratory Depression Neo	2
Rhabdomyolysis	2
Rhinitis	2
Rigors	3
Saliva Increased	2
Salivary Gland Enlargement	1
Sensory Disturbance	4
Serotonin Syndrome	3
Sex Chromosome Disorder	1
Sexual Function Abnormal	2
Sgpt Increased	1
Siadh	4
Sialoadenitis	3
Sleep Disorder	10
Somnolence	14
Spasm Generalized	1
Speech Disorder	6
Stevens Johnson Syndrome	1
Stomatitis	4
Stomatitis Ulcerative	2
Stupor	3
Sudden Death	4

Table 2, continued. Adverse reactions to citalopram reported to World Health Organization Collaborating Center for International Drug Monitoring as of September 1, 1997, alphabetically sorted.

Adverse Reaction	No.
Suicide Attempt	14
Sweating Increased	41
Syncope	14
Tachycardia	5
Taste Loss	2
Taste Perversion	8
Teeth-grinding	2
Temperature Changed Sensat	6
Tenesmus	1
Therapeutic Response Decre	2
Therapeutic Response Incre	4
Thinking Abnormal	1
Throat Tightness	2
Thrombocytopenia	8
Thrombophlebitis	1
Thrombophlebitis Deep	2
Thrombosis	2
Thrombosis Cerebral	3
Tinnitus	11
Tongue Oedema	1
Tooth Disorder	1
Torsade De Pointes	3
Transposition of Great Ves	1
Tremor	46
Unexpected Therapeutic Eff	1
Urinary Incontinence	8
Urinary Retention	13
Urine Abnormal	1
Urticaria	44
Urticaria Acute	1
Vasculitis	2
Vein Varicose	1
Ventricular Septal Defect	1
Vertigo	6
Vision Abnormal	11
Visual Field Defect	1
Vomiting	35
Weight Decrease	3
Weight Increase	7
Withdrawal Syndrome	10
Xerophthalmia	2
Yawning	2
Total Number Reported	1986

cc.
HFD-120 Burkhart/Dubitsky
HFD-730 O'Neill
HFD-733 Davis/Graham/Chron/Dru
HFD-735 Barash/Chen/Friedman

/S/ 10/20/17

Memorandum of Telephone Call

Date: October 20, 1997

NDA: 20-822

Firm: Forest Labs

Drug: Citalopram

Point of Contact: Kathryn Bishburg, Pharm.D.

Phone number: (212) 224-6866

In the ISS volume, p. 347, conflicting information is given on which studies the ECG data in Tables 8.1.6.5.1.2.1 and 8.1.6.5.2.1.1 represent. From the text, it's not clear if data from study 91203 is included, or just 85A, 86141, 89304, and 91206.

Similarly for the vital signs data, which studies are included in Tables 8.1.6.4.1.2.1 (means) and 8.1.6.4.2.1.1 (PCS incidence)?

I also asked for more detailed information on pregnancy exposure with citalopram. Specifically doses and times of exposure in relation to LMP of patients, along with outcomes. Any of this information that may be available on the 7 cases of fetal abnormalities documented was also specifically requested.

/S/

Susan Molchan, M.D.
Oct 20, 1997

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

MEMORANDUM OF TELECON

DATE: October 2, 1997

APPLICATION NUMBER: NDA 20-822

DRUG NAME: Sertin (citalopram HBr)

BETWEEN:

Name: Sheila Mahoney, Regulatory Affairs
Phone: (212) 421-7850
Fax: (212) 750-9152
Representing: Forest Pharmaceuticals

AND

Name: Paul David
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Additional Statistical Analyses

At the request of Dr. Laughren, I contacted Ms. Mahoney to inform her that the Agency was requesting additional statistical information pertaining to their pending NDA. The following requests were FAXED to the sponsor:

Please provide us with the following additional statistical analyses to assist us in evaluating the efficacy data relevant to the use of citalopram in the treatment of depression.

1) For each citalopram group completer in study 85A, please compute the mean dose of the final two weeks of treatment (weeks 3 and 4 combined) and provide us with a frequency distribution of these means, as shown below:

Number of patients					
Dose Interval (mg/day)	<20	20-40	41-60	61-80	>80

Also, to investigate the effect of dose on therapeutic response, please perform an analysis of covariance, with the week 3/4 mean dose as the covariate, for the mean change from baseline in HAM-D total score for study 85A completers.

2) For studies 85A and 91206, please perform an evaluation for any treatment-by-center interaction for each dose group versus placebo and provide us with the resulting p-values at the final study week. These analyses should be done using the LOCF mean change from baseline in HAM-D total score, based on the preferred LOCF methodology referenced in item #3 of your 8/14/97 submission.

3) Based on the LOCF mean change from baseline in HAM-D total score, please conduct formal statistical testing for an age-by-treatment interaction in study 85A. Also, in study 91206, kindly perform a similar analysis for each dose group, as well as for the pool of the four dose groups, to assess for an age-by-treatment, gender-by-treatment, and baseline

severity-by-treatment interaction. A similar analysis based on the pool of studies 85A and 91206 could also be done. Note that these should utilize the preferred LOCF methodology referred to under #2 above.

4) For study 91206, please perform an analysis of covariance of the mean change from baseline in HAM-D total score with serum citalopram concentration as the covariate. Again, the preferred LOCF methodology should be used. Please provide the resulting SAS printout.

Kindly provide a discussion and conclusions relevant to the above requested analyses.

Additionally, please either locate in the NDA or supply, if not provided in the NDA, the following items:

I. Additional analyses and graphs for the two long-term studies, similar to what were provided for studies 85A and 91206 both in the NDA (for example, starting from page 10-45775) and from your submission dated August 14, 1997.

II. Subgroup (Race, Gender, Age) and covariate (Baseline Severity, Use of Benzodiazepine, and other detectable covariates) analyses for primary efficacy variables at last visit, along with covariation p-values, interaction p-values, and descriptive statistics. These are to be done individually for studies 85A and 91206 and the two long-term studies, and also based on the pooled combinable well-controlled studies data base.

III. Comprehensive Tables, and 95% confidence intervals side-by-side, for the well-controlled studies (samples were previously faxed to you), for the primary efficacy variables at last visit. One Table is to be for scores and also changes from baseline, with the significant results being starred (*), and the other Table for all pair-wise comparison p-values.

IV. 95% confidence intervals for the difference between a dose (may be flexible) and placebo (with respect to change from baseline at last visit for primary efficacy variables) should be presented side-by-side, with the following ordering: overall, largest center, next largest center, etc. The total sample size should be provided (may be below the X-axis).

cc:
NDA 20-822
HFD-120/Div file
HFD-120/PLeber/TLaughren/GDubitsky
HFD-120/PDavid
HFD-713/TSahlroot/JChoudhury

TELECON

MEMORANDUM OF TELECON

DATE: October 2, 1997

APPLICATION NUMBER: NDA 20-822

DRUG NAME: Sertin (citalopram HBr)

BETWEEN:

Name: Sheila Mahoney, Regulatory Affairs
Phone: (212) 421-7850
Fax: (212) 750-9152
Representing: Forest Pharmaceuticals

AND

Name: Paul David
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Additional Statistical Analyses

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baseline in HAM-D total score, based on the preferred LOCF methodology referenced in item #3 of your 8/14/97 submission.

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4) For study 91206, please perform an analysis of covariance of the mean change from baseline in HAM-D total score with serum citalopram concentration as the covariate. Again, the preferred LOCF methodology should be used. Please provide the resulting SAS printout.

Kindly provide a discussion and conclusions relevant to the above requested analyses.

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III. Comprehensive Tables, and 95% confidence intervals side-by-side, for the well-controlled studies (samples were previously faxed to you), for the primary efficacy variables at last visit. One Table is to be for scores and also changes from baseline, with the significant results being starred (*), and the other Table for all pair-wise comparison p-values.

IV. 95% confidence intervals for the difference between a dose (may be flexible) and placebo (with respect to change from baseline at last visit for primary efficacy variables) should be presented side-by-side, with the following ordering: overall, largest center, next largest center, etc. The total sample size should be provided (may be below the X-axis).

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TELECON