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APPLICATION NUMBER:

21-299

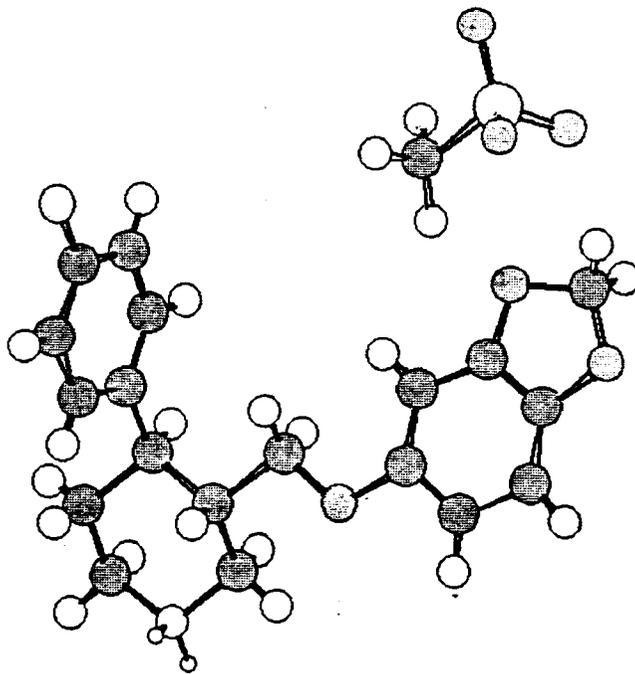
ADMINISTRATIVE DOCUMENTS

Synthon Pharmaceuticals Ltd.
6330 Quadrangle Drive
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Chapel Hill NC 27514
USA

A GENERAL

New Drug Application
Paroxetine (as mesylate) tablets

Section A 3
Patent Certification



Version number:	A3.POT.tab.001.01
Supersedes document of issue date:	None, new document
Number of Exhibits:	None
Prepared by:	Drs. F. Kalmoua
Issue date:	11-07-00

Paragraph IV Patent Certification

Synthon Pharmaceuticals Ltd. has caused all of the following actions to be taken with respect to the following patent certification concerning its paroxetine (as mesylate) tablets, 10 mg, 20 mg, 30 mg, and 40 mg:

1. The publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book), 20th Edition, 2000, and Cumulative Supplement 4 to the 20th Edition (April 2000) have been examined for patent entries related to the listed drug (Paxil® tablets).
2. The U.S. Patent and Trademark Office's ("PTO's") June 6, 2000 list of Patent Terms Extended Under 35 U.S.C. § 156 (Waxman-Hatch extensions) has been examined for entries related to the listed drug.
3. The June 21, 2000 entry in FDA's Docket Number 95S-0117 concerning information on "PATENT TERM EXTENSION AND NEW PATENTS" has been examined for entries related to the listed drug.

Based upon the above-identified actions, Synthon Pharmaceuticals Ltd. certifies that, in its opinion and to the best of its knowledge:

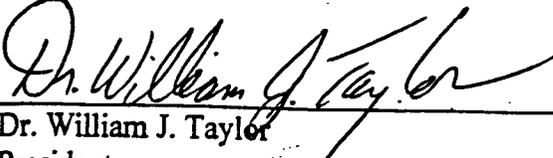
Paragraph IV

The following patents are invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the paroxetine (as mesylate) tablets for which this application is submitted:

<u>Patent Number</u>	<u>Inventor</u>	<u>Issue Date</u>	<u>Expiration Date</u>
4,721,723	Barnes et al.	Jan. 26, 1988	Sept. 25, 2008*
5,789,449	Norden	Aug. 4, 1998	Jan. 6, 2009
5,872,132	Ward et al.	Feb. 16, 1999	May 19, 2015
5,900,423	Ward et al.	May 4, 1999	May 19, 2015
6,063,927	Craig et al.	May 16, 2000	Apr. 23, 2019

* The expiration date of this patent is erroneously listed in the Orange Book as December 29, 2006.

Synthon Pharmaceuticals Ltd.



Dr. William J. Taylor
President

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Paroxetine (as mesylate)
tablets

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Paragraph IV Statement

Synthon Pharmaceuticals Ltd. hereby states, in accordance with Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act ("the Act") and 21 C.F.R. § 314.50(i)(1)(i)(A)(4), that, upon receipt from FDA of an acknowledgement letter stating that this new drug application is sufficiently complete to permit a substantive review, it will give notices containing the information required by Section 505(b)(3)(B) of the Act and 21 C.F.R. § 314.52(c) to the following persons by Federal Express with receipt verification:

1. The owner(s) of each of the following patent numbers:
4,721,723; 5,789,449; 5,872,132; 5,900,423; and 6,063,927; or the representative of each owner designated to receive the notice; and
2. The holder of approved NDA number 20-031 or the representative of the holder designated to receive the notice.

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New Indication Exclusivity Statement

The applicant's proposed labeling and its new drug application for paroxetine (as mesylate) tablets, 10 mg, 20 mg, 30 mg, and 40 mg do not include the indication for treatment of social anxiety disorder which is the subject of a new indication exclusivity for the listed drug (Paxil[®] tablets). That exclusivity expires on May 17, 2002. Synthon Pharmaceuticals Ltd. is not currently seeking approval of its application for that use.

issue date: 11-07-00

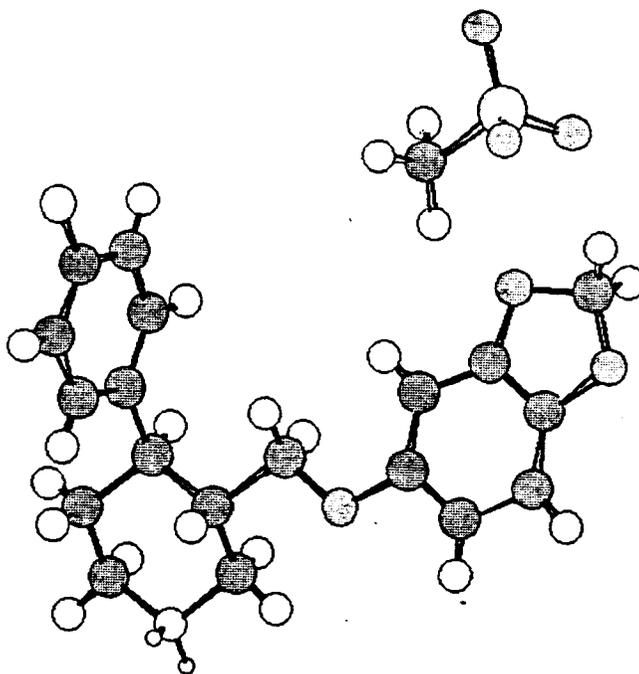
version: A3.POT.tab.001.01

approved: 

A GENERAL

New Drug Application
Paroxetine (as mesylate) tablets

Section A 2
Patent Information



Version number:	A2.POT.tab.001.01
Supersedes document of issue date:	None, new document
Number of Exhibits:	None
Prepared by:	Drs. F. Kalmoua
Issue date:	11-07-00

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Paroxetine (as mesylate)
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2 Patent Information

In accordance with the Federal Food, Drug, and Cosmetic Act, as amended September 24, 1984, information is provided about the patent(s) relevant to "Paroxetine (as mesylate) tablets" of which is the subject of the New Drug Application being submitted to the FDA.

The patent relevant to the application is:

Patent number:
US 5,874,447

Type of patent:
Drug, drug product, method of use

Assignee:
Synthon BV, Nijmegen, The Netherlands

US representative:
Synthon Pharmaceuticals, Ltd.
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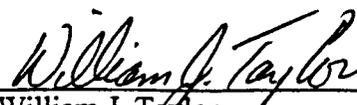
Patent application number:
872,023

Filed:
June 10, 1997

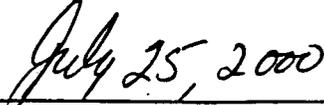
Patent issue date:
February 23, 1999

Expiration date:
June 10, 2017

The undersigned declares that Patent No. US 5,874,447 covers the formulation, composition, and method of use of "Paroxetine (as mesylate) tablets". This product is the subject of this application for which approval is being sought.



William J. Taylor
President



Date

New Drug Application
Paroxetine (as mesylate)
tablets

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United States patent 5,874,447



US005874447A

United States Patent [19]
Benneker et al.

[11] Patent Number: 5,874,447
[45] Date of Patent: Feb. 23, 1999

[54] 4-PHENYLPYPERIDINE COMPOUNDS FOR
TREATING DEPRESSION

[75] Inventors: Franciscus Bernardus Gemma
Benneker, Nijmegen; Frans Van
Dalen, Neunen; Jacobus Maria
Lammens, Mook; Theodorus
Hendricus Antonius Peters, Arnhem,
all of Netherlands; Frantisek Picha,
Brno, Czechoslovakia

[73] Assignee: Synthon B. V., Nijmegen, Netherlands

[21] Appl. No.: 872,023

[22] Filed: Jun. 10, 1997

[51] Int. Cl.⁴ A61K 31/445; C07D 405/12

[52] U.S. Cl. 514/321; 514/317; 514/319;
546/197; 546/198; 546/205; 546/206; 546/236

[58] Field of Search 546/197, 198,
546/205, 206, 236; 814/317, 319; 514/321

[56] References Cited

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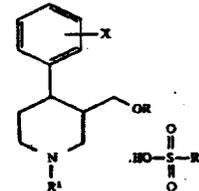
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Primary Examiner—Ceila Chang
Attorney, Agent, or Firm—Howrey & Simon

[57] ABSTRACT

The invention relates to a compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C₁₋₄ alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl.

R² represents hydrogen, trifluoro (C₁₋₄) alkyl, alkyl or alkynyl.

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy.

R¹ represents:
a C1-C10 alkyl group,
a phenyl group optionally substituted by one or more of the following groups:
a C1-C10 alkyl group,
a halogen group,
a nitro group,
hydroxy group,
and/or an alkoxy group.

29 Claims, No Drawings

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United States patent 5,874,447 (continued)

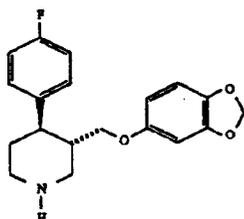
5,874,447

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4-PHENYLPYPERIDINE COMPOUNDS FOR
TREATING DEPRESSION

The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxycyclohexyl) piperidine having the formula below:



is known and has been used in medicaments for treating, amongst other ailments, depression.

Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

the anhydrous form in several crystalline modifications (PCT Appl. WO 96/24595);

the hydrated form—a hemihydrate (EP 223403) and in the solvated forms.

The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics 42, 135-143 (1988).

EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredictable amount of bound solvent which is difficult to remove.

The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tableting procedure.

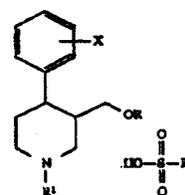
Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at in vivo administration could be rate-limiting in the absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

An object of the present invention is to provide a compound with improved characteristics.

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According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C₁₋₄ alkyl, alkythio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R¹ represents hydrogen, trifluoro (C₁₋₄) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

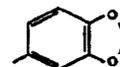
R² represents:

a C₁₋₁₀ alkyl group,
a phenyl group optionally substituted by one or more of the following groups:

a C₁₋₁₀ alkyl group,
a halogen group,
a nitro group,
hydroxy group,
and/or an alkoxy group.

The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

The R group is preferably the 3,4-methylenedioxyphenyl group of the formula:



The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

The R² group preferably represents a C₁₋₄ alkyl group, and most preferably represents a C₁₋₂ alkyl group in order to provide an optimum solubility.

The compounds can have a solubility at about 20° C. of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4-phenylpiperidine compound, a salt and/or a base thereof having the formula II:

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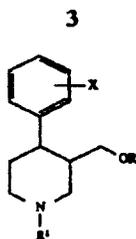
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United States patent 5,874,447 (continued)

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wherein:

R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C₁₋₄ alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

R₁ represents hydrogen, trifluoro (C₁₋₄) alkyl, alkyl or alkynyl,

X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,

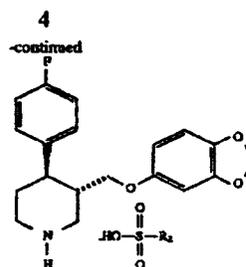
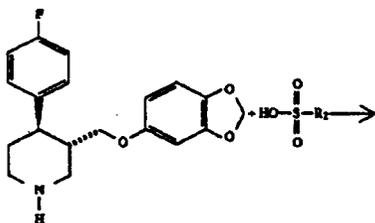
with a sulfonic acid of the general formula R₂-SO₃H, wherein R₂ represents:

- a C1-C10 alkyl group,
- a phenyl group optionally substituted by one or more of the following groups:
- a C1-C10 alkyl group,
- a halogen group,
- a nitro group,
- a hydroxy group, and/or
- an alkoxy group,

to form a solution, followed by separating the compound formed from this solution.

The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

The equation for paroxetine free base and sulfonic acids is as follows:

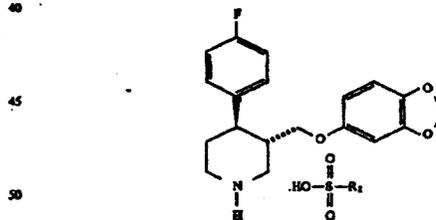
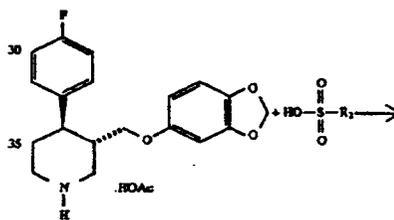


15 The forming of a solution may preferably proceed at temperatures from about 0° C. to the boiling point of the solvent.

Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

20 Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenylpiperidine having the formula II with an organic sulfonic acid.

For example the compounds of the invention may be prepared from a paroxetine C1-C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:



According to a third aspect of the present invention, there is provided a compound obtainable by this process.

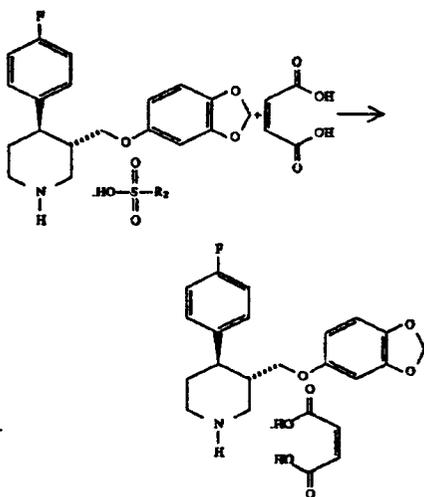
55 According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile dementia, migraines, anorexia, social phobia, depressions arising from pre-menstrual tension.

According to a sixth aspect of the present invention, there is provided the use of a compound of the invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for

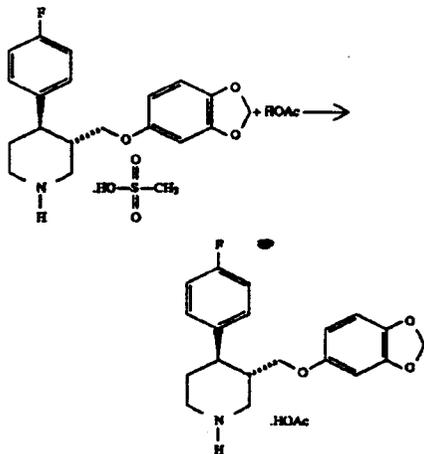
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 providing further paroxetine acid addition salts, by reacting with a suitable reagent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:



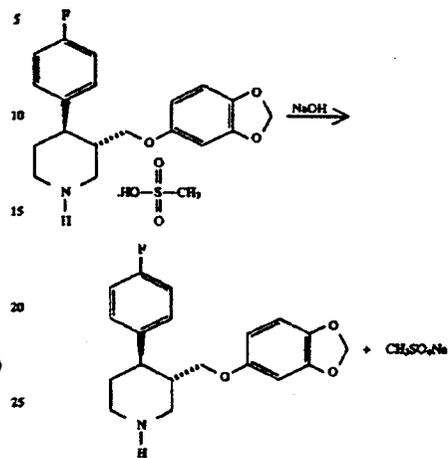
and the formation of paroxetine acetate proceeds as follows:



This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic

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 base, to form (liberate) free bases of the corresponding compounds. As exemplified on paroxetine, the reaction proceeds according to the equation:



30 The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example those of paroxetine, are the:

hydrochloride	maleate	dihydrate
hydrobromide	succinate	trihydrate
hydroiodide	tartrate	hexahydrate
acetate	citrate	methanolate
propionate	carbonate	ethanolate
malate	hemihydrate	
fumarate	hydrate	

The inventors have shown that such salts have a surprisingly high purity.

Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

Since the compounds according to the present invention exhibit high solubility, they can be dosed, for example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets,

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capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the in vitro release as well as good bioavailability after peroral application in vivo.

The tablets containing compounds of the present invention can be prepared both by tableting procedure in which water is present (e.g. aqueous granulation) as well as by tableting processing in which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

A seeding crystal of paroxetine methane sulfonate was made as follows:

2.7 g (8.2 mmol) of paroxetine was dissolved in 15 ml of hot ethanol.

1.0 g (10.4 mmol) of methanesulfonic acid in 15 ml of ethanol was added and the mixture was cooled to room temperature. When the mixture had reached room temperature the mixture was put in the freezer at -20° C. overnight. No crystal line compound was obtained. The mixture was evaporated to dryness leaving an oil. After 1 month at room temperature a waxy solid was obtained. Part of this solid was taken apart and the rest was dissolved in

10 ml of EtOAc. The waxy crystals were added and the mixture was put in the freezer at -20° C. overnight. A white crystalline product was precipitated. After filtration and drying in a vacuum oven

2.5 g (5.9 mmol) of paroxetine methane sulfonate was obtained.

Yield 72%

This seeding crystal was subsequently used in following examples 1 and 3.

EXAMPLES

Example 1

Paroxetine methane sulfonate from paroxetine

To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in U.S. Pat. No. 4,007,196, 12.7 g (132 mmol) of methane sulfonic acid was added to 150 ml of boiling ethyl acetate. The mixture was left at room temperature for 2 hours. Subsequently the mixture was placed overnight at -20° C., with a seeding crystal. The obtained solid was filtered off and washed with

50 ml of ether. The obtained white solid was dried overnight in a vacuum oven.

47.1 g (111 mmol) of product

Yield 99.5%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC).

Example 2

Paroxetine Benzene Sulfonate From Paroxetine

3.8 g (11.5 mmol) of paroxetine was dissolved in 10 ml of hot ethylacetate.

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1.82 g (11.5 mmol) of anhydrous benzenesulfonic acid was added. The mixture was left at room temperature for 2 h.

The mixture was evaporated to dryness and dissolved in dichloromethane, and evaporated again to dryness leaving an oil. This oil was solidified through high vacuum (0.1 mmHg) evaporation leaving

5.0 g (1.3 mmol) of an off white solid. To this solid was added

5 ml of acetone and the suspension was stirred for 5 minutes during which a white suspension was obtained. The solid was filtered off and dried under vacuum.

4.8 g (9.9 mmol) of product was obtained.

Yield 85%.

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 3

Paroxetine p-toluene Sulfonate From Paroxetine

5.0 g (15 mmol) of paroxetine was dissolved in 25 ml of hot ethylacetate.

2.9 g (15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h.

The solid was filtered off and washed once with 10 ml of n-hexane. The obtained white solid was dried overnight in a vacuum oven.

4.8 g (10 mmol) of a white solid was obtained.

Yield 67%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 4

Paroxetine p-chlorobenzene Sulfonate From Paroxetine

1.1 g (3.3 mmol) of paroxetine was dissolved in 3 ml of hot ethylacetate.

0.76 g (3.3 mmol) of 90% p-chlorobenzenesulfonic acid was added. The mixture was left at room temperature for 1 h and washed with

5 ml of water. The organic layer was dried with Na₂SO₄, filtered and evaporated to dryness leaving

1.5 g (2.9 mmol) of an off white solid.

Yield 88%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 5

Paroxetine Maleate From Paroxetine Methane Sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in 5 ml of hot water. To this solution was added

0.32 g (2.8 mmol) of maleic acid. The mixture was placed at 4° C. overnight after which a solid with a yellow oil was precipitated on the bottom of the flask. The solid/oil was filtered off and washed 3 times with

10 ml of ether and dried in a vacuum oven.

0.8 g (2.0 mmol) off white crystals were obtained

Yield 85%

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The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine Acetate From Paroxetine Methane Sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in 5 ml of hot iso-propanol. To this solution was added 0.2 g (3.2 mmol) of acetic acid. The mixture was placed at 4° C. overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with 10 ml of ether and dried in a vacuum oven. 0.5 g (1.3 mmol) of white crystals were obtained. Yield 54%

The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine free base from paroxetine methane sulfonate

10.0 g (24.0 mmol) of paroxetine methane sulfonate in 150 ml of water and 200 ml of ethyl acetate. To this was added 12.4 g (31 mmol) of an aqueous 10 wt % NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with 50 ml of ethyl acetate. The combined organic layers are washed once with 100 ml of water and dried over Na₂SO₄. The Na₂SO₄ was filtered off and washed once with 50 ml of ethyl acetate. The ethyl acetate was evaporated off, leaving 7.5 g (22.8 mmol) of an oily product. Yield 95%

The purity of the compound obtained was 99.5% (HPLC). A number of the compounds obtained were analysed, the results being shown in tables 1-5 below:

TABLE 1

Characterization of salts of paroxetine with certain organic acids R-SO₃H

R = CH₃ (paroxetine methane sulfonate):
m.p.: 142°-144° C.
DSC curve (closed pan, 10° C./min): onset 145.8° C. 79.0 Wg
IR spectrum (KBr, in cm⁻¹): 521, 544, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3029.
1H-NMR (ppm): 1.99 (br d, H_{3pp}, 1H); 2.27 (ddd, H_{2pp}, 1H); 2.40-2.65 (m, H₂, 1H); 2.82-2.92 (m, H₂, CH₂, 4H); 2.95-3.20 (m, H_{2pp}, H_{2pp}, 2H); 3.47 (dd, H₁, 1H); 3.58-3.74 (m, H_{2pp}, H_{2pp}, H_{3pp}); 5.88 (t, H₁, 2H); 6.30 (dd, H₂, 1H); 6.33 (d, H₂, 1H); 6.61 (d, H₂, 1H); 7.00 (dd, H₂, H₂, 2H); 7.22 (dd, H₂, H₂, 2H); 8.85 (br d, NH₃⁺, 1H); 9.11 (br d, NH₃⁺, 1H).
13C-NMR (ppm): 30.0 (s, C₁); 39.3 (s, C₂); 39.5 (s, C₂); 41.7 (s, C₃); 44.6 (s, C₄); 46.8 (s, C₅); 67.4 (s, C₆); 97.8 (s, C₇); 101.2 (s, C₈); 105.4 (s, C₉); 107.8 (s, C₁₀); 115.8 (s, C₁₁); 128.4 (s, C₁₂); 137.1 (s, C₁₃); 142.0 (s, C₁₄); 148.2 (s, C₁₅); 153.7 (s, C₁₆); 161.9 (d, C₁₇).
R = C₆H₅ (paroxetine benzene sulfonate):
m.p.: 53°-60° C.
IR spectrum (KBr, in cm⁻¹): 938, 964, 984, 998, 726, 764, 878, 978, 994, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029.
1H-NMR (ppm): 1.90 (br d, H_{3pp}, 1H); 2.30-2.28 (m, H_{2pp}, 1H); 2.38-2.52 (m, H₂, 1H); 2.82 (ddd, H₂, 1H); 3.02-3.18 (m, H_{2pp}, 2H); 3.37 (dd, H₁, 1H); 3.48 (d, H₂, 1H); 3.60-3.82 (m, H_{2pp}, 2H); 5.87 (s, H₁, 2H); 6.06 (dd, H₂, 1H); 6.29 (d, H₂, 1H); 6.60 (d, H₂, 1H); 6.90 (dd, H₂, H₂, 2H); 7.04 (dd, H₂, H₂, 2H); 7.40

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TABLE 1-continued

Characterization of salts of paroxetine with certain organic acids R-SO₃H

R = p-ClC₆H₄ (paroxetine p-toluenesulfonate):
m.p.: 148°-150° C.
DSC curve (closed pan, 10° C./min): onset 151.6° C. 71.6 Wg
IR spectrum (KBr, in cm⁻¹): 529, 557, 673, 771, 800, 834, 921, 936, 1000, 1029, 1100, 1157, 1156, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029.
1H-NMR (ppm): 1.89 (br d, H_{3pp}, 1H); 2.10-2.50 (m, H_{2pp}, H₂, CH₂, 8H); 2.82 (ddd, H₁, 1H); 2.97-3.18 (m, H_{2pp}, H_{2pp}, 2H); 3.36 (dd, H₁, 1H); 3.48 (dd, H₂, 1H); 3.52-3.77 (m, H₂, H_{2pp}, 2H); 5.87 (s, H₁, 2H); 6.06 (dd, H₂, 1H); 6.28 (d, H₂, 1H); 6.29 (d, H₂, 1H); 6.50 (dd, H₂, H₂, 2H); 7.05 (dd, H₂, H₂, 2H); 7.24 (d, CH, ArH, 2H); 7.83 (d, SArl, 2H); 8.91 (br d, NH₃⁺, 1H); 9.17 (br d, NH₃⁺, 1H).
13C-NMR (ppm): 21.3 (s, C₁); 29.9 (s, C₂); 39.2 (s, C₃); 41.5 (s, C₄); 44.7 (s, C₅); 46.9 (s, C₆); 67.3 (s, C₇); 97.8 (s, C₈); 101.1 (s, C₉); 105.5 (s, C₁₀); 107.8 (s, C₁₁); 115.8 (s, C₁₂); 125.6 (s, C₁₃); 129.8 (s, C₁₄); 129.3 (s, C₁₅); 137.2 (s, C₁₆); 140.8 (s, C₁₇); 141.5 (s, C₁₈); 141.9 (s, C₁₉); 148.2 (s, C₂₀); 153.8 (s, C₂₁); 161.8 (d, C₂₂).
R = p-ClC₆H₄ (paroxetine p-chlorobenzenesulfonate):
m.p.: 75°-80° C.
IR spectrum (KBr, in cm⁻¹): 496, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186, 1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029.
1H-NMR (ppm): 1.91 (br d, H_{3pp}, 1H); 2.15 (ddd, H_{2pp}, 1H); 2.37-2.52 (m, H₂, 1H); 2.81 (ddd, H₁, 1H); 2.93-3.21 (m, H_{2pp}, H_{2pp}, 2H); 3.37 (dd, H₁, 1H); 3.49 (d, H₂, 1H); 3.61-3.81 (m, H_{2pp}, H_{2pp}, 2H); 5.88 (s, H₁, 2H); 6.05 (dd, H₂, 1H); 6.27 (d, H₂, 1H); 6.59 (d, H₂, 1H); 6.91 (dd, H₂, H₂, 2H); 7.03 (dd, H₂, H₂, 2H); 7.39 (d, ClArH, 2H); 7.86 (d, SArl, 2H); 8.78 (br d, NH₃⁺, 1H); 9.02 (br d, NH₃⁺, 1H).
13C-NMR (ppm): 30.0 (s, C₁); 39.3 (s, C₂); 41.5 (s, C₃); 44.9 (s, C₄); 47.1 (s, C₅); 67.5 (s, C₆); 97.9 (s, C₇); 101.2 (s, C₈); 105.5 (s, C₉); 107.9 (s, C₁₀); 115.8 (s, C₁₁); 127.6 (s, C₁₂); 128.8 (s, C₁₃); 132.0 (s, C₁₄); 137.0 (s, C₁₅); 137.2 (s, C₁₆); 141.9 (s, C₁₇); 142.0 (s, C₁₈); 148.2 (s, C₁₉); 153.6 (s, C₂₀); 161.8 (d, C₂₁).

The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

In the following tables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

TABLE 2

Hygroscopicity of certain salts of paroxetine (40° C., 75% rel. hum.).

water content (in %)	t = 0	1 - 4 weeks
methane sulfonate	0.35	+0.04
p-toluenesulfonate	0.70	+0.02
hydrochloride	—	+2.5

New Drug Application
Paroxetine (as mesylate)
tablets

Synthon Pharmaceuticals Ltd.
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TABLE 3

Solubility of paroxetine salts in water (in mg/ml)		
	20° C.	30° C.
methane sulfonate	>1000	1300
p-toluene sulfonate	>1000	>1000
hydrochloride hemihydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.3

TABLE 4

Stability of paroxetine salts by HPLC (total amount of degradation in %)		
	degradation 20° C.	80° C.
methane sulfonate	not observed	<0.2%, 3 months
p-toluene sulfonate	not observed	<0.2%, 3 months
maleate	0.2%, 12 months	>50%, 5 days

TABLE 5

Solubility of salts of paroxetine in aqueous solvents (in mg/ml)		
	methane sulfonate	p-toluene sulfonate
Ethanol	20° C. 36	50
	28° C. 150	>300
2-Propanol	20° C. 7	14
	32° C. 330	>500
Acetone	20° C. 5	16
	56° C. 37	125
Dihyl acetate	20° C. 2	22
	77° C. 25	>300
n-Hexane	20° C. <0.05	<0.05
	66° C. 0.05	<0.05

Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

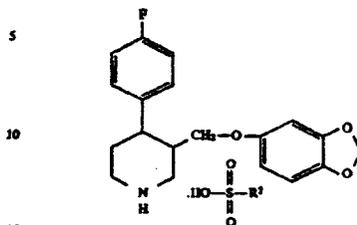
TABLE 6

Characterization of male/fine base of paroxetine	
<u>paroxetine maleate:</u>	
m.p.: 128-130° C.	
1H-NMR (ppm): 1.65-2.00 (m, H ₂₀ , 2H); 2.00-2.50 (m, H ₂ , 1H); 2.55-3.15 (m, H ₁₀ , H ₁₁ , H ₁₂ , H ₁₃ , 3H); 3.15-3.75 (m, H ₁₄ , H ₁₅ , 2H); 4.00-4.50 (m, H ₁₆ , 1H); 4.50-5.00 (m, H ₁₇ , 1H); 6.42 (d, H ₁₈ , 1H); 6.87 (d, H ₁₉ , 1H); 6.95-7.35 (m, H ₂₁ , H ₂₂ , H ₂₃ , H ₂₄ , 4H).	
<u>paroxetine acetate:</u>	
m.p.: 123-125° C.	
1H-NMR (ppm): 1.70-2.00 (m, H ₂₀ , H ₂₁ , 2H); 1.97 (s, H ₃ , 3H); 2.05-2.50 (m, H ₂ , 1H); 2.50-3.00 (m, H ₁₀ , H ₁₁ , H ₁₂ , H ₁₃ , 3H); 3.05-3.75 (m, H ₁₄ , H ₁₅ , H ₁₆ , 2H); 4.05 (s, H ₁₇ , 1H); 4.28 (dd, H ₁₈ , 1H); 4.58 (d, H ₁₉ , 1H); 6.65 (d, H ₂₂ , 1H); 7.10-7.50 (m, H ₂₃ , H ₂₄ , H ₂₅ , 4H).	
<u>paroxetine:</u>	
1H-NMR (ppm): 1.60-2.00 (m, H ₂₀ , H ₂₁ , 2H); 2.00-2.35 (m, H ₂ , 1H); 2.40-2.95 (m, H ₁₀ , H ₁₁ , H ₁₂ , 3H); 3.15-3.70 (m, H ₁₄ , H ₁₅ , 2H); 3.67 (s, H ₁₇ , 1H); 4.31 (dd, H ₁₈ , 1H); 4.43 (d, H ₁₉ , 1H); 6.42 (d, H ₂₂ , 1H); 6.80-7.35 (m, H ₂₃ , H ₂₄ , H ₂₅ , 4H).	

It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

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We claim:
1. A compound having the formula:



wherein R² represents C₁-C₁₀ alkyl group or a substituted or unsubstituted phenyl group wherein the substituents are selected from the group consisting of C₁-C₁₀ alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof.

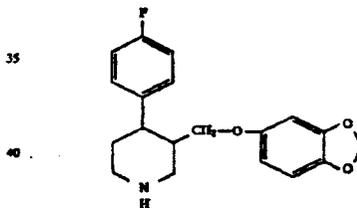
2. The compound according to claim 1, wherein the R² group represents a C₁-C₄ alkyl group.

3. The compound according to claim 1, wherein the R² group is a C₁-C₂ alkyl group.

4. The compound according to claim 1, having a solubility at about 20° C. of at least about 10 mg per ml water.

5. The compound according to claim 4, having a solubility in water of at least 1000 mg per ml at about 20° C.

6. A process, which comprises mixing together a compound, a salt, and/or a base thereof, having the formula:



with a sulfonic acid of the general formula R²-SO₃H, wherein

R² represents C₁-C₁₀ alkyl group or a substituted or unsubstituted phenyl group wherein the substituents are selected from the group consisting of C₁-C₁₀ alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof,

to produce a sulfonate salt compound according to claim 1.

7. The process according to claim 6, which further comprises mixing together said sulfonate salt compound with a reagent selected from the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, acetic acid, propionic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, tartaric acid, citric acid, embonic acid/pamoic acid, sulfuric acid, water, methanol, and ethanol, to form a salt or solvate of said reagent.

8. The process according to claim 7, wherein the salt of said reagent is produced and is recovered as a solid having a purity of at least 90 wt %.

9. The process according to claim 7, wherein said reagent is maleic acid; said mixing produces paroxetine maleate; and which further comprises recovering said paroxetine maleate in a purity of at least 98%.

New Drug Application
Paroxetine (as mesylate)
tablets

Synthon Pharmaceuticals Ltd.
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10. The process according to claim 7, wherein said reagent is acetic acid; said mixing produces paroxetine acetate; and which further comprises recovering said paroxetine acetate in a purity of at least 98%.

11. A process according to claim 6, which further comprises mixing together said sulfonate salt compound with at least one of an organic or an inorganic base to form a free base thereof.

12. The process according to claim 11, wherein the base is selected from the group consisting essentially of: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, and pyridine.

13. The process according to claim 11, further comprising isolating said free base in a purity of at least 95%.

14. The process according to claim 13, wherein said isolated free base has a purity of at least 98%.

15. The compound produced by the process according to claim 6.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and at least one pharmaceutically acceptable carrier or diluent.

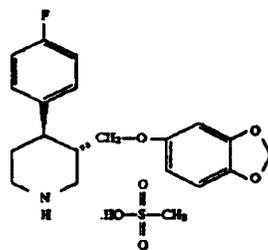
17. The pharmaceutical composition according to claim 16, wherein said composition is a solid dosage form.

18. A method for treating depression, obsessive/compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile dementia, migraine, or social phobias, which comprises administering to a patient in need thereof a therapeutically effective amount of the compound as claimed in claim 1.

19. The method according to claim 18, wherein said patient is a human.

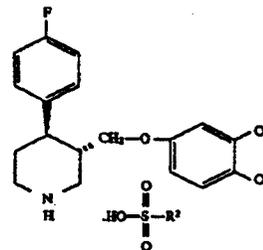
20. The method according to claim 18, wherein said method comprises administering an effective antidepressant amount of said compound to a patient suffering from depression.

21. A compound of the following formula:



22. A pharmaceutical composition comprising a therapeutically effective amount of a compound of the following formula:

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wherein R² is methyl, ethyl, benzyl, p-chlorobenzyl, or tolyl; and

a pharmaceutically acceptable carrier or diluent.

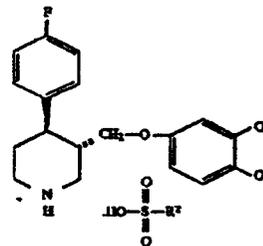
23. The pharmaceutical composition according to claim 22, wherein said composition is for oral administration.

24. The pharmaceutical composition according to claim 22, wherein R² is methyl.

25. The pharmaceutical composition according to claim 24, wherein said composition is a solid dosage form.

26. The pharmaceutical composition according to claim 25, wherein said composition is a tablet.

27. A method of treating depression, obsessive/compulsive disorders or panic disorders which comprises administering to a patient in need thereof an effective amount of a compound of the following formula:



wherein R² is methyl, ethyl, benzyl, p-chlorobenzyl, or tolyl.

28. The method according to claim 27, wherein R² is methyl.

29. The method according to claim 28, wherein an effective antidepressant amount is administered to said patient.

* * * * *

EXCLUSIVITY SUMMARY for NDA # 21-299

Trade Name Asimia (paroxetine mesylate) 10 mg, 20 mg, 30 mg, and 40 mg tablets

Applicant Name Synthon 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.

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:

This is a 505(b)(2) application

d) Did the applicant request exclusivity?

YES / ___/ NO/ X /

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

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

YES / / NO / /

Pediatric exclusivity granted to the innovator product, Paxil (paroxetine HCl); NDA 20-031; GSK, on 6-27-02.

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? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / / NO / /

NDA # 20-031 Drug Name: Paxil (paroxetine HCl) Tablets

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 / /

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 /__/ NO /__/

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

NDA #

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 /__/

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 /___/

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 /___/

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:

- (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 /___/

If yes, explain: _____

- (c) 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 #1_, Study # _____

Investigation #2_, 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 _____	
	!		
_____	!	_____	
_____	!	_____	
	!		

(c) 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
Title: Regulatory Project Manager

Date

Signature of Office of Division Director
Title: Division Director

Date

cc:
Archival NDA 21-299
HFD-120/Division File
HFD-120/P.David
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

MEMORANDUM

DATE: May 24, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-299

SUBJECT: Action Memo for NDA 21-299, for the use of Paroxetine Mesylate

NDA 21-299, for the use of 10, 20, 30, and 40 mg tablets of Paroxetine Mesylate, was submitted by Synthon Pharmaceuticals Ltd., on 7/26/00. The application was submitted as a 505(b)(2) application, in that it relies on the approved NDA for Paxil (paroxetine hydrochloride) for most of the clinical and pre-clinical data necessary for approval. The primary basis for the reliance on the approved product was a showing that the 40 mg tablet of the proposed product was bioequivalent to the 40 mg tablet of Paxil (the 10 mg tablet failed bioequivalence [BE] criteria for AUC, but as pointed out by various reviewers, this comparison was not required [BE is required to be demonstrated for the highest dose strength], and is undoubtedly related to high variability of paroxetine bioavailability).

I agree with the review team that the application is approvable. I have only 2 minor comments for the record.

The minutes of the divisional meeting held on 12/18/98 at the time of the submission of the IND note that 2 animal studies were performed to compare the toxicity of the mesylate and hydrochloride salts. The minutes state that the results for the 2 salts were "uncannily similar", and that the Agency might request a DSI investigation. I have discussed this with Dr. Linda Fossom, reviewing pharmacologist. She informs me that that statement referred to the calculated LD50's of the two salts, which were similar. However, there is no evidence that the toxicities or histopathology seen in the animal studies were identical, and therefore there was no reason to request a directed DSI investigation.

Finally, the firm's attorney notes (letter dated 11/30/00) that the application cannot be approved until 4/10/03, depending upon the outcome of litigation filed by SmithKline Beecham Corporation related to patent infringement issues. Paul David, project manager, has discussed this issue with Don Hare, project manager in the Office of Pharmaceutical Sciences, an Agency expert in these matters. Mr. Hare agrees that the application may not be approved until the legal issues have been dealt with.

ACTION

For the reasons stated above, I will issue the attached Approvable letter with appended draft labeling.

Russell Katz, M.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
5/25/01 07:59:24 AM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-299</u> Class: <u>2S</u>	
Drug <u>Paroxetine mesylate 10 mg, 20 mg, 30 mg, and 40 mg Tablets</u>	Applicant: <u>Synthon Pharmaceuticals</u>
RPM <u>Paul David</u>	Phone <u>x4-5530</u>
<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Reference listed drug <u>Paxil (paroxetine HCl) Tablets; NDA 20-031</u>	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) <u>57,407</u>	
Application classifications: Chem Class <u>2</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>5-26-01</u> Secondary <u>7-26-01</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information:
 - User Fee Paid
 - User Fee Waiver (attach waiver notification letter)
 - User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels
 - FDA revised labeling and reviews..... X
 - Original proposed labeling (package insert, patient package insert) X
 - Other labeling in class (most recent 3) or class labeling..... X (Paxil Labeling)
 - Has DDMAC reviewed the labeling? Yes (include review) No
 - Immediate container and carton labels X
 - Nomenclature review No Trade Name

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.

- Exception for review (Center Director's memo)..... _____
- OC Clearance for approval..... _____

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) Materials requested in AP letter
- ◆ Post-marketing Commitments N/A
 - Agency request for Phase 4 Commitments.....
 - Copy of Applicant’s commitments
- ◆ Was Press Office notified of action (for approval action only)?..... Yes No
 - Copy of Press Release or Talk Paper.....
- ◆ Patent N/A
 - Information [505(b)(1)] X
 - Patent Certification [505(b)(2)]..... X
 - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... X
- ◆ Exclusivity Summary X
- ◆ Debarment Statement X
- ◆ Financial Disclosure X
 - No disclosable information X
 - Disclosable information – indicate where review is located
- ◆ Correspondence/Memoranda/Faxes X
- ◆ Minutes of Meetings X
 - Date of EOP2 Meeting _____
 - Date of pre NDA Meeting 10-21-99
 - Date of Internal RTF Meeting 9-14-00
- ◆ Advisory Committee Meeting N/A
 - Date of Meeting
 - Questions considered by the committee
 - Minutes or 48-hour alert or pertinent section of transcript
- ◆ Federal Register Notices, DESI documents N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Summary memoranda (e.g., Office Director’s memo, Division Director’s memo, Group Leader’s memo) X
- ◆ Clinical review(s) and memoranda X
- ◆ Safety Update review(s) N/A
- ◆ Pediatric Information X
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page.....
 - Pediatric Exclusivity requested? Denied Granted Not Applicable

3 Page(s) Withheld

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT

**OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: May 6, 2003

DUE DATE: May 30, 2003

ODS CONSULT #: 01-0208-2

TO: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Paul David
Project Manager
HFD-120

PRODUCT NAME:
Oparo
(Paroxetine Mesylate Tablets)
10 mg, 20 mg, 30 mg, and 40 mg

NDA SPONSOR: Synthron Pharmaceuticals

NDA#: 21-299

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proposed proprietary name
2. DDMAC has no objections to the use of the name from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

7 Page(s) Withheld

V. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proposed proprietary name
2. DDMAC finds the name acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

.....
This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.
.....

/s/

Alina Mahmud
5/30/03 12:52:00 PM
PHARMACIST

Carol Holquist
5/30/03 04:39:56 PM
PHARMACIST

CONSULTATION RESPONSE
Division Of Medication Errors And Technical Support
Office Of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: JAN-23-2003 | DUE DATE: MAR-14-2003 | ODS CONSULT: 01-0208-1

TO:
Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH:

Paul David
Project Manager
HFD-120

PRODUCT NAME:
Asimia
(Paroxetine Mesylate Tablets)
10 mg, 20 mg, 30 mg, 40 mg

NDA SPONSOR:
Synthon Pharmaceuticals, Ltd.

NDA #: 21-299

SAFETY EVALUATOR: Marci Lee, PharmD

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a final review of the proposed proprietary name "Asimia" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. Upon further review, DMETS reverses the initial decision and does not recommend the use of the proprietary name, Asimia.
2. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DMETS recommends consulting Dan Boring (of the USAN council & LNC) for the proper designation of the established name.
4. DDMAC finds the proprietary name, Asimia, acceptable from a promotional perspective.

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

FINAL PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 14, 2003
NDA NUMBER: 21-299
NAME OF DRUG: Asimia (Paroxetine Mesylate Tablets)
10 mg, 20 mg, 30 mg, 40 mg
NDA SPONSOR: Synthon Pharmaceuticals, Ltd.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120), for assessment of the tradename "Asimia", regarding potential name confusion with other proprietary/generic drug names. The Division notes that the application for Asimia (paroxetine mesylate) is a 505(b)(2) and Paxil (paroxetine hydrochloride) is the reference-listed-drug. They are identical except for the salt form (mesylate vs. hydrochloride). However, unlike Paxil, Asimia is not available as an oral suspension of 10 mg/5 mL.

Asimia was found acceptable by DMETS in consult 01-0208, dated FEB-15-2002. Since that review, DMETS identified three additional names with potential for sound-alike or look-alike confusion with Asimia.

PRODUCT INFORMATION

Asimia is the proposed proprietary name for paroxetine mesylate tablets. Asimia is indicated for the treatment of depression, obsessive compulsive disorder, and panic disorder. Asimia will be supplied as 10 mg, 20 mg, 30 mg, and 40 mg oral tablets. The recommended dosage in treating depression is 20 mg/day up to a maximum of 50 mg/day as a single daily dose. The usual dosage in the treatment of obsessive compulsive disorder and panic disorder is 40 mg/day up to a maximum of 60 mg/day as a single daily dose. Elderly patients and/or patients with severe renal or hepatic impairment should begin with 10 mg/day (maximum 40 mg/day). The use of Asimia is contraindicated in patients concomitantly taking either monoamine oxidase inhibitors (MAOIs) or thioridazine.

II. RISK ASSESSMENT

The DMETS medication error staff conducted a search of several standard published drug product reference texts¹ as well as several FDA databases² for existing drug names which sound-alike or look-alike to "Asimia" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis³ Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Asimia. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. Three product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Asimia. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.
2. DDMAC did not have concerns about the name, Asimia, with regard to promotional claims.

Table 1. Potential sound-alike and look-alike names identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Look-alike or Sound-alike
Asimia	Paroxetine Mesylate Tablets 10 mg, 20 mg, 30 mg, 40 mg	Major Depressive Disorder: 20 mg to 50 mg PO daily Obsessive Compulsive Disorder: 20 mg to 60 mg PO daily; Panic Disorder: 10 - 60 mg PO daily	
Alinia	Nitazoxanide for Oral Suspension 100 mg/5 mL (60 mL bottle)	Age 12-47 months: 5 mL (100 mg) every 12 hours for 3 days Age 4-11 years: 10 mL (200 mg) every 12 hours for 3 days with food.	Look-alike and Sound-alike
Aviane	Ethinyl estradiol and Levonorgestrel 20 mcg and 0.1 mg; 28 day pack	Take 1 tablet by mouth daily.	Look-alike
Amicar	Aminocaproic acid 500 mg Tablets 250 mg/mL Oral syrup 250 mg/mL Injection	PO or IV: 5 grams, followed by 1 gram hourly – goal plasma level is 0.13 mg/mL IV infusion: 4 grams to 5 grams in 250 mL of diluent during first hour then 1 gram/hour in 50 mL of diluent. Continue for 8 hours or until bleeding is controlled.	Look-alike

* Frequently used, not all inclusive

¹ Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO. <http://www.efactsweb.com/index.asp> MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2003).

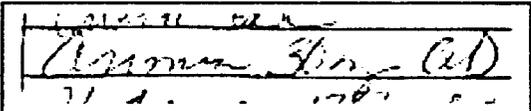
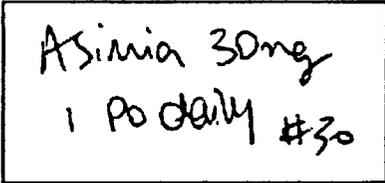
² The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

³ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology for Asimia studies

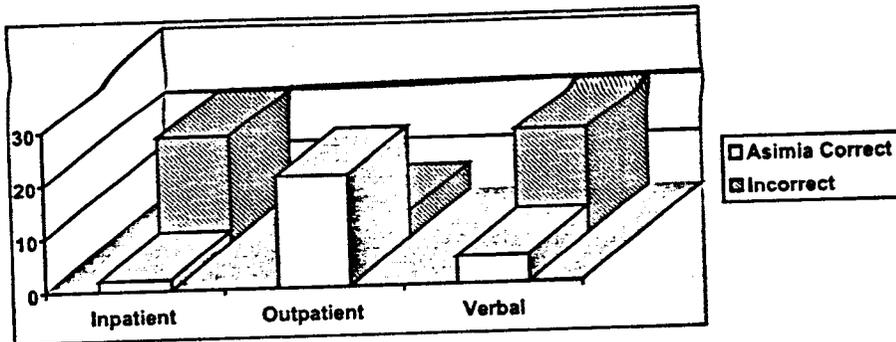
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Asimia with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 104 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote inpatient and outpatient prescriptions for Asimia, each consisting of a combination of marketed and unapproved drug products. These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTIONS		VERBAL PRESCRIPTION
Asimia (Final Review)		
Inpatient:		Verbal: "... The first prescription is for Asimia, thirty milligrams, one by mouth daily. Dispense number thirty."
Outpatient:		

2. Results for Asimia studies (Final Review)

Results of these exercises are summarized below:

Study	No. of participants	# of responses	"Asimia" response	Other response
Written: Inpatient	31	22 (71%)	2 (9%)	20 (91%)
Written Outpatient	39	26 (67%)	21 (81%)	5 (19%)
Verbal:	35	25 (71%)	5 (20%)	20 (80%)
Total:	105	73 (70%)	28 (38%)	45 (62%)



When examining the interpretations from the written inpatient prescriptions, 2 of 22 (9%) respondents interpreted the name correctly. In addition, 21 of the 26 respondents (81%) from the written outpatient prescriptions interpreted the name correctly. The most common misinterpretation from the inpatient study was *Anmin*. Other incorrect responses included *Ammia*, *Amnia*, *Anmia*, *Anmis*, *Aramex*, *Arimia*, *Arimin*, *Asimin* and *Orimin*. The most common misinterpretation from the outpatient study was *Asinia*. Other incorrect responses included *Asima* and *Asimia*.

Among the verbal outpatient *Asimia* prescriptions, 20 of 25 (80%) respondents interpreted the name incorrectly. Almost all of the misinterpretations were phonetically equivalent to "Asimia". These included *Isimmia*, *Assimia*, *Assymia*, *Asymea*, *Asymia*, *Asymmia*, *Acemia*, *Acimia*, and *Asemia*. Other misinterpretations included *Acinia* and *Asenia*.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Asimia", the primary concern for name confusion was *Alinia*, which already exists in the US marketplace. Other concerns included potential for look-alike confusion with *Aviane* and *Amicar*.

1. *Alinia* and *Asimia*

The initial DMETS safety review (ODS 01-0208) for *Asimia* was completed in February 2002. At that time the name was found acceptable by DMETS. On November 21, 2002, DMETS completed the review for *Alinia* (ODS 02-0186-1). *Alinia* was submitted as an alternative to _____ which DMETS found unacceptable on November 11, 2002. *Alinia* was approved on November 22, 2002. DMETS acknowledges that the potential safety of the name pair of *Alinia* and *Asimia* has been previously evaluated for the approval of *Alinia*. However, the safety evaluator had no specific knowledge of the *Asimia* approval timeline. Since *Asimia* did not exist in the US marketplace at the time of the *Alinia* review, it would not be a reason to reject the *Alinia* name.

While the *Alinia* review identifies various differences between *Alinia* and *Asimia* that may minimize the risk for confusion, upon careful reconsideration DMETS has identified several new concerns which may preclude the ability for these names to coexist safely in the marketplace. *Alinia* has potential for look-alike and sound-alike confusion with *Asimia*. *Alinia* was approved on November 22, 2002 for the treatment of diarrhea in children caused by *Cryptosporidium parvum* and *Giardia lamblia*. Both names begin with the letter "A-", end with "-ia", and have the same number of letters. In addition, the letters "-m-" and "-n-" in the middle of the names can look the same when handwritten and sound similar. Both names contain three syllables and the sound-alike similarity is

mainly due to their rhyming quality. Although Alinia and Asimia differ with respect to many characteristics, the name similarity is significant and the opportunities for errors are likely in any situation where the prescriber communication is not clear to the practitioners interpreting the medication order. This commonly occurs when the prescription is ambiguous or incomplete. DMETS anticipates that errors may occur between Alinia and Asimia despite their differing indications and characteristics. (See Table 2)

DMETS has identified significant potential for confusion with Alinia, particularly in the case of handwritten orders and considers the proposed name unacceptable based on 21 CFR 201.10(c)(5). This regulation states, "The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient."

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

Table 2. Comparison of Asimia and Alinia

Proprietary Name	Asimia	Alinia
	<i>Asimia</i>	<i>Alinia</i>
Established Name	Paroxetine Mesylate	Nitazoxanide
Approval Date	Pending	NOV-22-2002
Sponsor	Synthon	Romark
Indication	Depression, Obsessive Compulsive and Panic Disorder	Diarrhea caused by <i>C. parvum</i> and <i>G. lamblia</i>
Patient Population	Adults *Note: Paroxetine HCl has been used off-label in children over 8 years	Children between 1 and 11 years
Dosage Strength	10 mg, 20 mg, 30 mg, 40 mg	100 mg/5 mL Oral Suspension
How Supplied	All strengths as 30s 20 mg also as 100s and 500s.	60 mL bottle **Bottle of 60 tablets
Usual Dose and Range	20 mg – 50 mg	Age 12-47 months: 5 mL (100 mg) Age 4-11 years: 10 mL (200 mg)
Frequency	Daily	Every 12 hours for 3 days.
Route	Oral	Oral
Dosage formulation	Tablet	Oral Suspension
Storage conditions	Room Temperature On shelf near Alinia in some pharmacies	Room Temperature On shelf near Asimia in some pharmacies

Considerations for Confusion between Asimia and Alinia

- Asimia and Alinia differ in dosage strength (10 mg, 20 mg, 30 mg, and 40 mg vs.

100 mg/mL). However, since Alinia can be dosed by volume, there is some overlap between 10 mL of Alinia and 10 mg of Asimia. There is also potential for confusion *between "mg" and "mL" when handwritten*. These issues were not specifically addressed in the original safety assessment (ODS 02-0186-1).

- Another way the dosage strengths can indirectly overlap is when a prescriber uses a trailing zero after writing ten milligrams (Asimia 10.0 mg) and the decimal is not seen by the practitioner interpreting the order, who sees Alinia 100 mg in error.

Caroline Asimia 10.0mg

- There is also potential for overlap of the dispensing quantity if prescribers calculate the volume needed for the three-day course of Alinia. "Dispense 30" or "Dispense 60" could be interpreted as 30 mL or 30 tablets, and 60 mL or 60 tablets.
- Both products would be introduced into the US marketplace within six months of each other. An example of this type of problem would be Celexa (approved JUL-1998) and Celebrex (DEC-1998). Errors occurred between Celexa and Celebrex despite different characteristics of the drugs. In this scenario, there is not enough time for practitioners to become familiar with the first product and they easily confuse the characteristics of the two products.
- Asimia and Alinia have different dosing regimens (twice daily for three days vs. once daily on a chronic basis). However, the opportunity for errors exists whenever the prescription is ambiguous or incomplete. See example below.

Alinia 10
OD #60

- Alinia is approved only for children ages one to eleven years ~~and~~ and Asimia is indicated for use only in the adult patient population. Since Asimia contains the same active ingredient as Paxil, DMETS also considered the dosing information for Paroxetine Hydrochloride. Dosing information for off-label use of Paroxetine Hydrochloride in children over eight years to treat depression and obsessive-compulsive disorder can be found in the ePocrates reference for prescribers (<http://www.epocrates.com/>). Therefore, the highest risk population at this time includes children between the ages of eight and eleven because they could be considered by some practitioners as candidates for both treatments.
- In the inpatient setting, which is less likely to include both paroxetine salts on the formulary, there is an increased risk for a pediatric patient to receive the Paroxetine Hydrochloride Oral Suspension, in error. This scenario may involve an order for Alinia 10 mL that is misinterpreted as Asimia. The practitioner may know Asimia is paroxetine and dispense the paroxetine oral solution. The consequence of this type of error is unknown in this fragile patient population.
- Asimia and Alinia have different indications for use. Unfortunately this may not be enough to prevent confusion and errors because this information is not always available to the pharmacist or practitioner interpreting the drug order.

- Although Asimia and Alinia are available in different dosage formulations at this time, they are both administered by mouth.
-
-
-

2. Aviane and Asimia

Aviane and Asimia have potential for look-alike confusion. Aviane is an oral contraceptive drug product. While both medications are dosed once daily on a chronic basis, Asimia is a single-ingredient product available in multiple dosage strengths and Aviane is a combination product available in a single strength as a 28-day package. DMETS expects these products to safely coexist based on the degree of look-alike similarity and differing characteristics between Asimia and Aviane.

Asimia Aviane

3. Amicar and Asimia

Amicar and Asimia have potential for look-alike confusion. Amicar is used to manage bleeding conditions. Amicar is typically administered in an inpatient setting with specialized patient monitoring. DMETS expects that Asimia and Amicar will safely coexist due to their vastly differing indications and conditions for use.

Asimia Amicar

III. COMMENTS TO THE SPONSOR

In reviewing the proprietary name "Asimia", the primary concern for name confusion was Alinia, which already exists in the US marketplace.

Alinia has potential for look-alike and sound-alike confusion with Asimia. Alinia was approved on November 22, 2002 for the treatment of diarrhea in children caused by *Cryptosporidium parvum* and *Giardia lamblia*. Both names begin with the letter "A-", end with "-ia", and have the same number of letters. In addition, the letters "-m-" and "-n-" in the middle of the names can look the same when handwritten and sound similar. Both names contain three syllables and the sound-alike similarity is mainly due to their rhyming quality. Although Alinia and Asimia differ with respect to many characteristics, the name similarity is significant and the opportunities for errors are likely in any situation where the prescriber communication is not clear to the practitioners interpreting the medication order. This commonly occurs when the prescription is ambiguous or incomplete. DMETS anticipates that errors may occur between Alinia and Asimia despite their differing indications and characteristics. (See Table 1 on page 9)

DMETS has identified significant potential for confusion with Alinia, particularly in the case of handwritten orders and considers the proposed name unacceptable based on 21 CFR 201.10(c)(5). This regulation states, "The labeling of a drug may be misleading by reason of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient."

Table 1. Comparison of Asimia and Alinia

Proprietary Name	Asimia	Alinia
	<i>Asimia</i>	<i>Alinia</i>
Established Name	Paroxetine Mesylate	Nitazoxanide
Approval Date	Pending	NOV-22-2002
Sponsor	Synthon	Romark
Indication	Depression, Obsessive Compulsive and Panic Disorder	Diarrhea caused by <i>C. parvum</i> and <i>G. lamblia</i>
Patient Population	Adults *Note: Paroxetine HCl has been used off-label in children over 8 years	Children between 1 and 11 years
Dosage Strength	10 mg, 20 mg, 30 mg, 40 mg	100 mg/5 mL Oral Suspension
How Supplied	All strengths as 30s 20 mg also as 100s and 500s.	60 mL bottle
Usual Dose and Range	20 mg – 50 mg	Age 12-47 months: 5 mL (100 mg) Age 4-11 years: 10 mL (200 mg)
Frequency of Administration	Daily	Every 12 hours for 3 days.
Route of Administration	Oral	Oral
Dosage formulation	Tablet	Oral Suspension
Storage conditions	Room Temperature On shelf near Alinia in some pharmacies	Room Temperature On shelf near Asimia in some pharmacies

Considerations for Confusion between Asimia and Alinia

- Asimia and Alinia differ in dosage strength (10 mg, 20 mg, 30 mg, and 40 mg vs. 100 mg/mL). However, since Alinia can be dosed by volume, there is some overlap between 10 mL of Alinia and 10 mg of Asimia. There is also potential for confusion between "mg" and "mL" when handwritten.
- Another way the dosage strengths can indirectly overlap is when a prescriber uses a trailing zero after writing ten milligrams (Asimia 10.0 mg) and the decimal is not seen by the practitioner interpreting the order, who sees Alinia 100 mg in error.

Continue Asimia 10.0mg

- There is also potential for overlap of the dispensing quantity if prescribers calculate the volume needed for the three-day course of Alinia. “Dispense 30” or “Dispense 60” could be *interpreted as 30 mL or 30 tablets, and 60 mL or 60 tablets.*
- Both products would be introduced into the US marketplace within six months of each other. An example of this type of problem would be Celexa (approved JUL-1998) and Celebrex (DEC-1998). Errors occurred between Celexa and Celebrex despite different characteristics of the drugs. In this scenario, there is not enough time for practitioners to become familiar with the first product and they easily confuse the characteristics of the two products.
- Asimia and Alinia have different dosing regimens (twice daily for three days vs. once daily on a chronic basis). However, the opportunity for errors exists whenever the prescription is ambiguous or incomplete. See example below.

Alinia 10
OD #60

- Alinia is approved only for children ages one to eleven years at this time and Asimia is indicated for use only in the adult patient population. Since Asimia contains the same active ingredient as Paxil, DMETS also considered the dosing information for Paroxetine Hydrochloride. Dosing information for off-label use of Paroxetine Hydrochloride in children over eight years to treat depression and obsessive-compulsive disorder can be found in the ePocrates reference for prescribers (<http://www.epocrates.com/>). Therefore, the highest risk population at this time includes children between the ages of eight and eleven because they could be considered by some practitioners as candidates for both treatments.
- In the inpatient setting, which is less likely to include both paroxetine salts on the formulary, there is an increased risk for a pediatric patient to receive the Paroxetine Hydrochloride Oral Suspension, in error. This scenario may involve an order for Alinia 10 mL that is misinterpreted as Asimia. The practitioner may know Asimia is paroxetine and dispense the paroxetine oral solution. The consequence of this type of error is unknown in this fragile patient population.
- Asimia and Alinia have different indications for use. Unfortunately this may not be enough to prevent confusion and errors because this information is not always available to the pharmacist or practitioner interpreting the drug order.
- Although Asimia and Alinia are available in different dosage formulations at this time, they are both administered by mouth. Due to post-marketing experience, we must also consider the possibility of future dosage forms that may have potential overlap.

In review of the container labels and insert labeling of Asimia, DMETS has attempted to focus on the safety issues relating to possible medication errors. DMETS has reviewed the current *container labels and insert labeling and has identified several areas of possible improvement*, which might minimize potential user error. Carton labeling was not provided for review at this time.

A. GENERAL COMMENTS

In accordance with the Poison Prevention Act, drugs packaged in "unit of use" bottles and dispensed on an outpatient basis, such as the 30 capsule bottles, should include Child Resistant Closures (CRC). Please ensure the bottles utilize such a closure.

B. CONTAINER LABELS (10 mg, 20 mg, 30 mg, 40 mg – 30 tablets;
20 mg – 100 tablets, 20mg – 500 tablets)

1. We note the established name and strength is confusing. From the label it is difficult to know whether the product is present as 10 mg paroxetine mesylate or 10 mg paroxetine. If the established name is expressed as _____ there is potential for confusion between the mesylate and hydrochloride formulations. We recommend one of the following formats:

a. _____

b. _____

Side panel should state: "" _____

IV. RECOMMENDATIONS

- A. DMETS does not recommend use of the proprietary name, Asimia.
- B. DMETS recommends implementation of the labeling revisions described in Section III.
- C. DDMAC finds the proprietary name, Asimia, acceptable from a promotional perspective.
- D. DMETS recommends consulting Dan Boring (of the USAN council & LNC) for the proper designation of the established name.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)

Concur:

Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.
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/s/

Marci Ann Lee
3/27/03 01:32:23 PM
PHARMACIST

Denise Toyer
3/27/03 01:34:49 PM
PHARMACIST

Denise Toyer
3/27/03 02:06:10 PM
PHARMACIST

Jerry, Carol's DFS is not working

Jerry Phillips
3/28/03 08:53:10 AM
DIRECTOR

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 10/1/01

DUE DATE: 2/19/02

ODS CONSULT: 01-0208

TO:

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH:

Paul David
Project Manager
HFD-120

PRODUCT NAME:

Asimia
(Paroxetine mesylate tablets)
10 mg, 20 mg, 30 mg, 40 mg

NDA SPONSOR:

Synthon Pharmaceuticals, Ltd.

NDA #: 21-299

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Asimia" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS has no objection to the use of the proprietary name, Asimia. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names from the signature date of this document. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Carol Holquist, RPh
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Office of Drug Safety
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Jerry Phillips, RPh
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