



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP96/03252 (22) International Filing Date: 19 July 1996 (19.07.96) (30) Priority Data: 9514842.5 20 July 1995 (20.07.95) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). EDLER, David, Philip [GB/GB]; SmithKline Beecham Pharmaceuticals, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). (74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PAROXETINE CONTROLLED RELEASE COMPOSITIONS		
(57) Abstract A controlled release or delayed release formulation contains a selective serotonin reuptake inhibitor (SSRI) such as paroxetine.		

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PAROXETINE CONTROLLED RELEASE COMPOSITIONS

The present invention relates to a novel formulation containing paroxetine or a pharmaceutically acceptable salt thereof, and to its use in the treatment
5 and/or prophylaxis of certain disorders.

US Patent No 4,007,196 describes *inter alia* a compound which is commonly known as paroxetine. This compound is a Selective Serotonin Reuptake Inhibitor (SSRI) and is currently marketed world-wide for the treatment and/or prophylaxis of depression.

10 The current formulation which is the only marketed formulation of paroxetine hydrochloride is a swallow tablet.

It has now been surprisingly found that controlled release and delayed release formulations containing paroxetine give rise to an unexpected reduction in the side effects associated with swallow tablets.

15 Accordingly, the present invention provides a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a controlled release or delayed release formulation containing an SSRI. Examples of SSRIs other than
20 paroxetine include fluoxetine (US Patent No. 4,314,081), fluvoxamine (US Patent No. 4,085,225), and sertraline (US Patent No. 4,536,518).

By controlled release is meant any formulation technique wherein release of the active substance from the dosage form is modified to occur at a slower
25 rater than that from an immediate release product, such as a conventional swallow tablet or capsule.

By delayed release is meant any formulation technique wherein release of the active substance from the dosage form is modified to occur at a later time than that from a conventional immediate release product. The subsequent release of active substance from a delayed release formulation may also be controlled as
30 defined above.

Examples of controlled release formulations which are suitable for incorporating paroxetine and other SSRIs are described in:

Sustained Release Medications, Chemical Technology Review No. 177.
Ed. J.C. Johnson. Noyes Data Corporation 1980.

35 Controlled Drug Delivery, Fundamentals and Applications, 2nd Edition.
Eds. J.R. Robinson, V.H.L. Lee. Mercel Dekkes Inc. New York 1987.

Examples of delayed release formulations which are suitable for incorporating paroxetine and other SSRIs are described in:

Remington's Pharmaceutical Sciences 16th Edition, Mack Publishing Company 1980, Ed. A. Osol.

5 Such controlled release formulations are preferably formulated in a manner such that release of active substance such as paroxetine is effected predominantly during the passage through the stomach and the small intestine, and delayed release formulations are preferably formulated such that release of active substance such as paroxetine is avoided in the stomach and is effected
10 predominantly during passage through the small intestine

 Said formulations are preferably formulated such that the release of the active substance is predominantly 1½ to 3 hours post ingestion.

 The small intestine is suitably the duodenum, the ileum or the jejunum.

15 Patients who benefit most from the formulations of the present invention are those who are known to suffer from nausea upon oral administration using swallow tablets.

 Preferred formulations are ultimately enteric coated tablets or caplets, wax or polymer coated tablets or caplets or time-release matrices, or combinations thereof.

20 Particularly preferred formulations are described in US Patent No. 5,102,666.

 Thus, a particular aspect of the invention provides a polymeric controlled release composition comprising a reaction complex formed by the interaction of (1) a calcium polycarbophil component which is a water-swella-
25 ble, but water insoluble, fibrous cross-linked carboxy-functional polymer, said polymer containing (a) a plurality of repeating units of which at least about 80% contain at least one carboxyl functionality, and (b) about 0.05 to about 1.5% cross-linking agent substantially free from polyalkenyl polyether, said percentages being based upon the weights of unpolymerised repeating unit and cross-linking agent,
30 respectively, with (2) water, in the presence of an active agent selected from the group consisting of SSRIs such as paroxetine. The amount of calcium polycarbophil present is from about 0.1 to about 99% by weight, for example about 10%. The amount of active agent present is from about 0.0001 to about 65% by weight, for example between about 5 and 20%. The amount of water
35 present is from about 5 to about 200% by weight, for example between about 5 and 10%. The interaction is carried out at a pH of between about 3 and about 10,

for example about 6 to 7. The calcium polycarbophil is originally present in the form of a calcium salt containing from about 5 to about 25% calcium.

Further particularly preferred formulations are described in US Patent No. 5,422,123.

5 Thus, a further particular aspect of the invention provides a system for the controlled release of an active substance which is an SSRI such as paroxetine, comprising (a) a deposit-core comprising an effective amount of the active substance and having defined geometric form, and (b) a support-platform applied to said deposit-core, wherein said deposit-core contains at least the active
10 substance, and at least one member selected from the group consisting of (1) a polymeric material which swells on contact with water or aqueous liquids and a gellable polymeric material wherein the ratio of the said swellable polymeric material to said gellable polymeric material is in the range 1:9 to 9:1, and (2) a single polymeric material having both swelling and gelling properties, and
15 wherein the support-platform is an elastic support, applied to said deposit-core so that it partially covers the surface of the deposit-core and follows changes due to hydration of the deposit-core and is slowly soluble and/or slowly gellable in aqueous fluids. The support-platform may comprise polymers such as hydroxypropylmethylcellulose, plasticizers such as a glyceride, binders such as
20 polyvinylpyrrolidone, hydrophilic agents such as lactose and silica, and/or hydrophobic agents such as magnesium stearate and glycerides. The polymer(s) typically make up 30 to 90% by weight of the support-platform, for example about 35 to 40%. Plasticizer may make up at least 2% by weight of the support-platform, for example about 15 to 20%. Binder(s), hydrophilic agent(s) and
25 hydrophobic agent(s) typically total up to about 50% by weight of the support-platform, for example about 40 to 50%.

Paroxetine used in the present invention is suitably in the form of the free base or a pharmaceutically acceptable salt thereof. Preferably, paroxetine is suitably in the form of the hydrochloride hemihydrate.

30 Paroxetine hydrochloride hemihydrate may be prepared according to the procedures generally outlined in US Patent 4,721,723..

Paroxetine in the form of a controlled release or delayed release formulation can be used to treat and prevent the following disorders:

35 Alcoholism
 Anxiety
 Depression

5 Obsessive Compulsive Disorder
 Panic Disorder
 Chronic Pain
 Obesity
 Senile Dementia
 Migraine
 Bulimia
 Anorexia
 Social Phobia
 10 Pre-Menstrual Syndrome (PMS)
 Adolescent Depression
 Trichotillomania
 Dysthymia
 Substance Abuse

15

These disorders are herein after referred to as "the disorders".

The present invention provides a method of treating and/or preventing the disorders by administering an effective and/or a prophylactic amount of a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof, to a sufferer in need thereof.

20

The present invention further provides the use of a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for treating and/or preventing the disorders.

25

The present invention also provides a pharmaceutical composition for use in the treatment and/or prevention of the disorders which comprises a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof.

The following examples illustrate the present invention.

30

Example 1 (Hydrophilic Matrix)

Intrgranular		<u>% w/w</u>
	Paroxetine Hydrochloride	11.45
35	Methocel E5	1.25
	Lactose	12.3
Extragranular		
	Methocel K100LV	30.0

Lactose	44.0
Magnesium Stearate	1.0
TOTAL	100.0

5 Example 2 (Hydrophilic Matrix)

	Intragranular	<u>% w/w</u>
	Paroxetine Hydrochloride	11.45
	Methocel E5	1.25
10	Lactose	12.3
	Extragranular	
	Methocel K100LV	27.5
	Methocel K4M	7.5
	Lactose	39.0
15	Magnesium Stearate	1.0
	TOTAL	100.0

Example 3 (pH Sensitive Coat on Immediate Release Core)

20	Tablet Core	<u>%w/w</u>
	Paroxetine Hydrochloride	11.45
	Lactose	64.05
	Microcrystalline Cellulose	20.0
	Sodium Starch Glycollate	4.0
25	Magnesium Stearate	0.5
	TOTAL	100.0

	Tablet Coating (apply approximately 6-10% of tablet core weight)	<u>%w/w</u>
	Hydroxypropylmethylcellulose Phthalate	90.0
30	Triacetin	10.0

Example 4 (pH Sensitive Coat on Immediate Release Core)

	Tablet Core as in Example 3	
35	Tablet Coating (apply approximately 6-10% of tablet core weight)	<u>%w/w</u>

Cellulose Acetate Phthalate	90.0
Diethyl Phthalate	10.0

Example 5 (Controlled Release Coating on Immediate Release Core)

5

Tablet Core as in Example 3

Tablet Coating (apply approximately 5-12% of tablet core weight) %w/w

	Eudragit RS 100	86.0
10	Dibutyl Phthalate	10.0
	Talc	4.0
	FD&C Yellow No. 6	0.01

Example 6 (pH Sensitive Coat on Controlled Release Core.)

15

Tablet Core as in Example 3

Tablet Coating as in Example 3

20 **Example 7** (Encapsulated Controlled Release Coated Beads)Pellet %w/w (approx)

	Non Pareil Seed	30
	Paroxetine Hydrochloride	40
25	Gelatin	8
	Lactose	20
	Talc	2

Coating %w/w

30	Glycerylmonostearate	36.6
	Glyceryldistearate	53.4
	White Wax	10.0

Example 8 (Controlled release bilayer tablet)**Active Layer**

5

Component	mg/tablet	Function
Paroxetine Hydrochloride	22.89*	Active
Methocel K4M	15.00	Hydrogel polymer
Lactose monohydrate	62.0	Hydrophilic agent
10 Polyvinylpyrrolidone	3.0	Binder
Magnesium stearate	1.0	Hydrophobic agent
Syloid 244	1.0	Hydrophilic agent

Support platform

15

Component	mg/tablet	Function
Compritol 888	15.04	Plasticizer
Lactose monohydrate	29.32	Hydrophilic agent
20 Polyvinylpyrrolidone	4.0	Binder
Magnesium stearate	1.52	Hydrophobic agent
Methocel E5	29.32	Hydrogel polymer
Iron oxide	0.08	Colourant

25 Total tablet weight 184.89mg

*Equivalent to 20mg paroxetine as free base.

30 The powder blend for each layer was wet granulated in a high shear mixer/granulator and dried in a fluid bed drier. The bilayer tablets were compressed on a Manesty triple layer press.

Example 9 (Enteric coated calcium polycarbophil formulation)**Core**

5	Component	mg/tablet	Function
	Paroxetine Hydrochloride	22.89*	Active
	Calcium polycarbophil	20.00	Matrix
	Lactose anhydrous	146.11	Hydrophilic agent/diluent
	Polyvinylpyrrolidone	10.0	Binder
10	Magnesium stearate	1.0	Hydrophobic agent/lubricant
	Water**	0.024	Granulating liquid

Enteric coat

15	Component	mg/tablet	Function
	Eudragit	22.19	Polymer
	Talc	1.53	Lubricant
	Triethyl citrate	1.00	Plasticizer
20	Water**	24.6	Diluent

Film coat

	Opadry pink	10.5	Film coat
25	Water**	94.5	Diluent

Polish coat

	Opadry clear	0.750	
30	Water**	29.3	Diluent

*Equivalent to 20mg paroxetine as free base.

**Removed during processing.

35 The core constituents were wet granulated in a high shear mixer/granulator, and dried in a fluid bed drier. The magnesium stearate was then added and the

mixture processed in a low shear mixer. The mix was then compressed on a B type rotary tablet press. Coating was carried out using an Accela cota.

Example 10 (Controlled release bilayer tablet)

5

Active Layer

	Component	mg/tablet	Function
	Paroxetine Hydrochloride	22.89*	Active
10	Methocel K4M	20.00	Hydrogel polymer
	Lactose monohydrate	60.0	Hydrophilic agent
	Polyvinylpyrrolidone	5.0	Binder
	Magnesium stearate	1.0	Hydrophobic agent
	Syloid 244	1.0	Hydrophilic agent

15

Support platform

	Component	mg/tablet	Function
20	Compritol 888	14.72	Plasticizer
	Lactose monohydrate	30.60	Hydrophilic agent
	Polyvinylpyrrolidone	2.80	Binder
	Magnesium stearate	0.80	Hydrophobic agent
	Methocel E5	30.60	Hydrogel polymer
25	Syloid 244	0.40	Hydrophilic agent
	Iron oxide	0.08	Colourant

Total tablet weight 189.89mg

30 *Equivalent to 20mg paroxetine as free base.

The process was as described in Example 8.

Example 11 (Controlled release bilayer tablet)**Active Layer**

5	Component	mg/tablet	Function
	Paroxetine Hydrochloride	22.89*	Active
	Methocel K4M	15.00	Hydrogel polymer
	Lactose monohydrate	63.31	Hydrophilic agent
	Polyvinylpyrrolidone	2.0	Binder
10	Magnesium stearate	1.0	Hydrophobic agent
	Syloid 244	0.40	Hydrophilic agent

Support platform - as in Example 10.

15 Total tablet weight 184.60mg

*Equivalent to 20mg paroxetine as free base.

The process was as described in Example 8.

20

Example 12 (Enteric coated controlled release bilayer tablet)**Active Layer**

25	Component	mg/tablet	Function
	Paroxetine Hydrochloride	28.61*	Active
	Methocel K4M	18.75	Hydrogel polymer
	Lactose monohydrate	79.14	Hydrophilic agent
	Polyvinylpyrrolidone	2.50	Binder
30	Magnesium stearate	1.25	Hydrophobic agent
	Syloid 244	0.50	Hydrophilic agent

Support platform

	Component	mg/tablet	Function
5	Compritol 888	15.04	Plasticizer
	Lactose monohydrate	30.50	Hydrophilic agent
	Polyvinylpyrrolidone	4.00	Binder
	Magnesium stearate	0.80	Hydrophobic agent
	Methocel E5	29.32	Hydrogel polymer
10	Syloid 244	0.32	Hydrophilic agent
	Iron oxide	0.02	Colourant

Enteric coating

	Component	mg/tablet	Function
15	Eudragit	13.27	Polymer
	Talc	3.31	Lubricant
	Triethyl citrate	1.33	Plasticizer
20	Water**	36.25	Diluent

Total tablet weight 228.66mg

*Equivalent to 25mg paroxetine as free base.

25

**Removed during processing.

The process was as described in Example 9.

Example 13**GI tolerance study**

The design of the study is outlined below

- 5 **Subjects:** Normal healthy volunteers
 Design: Parallel group, placebo controlled, double blind
 Treatment: (a) Placebo, (b) Immediate release paroxetine, (c) Example
 8 formulation, (d) Example 8 formulation with enteric
 coating.
 10 **Dosage:** 30 mg once daily for 3 days
 Number of subjects: 452 evaluable (488 randomised, 485 evaluable)

- The study was conducted to compare the incidence, severity and duration of
 nausea and vomiting, and diarrhoea (theoretically if the controlled release
 15 formulations slow down absorption of paroxetine then, as paroxetine is known to
 be prokinetic to the GI tract there may be an increased incidence).

- Adverse experiences (AE) information was assessed each morning at the time of
 dosing and again 24 hours following the last dose. Investigators and subjects
 20 were given diary cards detailing how to classify severity of AEs in order to
 standardise as much as possible across all 6 centres.

- Of the 485 evaluable subjects, 18 (3.7%) withdrew, 17 because of adverse events.
 Subjects with nausea/vomiting on the day of withdrawal were more common on
 25 (b) than either of (c) and (d).

The incidence of nausea/vomiting and diarrhoea is shown in the table below:

	(b)	(c)	(d)	Placebo
Incidence of nausea	59%	49%	39%	13%
Incidence of diarrhoea	15%	21%	20%	7%

- 30 The incidence of nausea was increased for both (b) and placebo compared to the
 expected rates of approximately 25% and 5% respectively for volunteers at these
 dosages for 3 days duration. The overall incidence of nausea was less on (c) and

(d) than on (b). The severity of nausea was also decreased as shown in the next table.

Nausea severity	(b)	(c)	(d)	Placebo
None	50 (41%)	63 (52%)	74 (61%)	104 (87%)
Mild	45 (37%)	40 (33%)	30 (25%)	16 (13%)
Moderate	21 (17%)	17 (14%)	15 (12%)	0 (0%)
Severe	6 (5%)	1 (1%)	3 (2%)	0 (0%)

5 Severity of diarrhoea is reported in the table below:

Severity of diarrhoea	(b)	(c)	(d)	Placebo
None	104 (85%)	95 (79%)	97 (80%)	112 (93%)
Mild	16 (13%)	16 (13%)	16 (13%)	8 (7%)
Moderate	1 (1%)	8 (7%)	9 (7%)	0 (0%)
Severe	1 (1%)	2 (2%)	0 (0%)	0 (0%)

In conclusion, there appears to be a trend for (c) to reduce the incidence of nausea and the dropout rate due to adverse events in comparison to (b), but analysis of the results was complicated by a statistically significant treatment-by-centre difference. (d) shows a halving in the dropout rate and a fall in incidence of nausea of 20% (a proportional fall of 33%). In addition there is a reduction in severity of nausea of those individuals who report nausea on (c) and (d). There is an increase in incidence of diarrhoea on both of (c) and (d) in relation to (b), but this is confined to an increase in the number of individuals reporting moderate diarrhoea and there is no increase in those with severe diarrhoea.

Claims

1. A controlled release or delayed release formulation containing a selective serotonin reuptake inhibitor (SSRI).
2. A formulation according to claim 1 wherein the SSRI is paroxetine or a pharmaceutically acceptable salt thereof.
3. A formulation according to claim 1 or 2, which comprises enteric coated tablets or caplets, wax or polymer coated tablets or caplets or time-release matrices, or combinations thereof.
4. A formulation according to any preceding claim, which is a polymeric controlled release composition comprising a reaction complex formed by the interaction of (1) a calcium polycarbophil component which is a water-swella-
ble, but water insoluble, fibrous cross-linked carboxy-functional polymer, said polymer containing (a) a plurality of repeating units of which at least about 80% contain at least one carboxyl functionality, and (b) about 0.05 to about 1.5% cross-linking agent substantially free from polyalkenyl polyether, said percentages being based upon the weights of unpolymerised repeating unit and cross-linking agent, respectively, with (2) water, in the presence of an active agent selected from the group consisting of SSRIs.
5. A formulation according to any one of claims 1 to 3, which is a system for the controlled release of an active substance which is an SSRI, comprising (a) a deposit-core comprising an effective amount of the active substance and having defined geometric form, and (b) a support-platform applied to said deposit-core, wherein said deposit-core contains at least the active substance, and at least one member selected from the group consisting of (1) a polymeric material which swells on contact with water or aqueous liquids and a gellable polymeric material wherein the ratio of the said swellable polymeric material to said gellable polymeric material is in the range 1:9 to 9:1, and (2) a single polymeric material having both swelling and gelling properties, and wherein the support-platform is an elastic support, applied to said deposit-core so that it partially covers the surface of the deposit-core and follows changes due to hydration of the deposit-core and is slowly soluble and/or slowly gellable in aqueous fluids.

6. A method of treating and/or preventing the disorders by administering an effective and/or a prophylactic amount of a controlled release or delayed release formulation according to any preceding claim, to a sufferer in need thereof.
- 5
7. Use of a controlled release or delayed release formulation according to any one of claims 1 to 5 in the manufacture of a medicament, for treating and/or preventing the disorders.
- 10
8. A process for the preparation of a formulation according to any one of claims 1 to 5, which comprises combining the constituents thereof in the required proportions.

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/EP 96/03252

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,95 15155 (SMITHKLINE BEECHAM) 8 June 1995 see the whole document ---	1-8
A	EP,A,0 432 607 (JAGOTEC AG) 19 June 1991 cited in the application see the whole document ---	1-8
A	WO,A,92 03124 (ORAMED) 5 March 1992 cited in the application see the whole document ---	1-8
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
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- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

11 November 1996

Date of mailing of the international search report

20. 11. 96

Name and mailing address of the ISA

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Scarponi, U

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/EP 96/03252

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	<p>CHEMICAL ABSTRACTS, vol. 124, no. 10, 4 March 1996 Columbus, Ohio, US; abstract no. 127144, XP002018196 see abstract & CA,A,2 143 070 (P.MODI) 23 August 1995 -----</p>	1-8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 96/03252

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 6
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/EP 96/03252

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9515155	08-06-95	AU-A- 1219895	19-06-95
		CA-A- 2177721	08-06-95
		ZA-A- 9409567	10-10-95

EP-A-432607	19-06-91	IT-B- 1237904	18-06-93
		AT-T- 135906	15-04-96
		CA-A- 2031393	15-06-91
		DE-D- 69026215	02-05-96
		DE-T- 69026215	22-08-96
		ES-T- 2085316	01-06-96
		JP-A- 6172162	21-06-94
		US-A- 5422123	06-06-95

WO-A-9203124	05-03-92	US-A- 5110605	05-05-92
		US-A- 5102666	07-04-92
		AT-T- 137404	15-05-96
		AU-A- 8444291	17-03-92
		DE-D- 69119217	05-06-96
		DE-T- 69119217	31-10-96
		EP-A- 0497956	12-08-92
		ES-T- 2088500	16-08-96
		JP-T- 5502894	20-05-93

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