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(54) Title: PRUCALOPRIDE-N-OXIDE

(57) Abstract: The present invention is concerned with a novel benzamide derivative and the pharmaceutically acceptable acid addition salts thereof, pharmaceutical compositions comprising said novel compound, processes for preparing said compounds and compositions, and the use thereof as a medicine in the treatment of gastrointestinal motility disorders.



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PRUCALOPRIDE-N-OXIDE

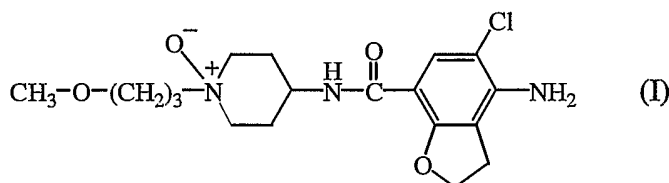
The present invention is concerned with a novel benzamide derivative and the
5 pharmaceutically acceptable acid addition salts thereof, pharmaceutical compositions
comprising said novel compound, processes for preparing said compounds and
compositions, and the use thereof as a medicine in the treatment of gastrointestinal
motility disorders.

10 EP-0,445,862-A, published on September 11, 1991, N-(4-piperidiny) (dihydrobenzo-
furan or dihydro-2H-benzopyran)carboxamide derivatives are disclosed having
gastrointestinal motility stimulating properties.

WO-96/16060, published on 30 May 1996, specifically discloses the compound 4-amino-
5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidiny]-7-benzofuran-
15 carboxamide which is generically known as "prucalopride".

The compounds of the present invention differ therefrom by the fact that they invariably
contain a 1-piperidine oxide moiety and by their improved pharmacological properties.

20 The present invention concerns a compound of formula (I)



25 and stereochemically isomeric forms and pharmaceutically acceptable acid addition
salts thereof.

The term "stereochemically isomeric forms" as used hereinbefore defines all the
possible isomeric forms which the compounds of formula (I) may possess. Unless
otherwise mentioned or indicated, the chemical designation of compounds denotes the
30 mixture of all possible stereochemically isomeric forms, said mixtures containing all
diastereomers and enantiomers of the basic molecular structure. More in particular, the
substituents on the piperidine moiety have either the cis- or trans-configuration.
Stereochemically isomeric forms of the compounds of formula (I) are obviously
35 intended to be embraced within the scope of this invention.

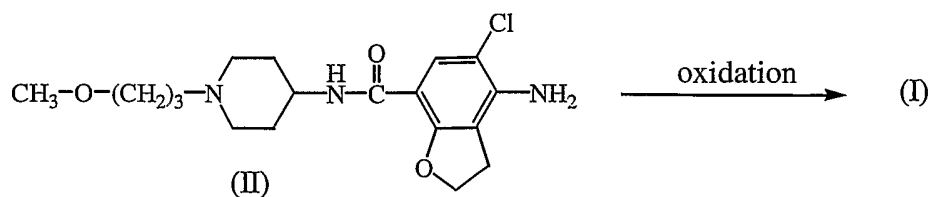
-2-

The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such
5 appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic,
10 benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

15 The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

20 The compounds of formula (I) can be prepared following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting a compound of formula (II) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide,
25 potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzene-carboperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene,
30 ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.



The compounds of formula (I) as prepared in the hereinabove described process may be synthesized in the form of mixture of cis- and trans-stereoisomers which can be separated from one another following art-known resolution procedures. Alternatively, depending upon the reaction conditions of the oxidation reaction, said oxidation
5 reaction may yield either the cis-stereoisomer or the trans-stereoisomer.

The compounds of formula (II) are known compounds and can be prepared according to the procedures described in WO-96/16060.

10 Upon oral administration the N-oxide compounds of formula (I) of the present invention are converted into compounds of formula (II) by bacterial or enzymatic reduction. Furthermore it was found that unexpectedly systemic exposure to compounds of formula (II) was lower upon oral administration of a N-oxide compound
15 of formula (I) compared to oral administration of an equimolar amount of compound of formula (II) while the motility enhancing effect remains. A lower systemic exposure may be beneficial in reducing potential adverse effects.

The compound of formula (II), generically known as prucalopride, facilitates both cholinergic and non-cholinergic non-adrenergic (NANC) excitatory neurotransmission
20 and stimulates colonic motility and defecation in animals. It has no affinity for 5-HT_{2A} and 5-HT_{3A} receptors but is a potent and selective agonist of 5-HT₄ receptors. Prucalopride induces giant contractions in the colon that are propagated over the length of the colon as a peristaltic wave and therefore has significant motility enhancing effects on the large intestine. Furthermore, it is believed that prucalopride is also useful
25 for the treatment of upper GI tract motility disorders such as gastro-oesophageal reflux.

In view of its enterokinetic properties, prucalopride is useful in the treatment of motility disorders of the intestinal system, such as, e.g. gastroparesis, dyspepsia, constipation, pseudo-obstruction, intestinal atony, post-operative intestinal atony, irritable bowel
30 syndrome (IBS), and drug-induced delayed transit. The subject compounds may also be used to facilitate large bowel cleaning or to facilitate intubation and/or endoscopy. Said method comprises the systemic administration of an effective motility stimulating amount of prucalopride to warm-blooded animals, including humans.

35 In view of the utility of the compounds of formula (I), it follows that the present invention also provides a method of treating warm-blooded animals, including humans, (generally called herein patients) suffering from motility disorders of the intestinal

system. Consequently a method of treatment is provided for relieving patients suffering from conditions, such as, for example, constipation, pseudo-obstruction, intestinal atony, post-operative intestinal atony, irritable bowel syndrome (IBS), drug-induced delayed transit, large bowel cleaning.

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Hence, the use of a compound of formula (I) as medicine is provided, and in particular the use of a compound of formula (I) for the manufacture of a medicine for treating conditions involving a disordered motility or transit of the upper and lower gastrointestinal tract.

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To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection.

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For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. Acid addition salts of (I) due to their increased water solubility over the

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corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

5 Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers,
10 injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

For oral administration, the pharmaceutical compositions may take the form of solid dose forms, for example, tablets (both swallowable-only and chewable forms), capsules
15 or gels, prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting
20 agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for
25 constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means, optionally with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxypropyl methylcellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and
30 preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

Pharmaceutically acceptable sweeteners comprise preferably at least one intense sweetener such as saccharin, sodium or calcium saccharin, aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, monellin,
35 stevioside or sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), preferably saccharin, sodium or calcium saccharin, and optionally a bulk sweetener such as

sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey.

Intense sweeteners are conveniently employed in low concentrations. For example, in
5 the case of sodium saccharin, the concentration may range from 0.04% to 0.1% (w/v)
based on the total volume of the final formulation, and preferably is about 0.06% in the
low-dosage formulations and about 0.08% in the high-dosage ones. The bulk sweetener
can effectively be used in larger quantities ranging from about 10% to about 35%,
preferably from about 10% to 15% (w/v).

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The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients
in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry,
black currant or strawberry flavour. A combination of two flavours may yield very
good results. In the high-dosage formulations stronger flavours may be required such
15 as Caramel Chocolate flavour, Mint Cool flavour, Fantasy flavour and the like
pharmaceutically acceptable strong flavours. Each flavour may be present in the final
composition in a concentration ranging from 0.05% to 1% (w/v). Combinations of said
strong flavours are advantageously used. Preferably a flavour is used that does not
undergo any change or loss of taste and colour under the acidic conditions of the
20 formulation.

The compounds of the invention may also be formulated as depot preparations. Such
long acting formulations may be administered by implantation (for example
subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example,
25 the compounds may be formulated with suitable polymeric or hydrophobic materials
(for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly
soluble derivatives, for example as a sparingly soluble salt.

The compounds of the invention may be formulated for parenteral administration by
30 injection, conveniently intravenous, intramuscular or subcutaneous injection, for
example by bolus injection or continuous intravenous infusion. Formulations for
injection may be presented in unit dosage form e.g. in ampoules or in multidose
containers, with an added preservative. The compositions may take such forms as
suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain
35 formulatory agents such as isotonicizing, suspending, stabilising and/or dispersing agents.
Alternatively, the active ingredient may be in powder form for constitution with a
suitable vehicle, e.g. sterile pyrogen-free water before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

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The formulations of the present invention may optionally include an anti-flatulent, such as simethicone, alpha-D-galactosidase and the like. Furthermore, the formulations may optionally comprise other active ingredients e.g. δ -opiate antagonists such as naltrindole and the like.

10

In general it is contemplated that a therapeutically effective amount would be from about 0.001 mg/kg to about 2 mg/kg body weight, preferably from about 0.02 mg/kg to about 0.5 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day, or on

15

demand.

The amount of prucalopride-N-oxide, or a pharmaceutically acceptable acid addition salt thereof, required as daily dose in treatment will vary not only with the route of administration, the nature of the condition being treated and the age, weight and condition of the patient and will ultimately be at the discretion of the attendant physician. In general, however, a suitable daily dose will be in the range of from about 0.05 to about 200 mg per day, in particular from about 0.1 to 20 mg per day, more particular from about 0.5 to 10 mg per day. A suitable daily dose for use in prophylaxis will generally be in the same range. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Administration can be before or after the intake of food (*i.e.* preprandial or postprandial).

20

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Experimental part

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A. Preparation

For some chemicals the chemical formula was used, e.g. CH₃CN for acetonitril, CH₂Cl₂ for dichloromethane, NH₄OAc for ammonium acetate and CH₃OH for methanol.

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Example A.1

4-Amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofuran-carboxamide (0.012 mol) was dissolved in dichloromethane (200 ml) and 3-chloro-

benzenecarboperoxoic acid (0.015 mol) was added. This mixture was stirred for 3 hours at room temperature. The mixture was diluted with aqueous ammonia and the resulting precipitate was filtered off and recrystallized from CH₃CN/2-propanol. The precipitate was filtered off and dried, yielding 2.15 g of cis-4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide, N-oxide monohydrate (compound (1), mp. 179.8°C).

Example A.2

4-Amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide (0.05 mol) was dissolved in dichloromethane (500 ml) and 3-phenyl-2-(phenylsulfonyl)-oxaziridine (Davis' reagent) (0.055 mol) was added. This mixture was stirred for 4 hours at room temperature. The mixture was concentrated to a volume of about 200 ml and the resulting precipitate was filtered off, dried and was purified by column chromatography over silica gel (eluent : CH₂Cl₂/CH₃OH 95/5). The pure fractions were collected and the solvent was evaporated. The residue was triturated in DIPE, filtered off and dried and purified by high-performance liquid chromatography over RP-18 (eluent: (0.5% NH₄OAc in H₂O)/CH₃CN 85/15 v/v). The pure fractions were collected and the solvent was evaporated. The residue was triturated in DIPE, filtered off and dried, yielding 1.26 g trans-4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofurancarboxamide, N-oxide monohydrate (compound (2), mp. 230°C).

B. Pharmacological Examples

Example B.1

Two male beagle dogs were dosed orally with 1 ml of a test formulation comprising 2.5 mg/kg of 4-amino-5-chloro-2,3-dihydro-N-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofuran-carboxamide ("prucalopride").

After a wash-out period of four weeks, the same two dogs were dosed orally with 1 ml of a test formulation comprising 2.61 mg/kg of compound (1).

Blood samples were taken via the jugular vein immediately before dosing (blank sample) and at 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h, and 24 h after dosing. Aliquots of 10 ml were collected in EDTA tubes. Immediately after collection of the blood samples, plasme samples were prepared by centrifugation at approximately 1700 x g for approximately 10 minutes.

Concentrations of of prucalopride in the plasma samples were determined by LC/MS/MS. The quantification limit for prucalopride was 5.0 ng/ml.

Based on the individual plasma concentration-time data, using the actual sampling times, the following pharmacokinetic parameters were determined for prucalopride after oral administration of prucalopride and compound (1) and summarized in Table 1.

- 5 C_{\max} peak plasma concentration, determined by visual inspection of the data
 T_{\max} time to reach the peak plasma concentration, determined by visual inspection of the data.
 $AUC_{0-\infty}$ area under the plasma concentration-time extrapolated to infinity

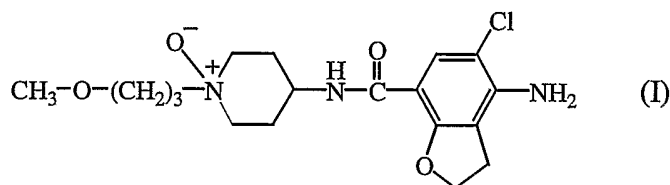
10 **Table 1** : pharmacokinetic parameters for prucalopride after single oral administration of prucalopride and compound (1)

	oral administration of prucalopride		oral administration of compound (1)	
	Dog 1	Dog 2	Dog 1	Dog 2
C_{\max}	556 ng/ml	660 ng/ml	222 ng/ml	488 ng/ml
T_{\max}	1.0 h	0.5 h	2.0 h	2.0 h
$AUC_{0-\infty}$	4226 ng.h/ml	4372 ng.h/ml	2265 ng.h/ml	4093 ng.h/ml

15 As can be seen in Table 1, oral administration of compound (1) gives a lower peak plasma concentration C_{\max} of prucalopride and the time T_{\max} to reach said C_{\max} is later. Hence systemic exposure to prucalopride after oral administration of compound (1) is substantially lower than after oral administration of prucalopride itself.

Claims

1. A compound of formula (I)



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and stereochemically isomeric forms and pharmaceutically acceptable acid addition salts thereof.

2. A compound as claimed in claim 1 having the cis configuration.
3. A compound as claimed in claim 1 having the trans configuration.
4. A compound as claimed in any of claims 1 to 3 wherein the compound of formula (I) is the (1:1) hydrate.
5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 4.
6. A process for preparing a pharmaceutical composition as claimed in claim 5 wherein a therapeutically active amount of a compound as claimed in any of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.
7. A compound as claimed in any of claims 1 to 4 for use as a medicine.
8. A process for preparing a compound of formula (I) by oxidizing a compound of formula (II) with a suitable oxidans in a reaction-inert solvent.

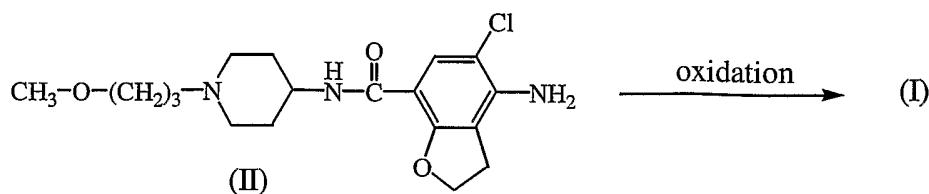
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/00276

A. CLASSIFICATION OF SUBJECT MATTER
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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 7 C07D

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)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 16060 A (JANSSEN PHARMACEUTICA NV ;HENDRICKX MARIE LOUISE & HF (BE); DAELE) 30 May 1996 (1996-05-30) cited in the application * see examples 1, 6-8 and the claims * the whole document	1-8
Y	EP 0 445 862 A (JANSSEN PHARMACEUTICA NV) 11 September 1991 (1991-09-11) cited in the application * see p. 4, line 39-41 * the whole document	1-8
Y	EP 0 389 037 A (JANSSEN PHARMACEUTICA NV) 26 September 1990 (1990-09-26) * see p.3, line 49-51 * 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.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/00276

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 374 637 A (VAN DAELE GEORGES H P ET AL) 20 December 1994 (1994-12-20) * see col. 3, line 56-60 * the whole document ----	1-8
Y	WO 96 10027 A (JANSSEN PHARMACEUTICA NV ;HENDRICKX MARIE LOUISE & HF (BE); DAELE) 4 April 1996 (1996-04-04) * see par. bridging p.3/4 * the whole document ----	1-8
Y	WO 97 31897 A (JANSSEN PHARMACEUTICA NV ;BOSMANS JEAN PAUL R M (BE); LOVE CHRISTO) 4 September 1997 (1997-09-04) * see p.8, line 13-16 * the whole document ----	1-8
Y	WO 97 24356 A (JANSSEN PHARMACEUTICA NV ;JANSSENS FRANS EDUARD (BE); LEENAERTS JO) 10 July 1997 (1997-07-10) * see par. bridging p.5/6 * the whole document ----	1-8
Y	WO 97 30031 A (JANSSEN PHARMACEUTICA NV ;BOSMANS JEAN PAUL R M A (BE); LOVE CHRIS) 21 August 1997 (1997-08-21) * see p.6, line 25- 28 * the whole document ----	1-8
Y	EP 0 299 586 A (SHELL INT RESEARCH) 18 January 1989 (1989-01-18) * see p.3, line 6-8 * the whole document ----	1-8
Y	WO 00 30640 A (JANSSEN PHARMACEUTICA NV ;SCHUURKES JOANNES ADRIANUS JAC (BE)) 2 June 2000 (2000-06-02) * see claims ; p.2, line 2-4 * the whole document ----	1-8
Y	WO 00 66170 A (JANSSEN PHARMACEUTICA NV ;PROOST EDDY ANDRE JOSEE DE (BE)) 9 November 2000 (2000-11-09) * see claims ; p.2, line 26-28 * the whole document -----	1-8

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/00276

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9616060	A	30-05-1996	AP 777 A	28-10-1999
			AT 217306 T	15-05-2002
			AU 704043 B2	15-04-1999
			AU 4299296 A	17-06-1996
			BG 63710 B1	31-10-2002
			BG 101605 A	27-02-1998
			BR 9509819 A	30-09-1997
			CA 2205573 A1	30-05-1996
			CN 1164233 A ,B	05-11-1997
			CZ 9701555 A3	17-09-1997
			DE 69526679 D1	13-06-2002
			DE 69526679 T2	05-12-2002
			DK 807110 T3	02-09-2002
			EE 3313 B1	15-12-2000
			WO 9616060 A1	30-05-1996
			EP 0807110 A1	19-11-1997
			ES 2177671 T3	16-12-2002
			FI 972203 A	23-05-1997
			HR 950571 A1	31-08-1997
			HU 77375 A2	28-04-1998
			IL 116101 A	17-08-1999
			JP 3046076 B2	29-05-2000
			JP 9512832 T	22-12-1997
			KR 233489 B1	01-12-1999
			NO 972143 A	09-05-1997
			NZ 297753 A	27-05-1998
			PL 320297 A1	15-09-1997
			PT 807110 T	31-10-2002
			RO 116279 B	29-12-2000
			RU 2154643 C2	20-08-2000
			SI 807110 T1	31-08-2002
			SK 65297 A3	08-10-1997
			TR 960495 A2	21-07-1996
US 5948794 A	07-09-1999			
US 6310077 B1	30-10-2001			
US 5854260 A	29-12-1998			
ZA 9509996 A	23-05-1997			
EP 0445862	A	11-09-1991	AT 191912 T	15-05-2000
			AU 636012 B2	08-04-1993
			AU 7207991 A	12-09-1991
			BG 60381 B1	31-01-1995
			CA 2037575 A1	07-09-1991
			CN 1054598 A ,B	18-09-1991
			CN 1054778 A	25-09-1991
			CS 9100460 A2	15-10-1991
			DE 69132119 D1	25-05-2000
			DE 69132119 T2	21-12-2000
			DK 445862 T3	04-09-2000
			EP 0445862 A2	11-09-1991
			ES 2147175 T3	01-09-2000
			FI 911096 A	07-09-1991
			GR 3033461 T3	29-09-2000
			HK 1010727 A1	08-09-2000
			HR 930483 A1	31-12-1995
			HU 60733 A2	28-10-1992
			HU 9500241 A3	28-08-1995
			IE 910710 A1	11-09-1991

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/00276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 0445862	A	IL 97018 A	27-11-1995	
		JP 2601566 B2	16-04-1997	
		JP 4211685 A	03-08-1992	
		KR 177521 B1	20-03-1999	
		LT 846 A , B	27-02-1995	
		LV 10085 A , B	10-05-1994	
		NO 910863 A , B ,	09-09-1991	
		NZ 237189 A	25-11-1992	
		PL 289323 A1	09-03-1992	
		PL 168384 B1	29-02-1996	
		PL 168686 B1	29-03-1996	
		PL 168693 B1	29-03-1996	
		PL 168356 B1	29-02-1996	
		PL 169238 B1	28-06-1996	
		PT 96937 A , B	31-10-1991	
		SG 47482 A1	17-04-1998	
		SI 9110396 A , B	31-12-1997	
		SK 282406 B6	07-01-2002	
		SK 282407 B6	07-01-2002	
		RU 2070884 C1	27-12-1996	
		US 5185335 A	09-02-1993	
		US 5262418 A	16-11-1993	
		ZA 9101611 A	25-11-1992	
		ZW 2391 A1	07-09-1992	
EP 0389037	A	26-09-1990	AT 128132 T	15-10-1995
		AU 616838 B2	07-11-1991	
		AU 5209190 A	27-09-1990	
		CA 2012432 A1	22-09-1990	
		CN 1045781 A , B	03-10-1990	
		CY 1921 A	07-03-1997	
		DE 69022453 D1	26-10-1995	
		DK 389037 T3	16-10-1995	
		EP 0389037 A1	26-09-1990	
		ES 2081340 T3	01-03-1996	
		FI 101624 B1	31-07-1998	
		FI 944076 A	05-09-1994	
		GR 3017992 T3	29-02-1996	
		HK 131596 A	26-07-1996	
		HU 58322 A2	28-02-1992	
		HU 9500311 A3	28-09-1995	
		IE 67184 B1	06-03-1996	
		IL 93817 A	30-03-1995	
		IL 110397 A	26-05-1995	
		JP 2289566 A	29-11-1990	
		JP 2845341 B2	13-01-1999	
		KR 163587 B1	01-12-1998	
		NO 901306 A , B ,	24-09-1990	
		NZ 232964 A	26-07-1991	
		PT 93531 A , B	07-11-1990	
		RU 2108332 C1	10-04-1998	
		RU 2037492 C1	19-06-1995	
US 5552553 A	03-09-1996			
US 5616738 A	01-04-1997			
US 5521314 A	28-05-1996			
US 5576448 A	19-11-1996			
US 5554772 A	10-09-1996			
US 5565582 A	15-10-1996			

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/00276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0389037	A	US 5616583 A	01-04-1997
		US 5536733 A	16-07-1996
		US 5602129 A	11-02-1997
		US 5610157 A	11-03-1997
		US 5739134 A	14-04-1998
		US 5374637 A	20-12-1994
		ZA 9002188 A	27-11-1991
		ZM 1290 A1	31-07-1992
		ZW 3390 A1	23-10-1991
US 5374637	A	20-12-1994	
		US 5552553 A	03-09-1996
		US 5616738 A	01-04-1997
		US 5521314 A	28-05-1996
		US 5576448 A	19-11-1996
		US 5554772 A	10-09-1996
		US 5565582 A	15-10-1996
		US 5616583 A	01-04-1997
		US 5536733 A	16-07-1996
		US 5602129 A	11-02-1997
		US 5610157 A	11-03-1997
		US 5739134 A	14-04-1998
		AT 128132 T	15-10-1995
		AU 616838 B2	07-11-1991
		AU 5209190 A	27-09-1990
		CA 2012432 A1	22-09-1990
		CN 1045781 A ,B	03-10-1990
		CY 1921 A	07-03-1997
		DE 69022453 D1	26-10-1995
		DK 389037 T3	16-10-1995
		EP 0389037 A1	26-09-1990
		ES 2081340 T3	01-03-1996
		FI 101624 B1	31-07-1998
		FI 944076 A	05-09-1994
		GR 3017992 T3	29-02-1996
		HK 131596 A	26-07-1996
		HU 58322 A2	28-02-1992
		HU 9500311 A3	28-09-1995
		IE 67184 B1	06-03-1996
		IL 93817 A	30-03-1995
		IL 110397 A	26-05-1995
		JP 2289566 A	29-11-1990
		JP 2845341 B2	13-01-1999
KR 163587 B1	01-12-1998		
NO 901306 A ,B,	24-09-1990		
NZ 232964 A	26-07-1991		
PT 93531 A ,B	07-11-1990		
RU 2108332 C1	10-04-1998		
RU 2037492 C1	19-06-1995		
ZA 9002188 A	27-11-1991		
ZM 1290 A1	31-07-1992		
ZW 3390 A1	23-10-1991		
WO 9610027	A	04-04-1996	
		AT 187453 T	15-12-1999
		AU 699152 B2	26-11-1998
		AU 3608195 A	19-04-1996
		BR 9509036 A	14-10-1997
		CA 2200578 A1	04-04-1996
CN 1166171 A ,B	26-11-1997		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/00276

Patent document cited in search report	Publication date	Patent family member(s)	Publication date		
WO 9610027	A	CZ	9700918 A3	17-12-1997	
		DE	69513846 D1	13-01-2000	
		DE	69513846 T2	06-07-2000	
		DK	784620 T3	22-05-2000	
		WO	9610027 A1	04-04-1996	
		EP	0784620 A1	23-07-1997	
		ES	2141383 T3	16-03-2000	
		FI	971274 A	26-03-1997	
		GR	3032646 T3	30-06-2000	
		HU	77173 A2	02-03-1998	
		IL	115413 A	17-02-2000	
		JP	10506118 T	16-06-1998	
		NO	971376 A	05-05-1997	
		NZ	293605 A	28-07-1998	
		PL	319997 A1	01-09-1997	
		PT	784620 T	31-05-2000	
		RU	2154064 C2	10-08-2000	
ZA	9508081 A	26-03-1997			
TW	448173 B	01-08-2001			
WO 9731897	A	04-09-1997	AU	724401 B2	21-09-2000
		AU	1767897 A	16-09-1997	
		CA	2242494 A1	04-09-1997	
		WO	9731897 A1	04-09-1997	
		EP	0885190 A1	23-12-1998	
		JP	2000505461 T	09-05-2000	
		TW	445263 B	11-07-2001	
		US	6291481 B1	18-09-2001	
		US	2002042430 A1	11-04-2002	
		ZA	9701735 A	27-08-1998	
WO 9724356	A	10-07-1997	AT	208392 T	15-11-2001
		AU	716071 B2	17-02-2000	
		AU	1308697 A	28-07-1997	
		BR	9612307 A	13-07-1999	
		CA	2238817 A1	10-07-1997	
		CN	1206417 A , B	27-01-1999	
		CZ	9801865 A3	11-11-1998	
		DE	69616802 D1	13-12-2001	
		DE	69616802 T2	04-07-2002	
		DK	843679 T3	25-02-2002	
		EA	1374 B1	26-02-2001	
		WO	9724356 A1	10-07-1997	
		EP	0843679 A1	27-05-1998	
		ES	2167619 T3	16-05-2002	
		HK	1011206 A1	22-03-2002	
		HU	9903948 A2	28-03-2000	
		IL	124641 A	25-11-2001	
		JP	2000506503 T	30-05-2000	
		NO	982405 A	19-08-1998	
		NZ	325845 A	29-06-1999	
		PL	327136 A1	23-11-1998	
		PT	843679 T	29-04-2002	
		SI	843679 T1	30-06-2002	
SK	83098 A3	11-01-1999			
TR	9801210 T2	21-10-1999			
TW	382017 B	11-02-2000			
US	6251894 B1	26-06-2001			

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/00276

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9724356	A		ZA 9610889 A	23-06-1998
WO 9730031	A	21-08-1997	AT 221519 T	15-08-2002
			AU 718695 B2	20-04-2000
			AU 1722897 A	02-09-1997
			BR 9707550 A	27-07-1999
			CA 2235133 A1	21-08-1997
			DE 69714413 D1	05-09-2002
			WO 9730031 A1	21-08-1997
			EP 0880500 A1	02-12-1998
			ES 2180930 T3	16-02-2003
			JP 2000504701 T	18-04-2000
			NO 981717 A	13-08-1998
			NZ 330263 A	29-06-1999
			TW 412532 B	21-11-2000
			US 6096761 A	01-08-2000
			ZA 9701235 A	13-08-1998
EP 0299586	A	18-01-1989	AT 104293 T	15-04-1994
			DE 3889022 D1	19-05-1994
			DE 3889022 T2	21-07-1994
			EP 0299586 A2	18-01-1989
			FI 883314 A ,B,	15-01-1989
			JP 1031777 A	02-02-1989
			JP 2632191 B2	23-07-1997
			US 4889940 A	26-12-1989
WO 0030640	A	02-06-2000	AU 1385700 A	13-06-2000
			CA 2352278 A1	02-06-2000
			WO 0030640 A1	02-06-2000
			EP 1135130 A1	26-09-2001
			JP 2002530334 T	17-09-2002
			NZ 511117 A	26-11-2002
WO 0066170	A	09-11-2000	AU 4913700 A	17-11-2000
			BG 106031 A	31-05-2002
			BR 0010150 A	15-01-2002
			CN 1348386 T	08-05-2002
			CZ 20013735 A3	13-02-2002
			EE 200100539 A	16-12-2002
			WO 0066170 A1	09-11-2000
			EP 1176982 A1	06-02-2002
			HU 0202324 A2	28-12-2002
			JP 2002543161 T	17-12-2002
			NO 20014794 A	02-10-2001
			SK 15192001 A3	05-03-2002
			TR 200103121 T2	21-05-2002
			US 6413988 B1	02-07-2002