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WO 2004/000855 A1

(54) Title: COMBINATION OF AN ACID SECRETION INHIBITING AGENT AND A REFLUX INHIBITOR FOR THE TREATMENT OF GERD

(57) Abstract: The present invention relates to a medicament comprising, separately or together, (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor. A further aspect of the invention relates to methods of treatment of gastro-esophageal reflux disease, regurgitation, asthma, failure to thrive and lung disease.

COMBINATION OF AN ACID SECRETION INHIBITING AGENT AND A REFLUX INHIBITOR FOR THE TREATMENT OF GERD

Field of the invention

The present invention relates to a combination of an acid secretion inhibiting agent and a reflux inhibitor. A further aspect of the invention is prevention of reflux for the treatment of gastro-esophageal reflux disease.

Background of the invention

The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lost at such times, an event hereinafter referred to as "reflux".

Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter. However, more detailed studies (e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535)* have shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESR), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD.

GERD is caused by reflux of gastric contents into the esophagus leading to heartburn and other typical symptoms. In many cases, an inflammation develops in the distal esophagus (esophagitis). It has been known for a long time that suppression of production of gastric acid ameliorates both symptoms and esophagitis. However, some patients continue to have symptoms despite adequate control of acid secretion. Reflux of other noxious factors is believed to be responsible for those symptoms. Most focus has been centered on the importance of bile acids, and the development of severe GERD is related to the degree of esophageal bile acid exposure.

The combination therapy of idiopathic chronic hiccup with cisapride, omeprazole and baclofen has been described by *Petroianu G. et al. Clinical Therapeutics (1997), 19, pp. 1031-1038*. The combination therapy of idiopathic chronic hiccup with cisapride, omeprazole and gabapentin has been disclosed by *Petroianu G. et al. Journal of Clinical Gastroenterology (2000), 20, pp. 321-324*.

Outline of the invention

The present invention provides a combination comprising, separately or together, (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor.

The present invention relates to a combination of an acid secretion inhibiting agent and a reflux inhibitor. Further, the invention relates to the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the preparation of a medicament for the treatment of gastro-esophageal reflux disease, regurgitation, asthma, failure to thrive and lung disease.

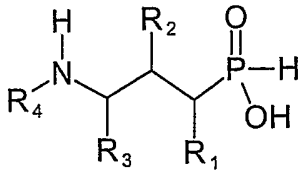
Acid secretion inhibiting agents

The wording "acid secretion inhibiting agent" used in accordance with the present invention comprises inter alia H2 blocking agents, such as cimetidine, ranitidine; as well as proton pump inhibitors. Examples of proton pump inhibitors useful in accordance with the present invention are pyridinylmethylsulfinyl benzimidazoles such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole or related substances such as leminoprazole. Proton pump inhibitors useful in accordance with the present invention may be reversible or irreversible.

Reflux inhibitor

The wording "reflux inhibitor" is defined herein as an agent preventing reflux of gastric contents. $GABA_B$-receptor agonists are examples of reflux inhibitors. $GABA_B$-receptor agonists have been shown to inhibit TLESR, which is disclosed in i.a. WO 98/11885 A1.

Examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula I



(I)

wherein

R_1 represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R_2 represents hydroxy, mercapto, halogen, or an oxo group;

R_3 represents hydrogen or lower alkyl (optionally substituted by hydroxy, mercapto, lower alkoxy, lower thioalkoxy or aryl);

R_4 represents hydrogen, lower alkyl (optionally substituted by aryl), or aryl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof. Examples of such compounds are (3-amino-2-fluoropropyl)phosphinic acid, (2*R*)-(3-amino-2-fluoropropyl)phosphinic acid, (2*S*)-(3-amino-2-fluoropropyl)phosphinic acid, (3-amino-2-fluoro-1-methylpropyl)phosphinic acid, (3-amino-2-oxopropyl)phosphinic acid, (*S*)-(3-amino-2-hydroxypropyl)phosphinic acid,), (*R*)-(3-amino-2-hydroxypropyl)phosphinic acid and (3-amino-1-fluoro-2-hydroxypropyl)phosphinic acid.

In the definition of formula I above, it is to be understood that when R_2 is an oxo group the bond between R_2 and the carbon is a double bond.

In the definition of formula I above, it is to be understood by "lower" radicals for example those having up to and including 7, especially up to and including 4, carbon atoms. Also the general terms have the following meanings:

Lower alkyl is, for example, C_1-C_4 alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C_5-C_7 alkyl group such as a pentyl, hexyl or heptyl group.

Lower alkoxy is, for example, C_1-C_4 alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C_5-C_7 alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

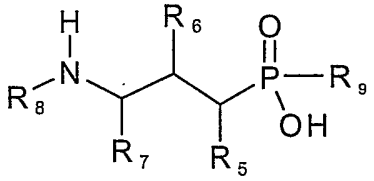
Lower thioalkoxy is, for example, C_1-C_4 thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C_5-C_7 thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

Halogen is, for example, halogen of an atomic number up to and including 35, such as fluorine, chlorine or bromine.

The compounds according to formula I of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as ammonium salts, such as those with ammonia or organic amines.

When one or more stereocentre is present in the molecule, the compounds according to formula I can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The compounds can also be in the form of solvates, e.g. hydrates.

Still further examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula II



(II)

wherein

R_5 represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R_6 represents hydroxy, mercapto, halogen, or an oxo group;

R_7 represents hydrogen or lower alkyl (optionally substituted by hydroxy, mercapto, lower alkoxy, aryl or lower thioalkoxy);

R_8 represents hydrogen, lower alkyl (optionally substituted by aryl) or aryl;

R_9 represents methyl, fluoromethyl, difluoromethyl or trifluorormethyl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof.

Examples of such compounds are (3-amino-2-fluoropropyl)(methyl)phosphinic acid, (2*R*)-(3-amino-2-fluoropropyl)(methyl)phosphinic acid, (2*S*)-(3-amino-2-fluoropropyl)(methyl)phosphinic acid, (3-Amino-2-fluoro-1-

methylpropyl)(methyl)phosphinic acid or pharmaceutically acceptable salts, solvates or the stereoisomers thereof.

In the definition of formula II above, it is to be understood that when R_6 is an oxo group the bond between R_6 and the carbon is a double bond.

Furthermore, in the definition of formula II above, it is to be understood by "lower" radicals for example those having up to and including 7, especially up to and including 4, carbon atoms. Also the general terms have the following meanings:

Lower alkyl is, for example, C_1-C_4 alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C_5-C_7 alkyl group such as a pentyl, hexyl or heptyl group.

Lower alkoxy is, for example, C_1-C_4 alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C_5-C_7 alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

Lower thioalkoxy is, for example, C_1-C_4 thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C_5-C_7 thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

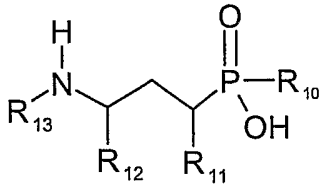
Halogen is, for example, halogen of an atomic number up to and including 35, such as flourine, chlorine or bromine.

The compounds according to formula II of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the

formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts as well as ammonium salts, such as those with ammonia or organic amines.

When one or more stereocentre is present in the molecule, the compounds according to formula II can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The present compounds can also be in the form of solvates, e.g. hydrates.

Still further examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula III



(III)

wherein

R_{10} represents hydrogen, methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

R_{11} represents hydrogen, hydroxy, C_1-C_7 alkyl, C_1-C_7 alkoxy or halogen;

R_{12} represents hydrogen, C_1-C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R_{13} represents hydrogen, C_1-C_7 alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof.

Examples of compounds according to formula III are (3-amino-1-fluoropropyl)phosphinic acid, 3-[(4-chlorobenzyl)amino]propyl(methyl)phosphinic acid and 3-[1-({3-[hydroxy(oxido)phosphino]propyl}amino)ethyl]benzoic acid.

In the definition of formula III above, C_1-C_7 alkyl can be straight, branched or cyclic alkyl and is, for example, C_1-C_4 alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C_5-C_7 alkyl group such as a pentyl, hexyl or heptyl group.

C_1-C_7 alkoxy is, for example, C_1-C_4 alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C_5-C_7 alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

C_1-C_7 thioalkoxy is, for example, C_1-C_4 thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C_5-C_7 thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

Halogen as used in Formula III is anyone of chlorine, fluorine, bromine or iodine.

The herein used term aryl means aromatic rings with 6-14 carbon atoms including both single rings and polycyclic compounds, such as benzyl or naphtyl, optionally substituted by one or more substituents such as C_1-C_7 alkyl, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, halogen, hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

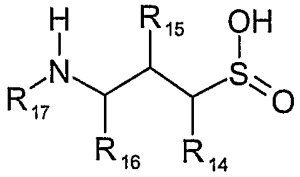
The term heteroaryl as used herein means aromatic rings with 5-14 carbon atoms, including both single rings and polycyclic compounds, in which one or several of the ring atoms is either oxygen, nitrogen or sulphur. The heteroaryl is optionally substituted by one

or more substituents such as C_1-C_7 alkyl, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, halogen, hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

The compounds according to formula III of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as ammonium salts, such as those with ammonia or organic amines. The salts may be prepared by conventional methods.

When one or more stereocentre is present in the molecule, the compounds according to formula III can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The compounds can also be in the form of solvates, e.g. hydrates.

Still further examples of reflux inhibitors useful in accordance with the present invention are compounds of the formula IV



(IV)

wherein

R_{14} represents hydrogen, hydroxy, C_1-C_7 alkyl, C_1-C_7 alkoxy or halogen;

R_{15} represents hydrogen, hydroxy, mercapto, halogen, or an oxo group;

R_{16} represents hydrogen or C_1-C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R_{17} represents hydrogen, C_1-C_7 alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

and pharmaceutically acceptable salts, solvates and the stereoisomers thereof.

Examples of compounds according to formula IV are (3-amino-2-fluoropropyl)sulphinic acid, (*2S*)-(3-amino-2-fluoropropyl)sulphinic acid, (*2R*)-(3-amino-2-fluoropropyl)sulphinic acid, (*2S*)-(3-amino-2-hydroxypropyl)sulphinic acid, (*2R*)–(3-amino-2-hydroxypropyl)sulphinic acid and (3-amino-2-oxopropyl)sulphinic acid.

In the definition of formula IV above, it is to be understood that when R_{15} is an oxo group the bond between R_{15} and the carbon is a double bond.

In the definition of formula IV above, C_1-C_7 alkyl can be straight, branched or cyclic alkyl and is, for example, C_1-C_4 alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C_5-C_7 alkyl group such as a pentyl, hexyl or heptyl group.

C_1-C_7 alkoxy is, for example, C_1-C_4 alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C_5-C_7 alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

C_1-C_7 thioalkoxy is, for example, C_1-C_4 thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C_5-C_7 thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

Halogen as used in Formula IV anyone of chlorine, fluorine, bromine or iodine.

The herein used term aryl means aromatic rings with 6-14 carbon atoms including both single rings and polycyclic compounds, such as benzyl or naphtyl, optionally substituted by one or more substituents such as membered rings optionally substituted by one or more substituents such as C_1-C_7 alkyl, C_1-C_7 alkoxy, halogen, C_1-C_7 thioalkoxy, hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

The term heteroaryl as used herein means aromatic rings with 5-14 carbon atoms, including both single rings and polycyclic compounds, in which one or several of the ring atoms is either oxygen, nitrogen or sulphur. The heteroaryl is optionally substituted by one or more substituents such as C_1-C_7 alkyl, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, halogen, hydroxy, mercapto, carboxylic acid, carboxylic acid ester, carboxylic acid amide or nitrile.

The compounds according to formula IV of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as ammonium salts, such as those with ammonia or organic amines. The salts may be prepared by conventional methods.

When one or more stereocentre is present in the molecule, the compounds according to formula IV can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer. The compounds can also be in the form of solvates, e.g. hydrates.

Combination of an acid secretion inhibiting agent and a reflux inhibitor

The present invention provides a medicament comprising separately, or together, (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor.

A "combination" according to the invention may be present as a "fix combination" or as a "kit of parts combination".

A "fix combination" is defined as a combination wherein the (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor are present in one unit. One example of a "fix combination" is a pharmaceutical composition wherein the (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor are present in admixture, such as in a formulation. Another example of a "fix combination" is a pharmaceutical combination wherein the (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor are present in one unit without being in admixture.

A "kit of parts combination" is defined as a combination wherein the (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor are present in more than one unit. One example of a "kit of parts combination" is a combination wherein the (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor are present separately. The components of the "kit of parts combination" may be administered simultaneously, sequentially or separately, i.e. separately or together.

The molar ratio of the acid secretion inhibiting agent to the reflux inhibitor used according to the invention in within the range of from 1:100 to 100:1, such as from 1:50 to 50:1 or from 1:20 to 20:1 or from 1:10 to 10:1. The two drugs may be administered separately in the same ratio.

A suitable daily dose of the acid secretion inhibiting agent is in the range of 10 to 400 mg per day, such as 10 or 20 or 50 or 100 or 200 mg per day. A suitable daily dose of the reflux inhibitor is in the range of 1 μg to 100 mg per day and kg body weight, preferably 10 μg to 20 mg per day and kg body weight.

TLESRs are known to allow gastric juice to flow back into the esophagus. Administration of an acid secretion inhibiting agent such as a proton pump inhibitor can provide control of acid reflux but has little effect on bile reflux. On the other hand, treatment with a reflux inhibitor, such as a $GABA_B$ receptor agonist can prevent most bile reflux but its effect on acid reflux is relatively small compared with a proton pump inhibitor. Thus, a combination of the two classes of agents would provide effective acid control and at the same time reduce bile acid retroflow into the esophagus.

Examples of reflux inhibitors useful in a "kit of parts" or in a "fix combination" as described above, are any reflux inhibitors of formula I, II, III or IV above, used in combination with any acid secretion inhibiting agent(s). Another aspect of the invention is the use of GABA (γ-aminobutyric acid) or baclofen as reflux inhibitor.

A further aspect of the present invention is a method for the treatment of GERD, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such treatment. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Effective management of regurgitation would be an important way of preventing, as well as curing lung disease due to aspiration of regurgitated gastric contents, and for managing failure to thrive due to excessive loss of ingested nutrient. Thus, a further aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the treatment of regurgitation. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the treatment of regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need

of such treatment. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the treatment or prevention of lung disease. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is a method for the treatment or inhibition of lung disease, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such treatment. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Another aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the management of failure to thrive due. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is a method for the management of failure to thrive, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such treatment. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the prevention of reflux. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the prevention of reflux, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid

secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such prevention. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the treatment of esophagitis. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the prevention of esophagitis, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such treatment. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the treatment of asthma, such as reflux-related asthma or non reflux-related asthma. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the treatment of asthma, such as reflux-related asthma or non reflux-related asthma, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such treatment. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the treatment of laryngitis, such as chronic laryngitis. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Another aspect of the present invention is a method for the treatment of laryngitis, such as chronic laryngitis, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such treatment. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

Still a further aspect of the invention is the use of a combination of an acid secretion inhibiting agent and a reflux inhibitor for the manufacture of a medicament for the inhibition of TLESRs. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

A further aspect of the present invention is a method for the inhibition of TLESRs, whereby a pharmaceutically and pharmacologically effective amount of a combination of an acid secretion inhibiting agent and a reflux inhibitor is administered to a subject in need of such inhibition. The acid secretion inhibiting agent and the reflux inhibitor are administered simultaneously, sequentially or separately.

For the purpose of this invention, the term "agonist " should be understood as including full agonists as well as partial agonists, whereby a "partial agonist" should be understood as a compound capable of partially, but not fully, activating a receptor.

The wording "TLESR", transient lower esophageal sphincter relaxations, is herein defined in accordance with *Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*

The wording "reflux" is defined as fluid from the stomach being able to pass into the esophagus, since the mechanical barrier is temporarily lost at such times.

The wording "GERD", gastro-esophageal reflux disease, is defined in accordance with *van Heerwarden, M.A., Smout A.J.P.M., 2000; Diagnosis of reflux disease. Baillière's Clin. Gastroenterol. 14, pp. 759-774.*

The term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Pharmaceutical formulations

For clinical use, the combination of an acid secretion inhibiting agent and a reflux inhibitor, are in accordance with the present invention suitably formulated into pharmaceutical formulations for oral administration. Also rectal, parenteral or any other route of administration may be contemplated to the skilled man in the art of formulations. Thus, the combination of an acid secretion inhibiting agent and a reflux inhibitor, are formulated with at least one pharmaceutically and pharmacologically acceptable carrier or adjuvant. The carrier may be in the form of a solid, semi-solid or liquid diluent. The acid secretion inhibiting agent and a reflux inhibitor are administered simultaneously, sequentially or separately.

In the preparation of oral pharmaceutical formulations in accordance with the invention, the combination of an acid secretion inhibiting agent and a reflux inhibitor, to be formulated is mixed with solid, powdered ingredients such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or compressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the combination of an acid secretion inhibiting agent and a reflux inhibitor, with vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain

the combination of an acid secretion inhibiting agent and a reflux inhibitor, in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance(s) mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the combination of an acid secretion inhibiting agent and a reflux inhibitor, in a mixture with a vegetable oil, paraffin oil, or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions, containing the combination of an acid secretion inhibiting agent and a reflux inhibitor, and the remainder of the formulation consisting of sugar or sugar alcohols, and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a combination of an acid secretion inhibiting agent and a reflux inhibitor, in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

In one aspect of the present invention, the combination of an acid secretion inhibiting agent and a reflux inhibitor, may be administered once or twice daily, depending on the severity

of the patient's condition. Usually, the amount of active agent in a dosage form is from 0.1% to 95% by weight of the preparation.

Biological studies

The effect of an acid secretion inhibiting agent, such as a proton pump inhibitor, and a reflux inhibitor, such as a $GABA_B$ receptor agonist, on acid and bile reflux is studied in freely moving dogs. An esophagostomy is formed surgically, and after recovery, the dog is equipped with a vest. A pH electrode as well as a bile acid sensor (Bilitec) are positioned 3 cm above the lower esophageal spincter, the location of which is determined manometrically. The data loggers are placed in pockets in the vest. Acid and bile reflux is measured in four conditions: 1) After placebo treatment; 2) After treatment with an acid secretion inhibiting agent; 3) After treatment with a reflux inhibitor; and 4) After combination treatment with an acid secretion inhibiting agent and a reflux inhibitor.

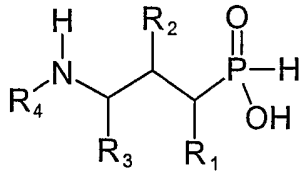
Claims

1. A combination comprising, separately or together, (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor.

2. A combination according to claim 1, said combination being a pharmaceutical composition, further comprising pharmaceutically and pharmacologically acceptable carriers and/or diluents.

3. A combination according to claim 1 or 2, wherein the acid secretion inhibiting agent is a proton pump inhibitor.

4. A combination according to any one of claims 1-3, wherein the reflux inhibitor is a compound according to formula I



(I)

wherein

R_1 represents hydrogen;

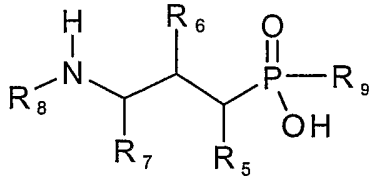
R_2 represents hydroxy, fluoro or an oxo group;

R_3 represents hydrogen;

R_4 represents hydrogen;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

5. A combination according to any one of claims 1-3, wherein the reflux inhibitor is a compound according to formula II



(II)

wherein

R_5 represents hydrogen or lower alkyl;

R_6 represents a fluoro group;

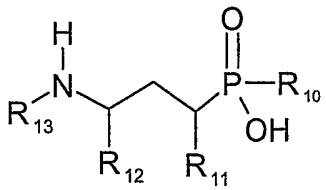
R_7 represents hydrogen;

R_8 represents hydrogen;

R_9 represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

6. A combination according to any one of claims 1-3, wherein the reflux inhibitor is a compound according to formula III



(III)

wherein

R_{10} represents hydrogen, methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

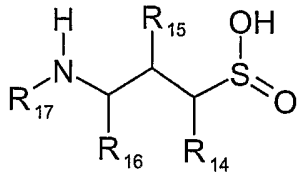
R_{11} represents hydrogen, hydroxy, C_1-C_7 alkyl, C_1-C_7 alkoxy or halogen;

R_{12} represents hydrogen, C_1-C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R_{13} represents hydrogen, C_1-C_7 alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

7. A combination according to any one of claims 1-3, wherein the reflux inhibitor is a compound according to formula IV



(IV)

wherein

R_{14} represents hydrogen, hydroxy, C_1-C_7 alkyl, C_1-C_7 alkoxy or halogen;

R_{15} represents hydrogen, hydroxy, mercapto, halogen, or an oxo group;

R_{16} represents hydrogen or C_1-C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R_{17} represents hydrogen, C_1-C_7 alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

8. A combination according to any one of claims 1-7, wherein the combination is a combined preparation for simultaneous, sequential or separate administration.

9. Use of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor for the manufacture of a combination for the inhibition of transient lower esophageal sphincter relaxations (TLESRs).

10. Use of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor for the manufacture of a combination for the treatment of gastro-esophageal reflux disease (GERD).

11. Use of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor for the manufacture of a combination for the prevention of reflux.

12. Use of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor for the manufacture of a combination for the treatment of, or prevention of, regurgitation.

13. Use of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor for the manufacture of a combination for the treatment of, or prevention of, asthma.

14. Use according to claim 13, wherein the asthma is reflux-related asthma.

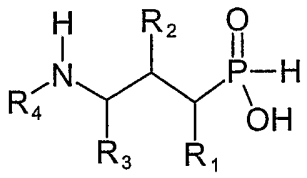
15. Use of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibtor for the manufacture of a combination for the treatment of, or prevention of, lung disease.

16. Use of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor for the manufacture of a combination for managing failure to thrive.

17. Use according to any one of claims 9-16, wherein the acid secretion inhibiting agent is a proton pump inhibitor.

18. Use according to any one of claims 9-17, wherein the reflux inhibitor is a $GABA_B$ receptor agonist.

19. Use according to any one of claims 9-18, wherein the reflux inhibitor is a compound according to formula I



(I)

wherein

R_1 represents hydrogen;

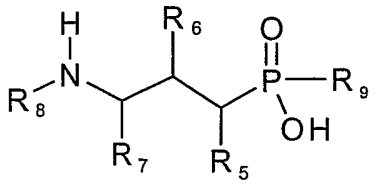
R_2 represents hydroxy, fluoro or an oxo group;

R_3 represents hydrogen;

R_4 represents hydrogen;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

20. Use according to any one of claims 9-18, wherein the reflux inhibitor is a compound according to formula II



(II)

wherein

R_5 represents hydrogen or lower alkyl;

R_6 represents a fluoro group;

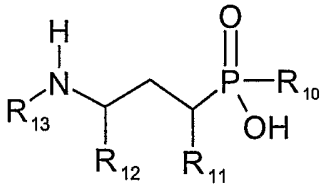
R_7 represents hydrogen;

R_8 represents hydrogen;

R_9 represents methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

21. Use according to any one of claims 9-18, wherein the reflux inhibitor is a compound according to formula III



(III)

wherein

R_{10} represents hydrogen, methyl, fluoromethyl, difluoromethyl or trifluoromethyl;

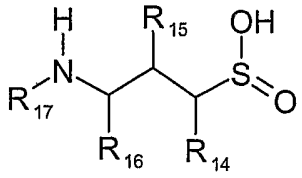
R_{11} represents hydrogen, hydroxy, C_1-C_7 alkyl, C_1-C_7 alkoxy or halogen;

R_{12} represents hydrogen, C_1-C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R_{13} represents hydrogen, C_1-C_7 alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

22. Use according to any one of claims 9-18, wherein the reflux inhibitor is a compound according to formula IV



(IV)

wherein

R_{14} represents hydrogen, hydroxy, C_1-C_7 alkyl, C_1-C_7 alkoxy or halogen;

R_{15} represents hydrogen, hydroxy, mercapto, halogen, or an oxo group;

R_{16} represents hydrogen or C_1-C_7 alkyl (optionally substituted by hydroxy, mercapto, C_1-C_7 alkoxy, C_1-C_7 thioalkoxy, aryl or heteroaryl), aryl or heteroaryl;

R_{17} represents hydrogen, C_1-C_7 alkyl (optionally substituted by aryl or heteroaryl), aryl or heteroaryl;

or a pharmaceutically acceptable salt, solvate or stereoisomer thereof.

23. A method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor, is administered to a subject in need of such inhibition.

24. A method for the treatment of gastro-esophageal reflux disease (GERD), whereby a pharmaceutically and pharmacologically effective amount of (i) at least one acid secretion inhibiting agent; and (ii) at least one reflux inhibitor, is administered to a subject in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01007

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07F 9/30; C07C 211/03, 313/04, 229/08; C07D 233/64, 307/52, 401/12, 213/65, 213/68; 213/69, 235/28; A61K 31/66, 31/185, 31/197, 31/4439, 31/4184, A61P 1/04

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)

IPC7: C07D, C07C, A61K

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

SE,DK,FI,NO classes as above

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

CHEM. ABS DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J Clin Gastroenterol, Vol. 32, no. 1, 2001, Jack A. DiPalma: "Management of Severe Gastroesophageal Reflux Disease", page 19 - page 26	1-24
Y	US 6313136 B1 (KOSRAT AMIN ET AL), 6 November 2001 (06.11.01), abstract; column 1, lines 38-44; column 10, lines 19-30; example; claim	1-24
Y	WO 9811885 A1 (ASTRA AKTIEBOLAG), 26 March 1998 (26.03.98), page 1, lines 5-7; page 2, lines 17-25; page 3, line 29 - page 6, line 6; page 13, table 1; pages 14-16, claim	1-24

[X] Further documents are listed in the continuation of Box C. [X] See patent family 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 application or patent 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

"P" document published prior to the international filing date but later than the priority date claimed

"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	Date of mailing of the international search report
15 Sept 2003	16 -09- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Per Renström/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01007

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 0142252 A1 (ASTRAZENECA AB), 14 June 2001 (14.06.01), pages 15-20, examples 1-8; page 34, lines 9-10; pages 35-44, claim --	1-24
Y	WO 0141743 A1 (ASTRAZENECA AB), 14 June 2001 (14.06.01), pages 16-18, examples 1-4; page 29, lines 12-15; pages 30-39, claim --	1-24
X	Clinical Therapeutics, Vol. 19, no. 5, 1997, Georg Petroianu, et al: "Idiopathic Chronic Hiccup: Combination Therapy with Cisapride, Omeprazole, and Baclofen", page 1031 - page 1038 -- --------	1-3,8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01007

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.: **23-24**
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☒ Claims Nos.: **1-24**
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:

see next sheet

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.

Box I.1

Claims 23-24 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Box I.2

Present claims 1-24 relate to compounds defined by reference to desirable properties, namely acid secretion inhibiting (claims 1-24), proton pump inhibiting (claim 3) and reflux inhibiting (claims 1-3, 8-18, 23-24) properties and agonism at $GABA_B$-receptors (claim 18). The claims cover combinations, and the use of combinations, comprising all compounds having these properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such combinations.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define compounds by reference to a result to be achieved. This lack of clarity is such as to render a meaningful search over the whole of the claimed scope impossible.

The search has been carried out only for the compounds with formulas I-IV in the claims 4-7, GABA and its derivative baclofen, in combination with some known acid secretion inhibiting agents of the types proton pump inhibitors (namely pyridinylmethylsulfinyl-benzimidazole derivatives whose names contain the letters prazole) and H_2-antagonists (namely cimetidine and ranitidine), as well as in combination with certain acid secretion inhibitors of the type imidazopyridines.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

International application No.
PCT/SE 03/01007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6313136 B1	06/11/01	AT 230985 T	15/02/03
		AU 727349 B	14/12/00
		AU 4300699 A	16/11/99
		AU 4300799 A	16/11/99
		AU 9098998 A	22/03/99
		BR 9909995 A	26/12/00
		BR 9909996 A	26/12/00
		CA 2329921 A	04/11/99
		CA 2329922 A	04/11/99
		CN 1306533 T	01/08/01
		CN 1307577 T	08/08/01
		DE 69810784 D	00/00/00
		DK 1011653 T	26/05/03
		EE 200000626 A	15/04/02
		EE 200000664 A	15/04/02
		EP 1011653 A,B	28/06/00
		SE 1011653 T3	
		EP 1073656 A	07/02/01
		EP 1073657 A	07/02/01
		HU 0102313 A	28/12/01
		HU 0102425 A	28/11/01
		IL 139200 D	00/00/00
		IL 139297 D	00/00/00
		JP 2001514215 T	11/09/01
		JP 2002513024 T	08/05/02
		JP 2002513025 T	08/05/02
		NO 20001087 A	02/03/00
		NO 20005450 A	22/12/00
		NO 20005451 A	27/12/00
		PL 338982 A	04/12/00
		PL 343797 A	10/09/01
		PL 343801 A	10/09/01
		SE 9801526 D	00/00/00
		SK 14912000 A	11/06/01
		SK 14922000 A	11/06/01
		TR 200003149 T	00/00/00
		TR 200003176 T	00/00/00
		TR 200102612 T	00/00/00
		TR 200102728 T	00/00/00
		TW 490466 B	00/00/00
		US 6245818 B	12/06/01
		US 6313137 B	06/11/01
		WO 9955705 A	04/11/99
		WO 9955706 A	04/11/99
		SE 9900662 D	00/00/00
		US D438954 S	13/03/01

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

International application No.
PCT/SE 03/01007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811885 A1	26/03/98	AU 714370 B	23/12/99
		AU 4406497 A	14/04/98
		BR 9711400 A	17/08/99
		CN 1237105 A	01/12/99
		CZ 9900930 A	15/09/99
		EE 3952 B	17/02/03
		EE 9900095 A	15/10/99
		EP 0936906 A	25/08/99
		HU 9903825 A	28/05/01
		IL 128961 D	00/00/00
		JP 2001501604 T	06/02/01
		KR 2000036185 A	26/06/00
		NO 991287 A	17/03/99
		NZ 334495 A	29/09/00
		NZ 504244 A	29/09/00
		PL 332497 A	13/09/99
		RU 2199316 C	27/02/03
		SE 9603408 D	00/00/00
		SK 30599 A	18/01/00
		TR 9900591 T	00/00/00
		US 6117908 A	12/09/00
WO 0142252 A1	14/06/01	AU 2036401 A	18/06/01
		BR 0016253 A	27/08/02
		CA 2397583 A	14/06/01
		CN 1409716 T	09/04/03
		CZ 20021983 A	13/11/02
		EP 1240172 A	18/09/02
		HU 0300301 A	28/06/03
		JP 2003516407 T	13/05/03
		NO 20022728 A	07/08/02
		SE 9904508 D	00/00/00
		SK 7642002 A	03/12/02
		US 6576626 B	10/06/03
		US 2002156053 A	24/10/02
		SE 0003640 D	00/00/00
WO 0141743 A1	14/06/01	AU 2241201 A	18/06/01
		BR 0016291 A	13/08/02
		CA 2393510 A	14/06/01
		CN 1413104 T	23/04/03
		CZ 20021984 A	13/11/02
		EP 1239843 A	18/09/02
		JP 2003516346 T	13/05/03
		NO 20022729 A	09/07/02
		SE 9904507 D	00/00/00