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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR ULCER

(57) Abstract

Pharmaceutical compositions for the therapy and the prevention of ulcer and dyspepsia relapses comprising as essential components the following components a) and b): component a): one or more components selected from the conventional anti–ulcer products; component b): organic compounds containing the $-ONO_2$ function, or inorganic compounds containing the –NO group, characterized in that they are NO nitric oxide donors.

PHARMACEUTICAL COMPOSITIONS FOR ULCER

The present invention relates to compositions to be used in, and methods for, the therapy and the prevention of the ulcer relapses and, in general of the dyspepsias. More particularly it relates to compositions and methods having an improved gastroprotective activity combined with a high acid secretion inhibition activity.

The products known in the art and those commercialized and used in the ulcer therapy are compounds which perform an anti-secretory activity (acid secretion inhibition). See for instance "New Guide to Medicine & Drugs" Brit. Medical Assoc. Editor, 1997, pages 108-109. Known products having higher therapeutic efficacy show an high anti-secretory activity and are used, both in the acute and in the long-term (6 months and more) therapies. The drawback of these products is that they have a poor gastroprotective activity, when present. From a practical point of view this means that the gastric protection is not optimal and causes inconveniences especially in the long-term therapy. In this case the presence of frequent relapses due to the enfeeblement of gastric mucosa is noticed.

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To overcome these inconveniences it is known in the art to add to said medicaments other anti-ulcer medicaments having a gastroprotective action: prostaglandins, bismuth salts (e.g. bismuth citrate) and antibiotics. In such way the removal of ulcerous pathology is achieved. However these combinations are not sastisfactory as to their tolerability in general. For example it is well known that prostglandins produce side effects (diarrhoea) towards the intestinal tract; bismuth salts frequently produce nausea and heartburn. Antibiotics produce undesired gastrointestinal effects.

The need was felt to have available compositions active in the ulcer and gastric dyspesia treatment having improved therapeutic characteristic and tolerability, general and local, in particular having an improved gastroprotective activity combined with an high anti-secretion activity.

The Applicant has unexpectedly and surprisingly found pharmaceutical anti-ulcer compositions having an improved therapeutic activity and tolerability.

The present invention provides pharmaceutical compositions comprising the following:

component a): one or more components selected from the following classes:

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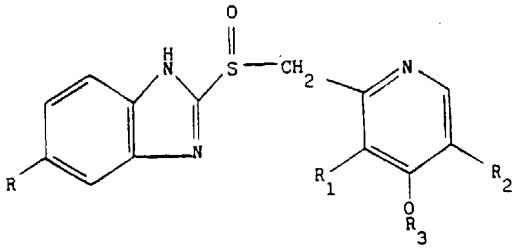
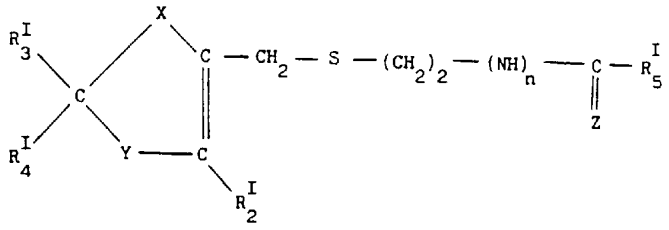


(A)



(B)

wherein in the (A) class compounds

R = H, OCH_3, $OCHF_2$;

R_1 = CH_3, OCH_3;

R_2 = H, CH_3;

R_3 = CH_3, CH_2-CF_3, $(CH_2)_3$-OCH_3;

wherein in the (B) class compounds:

R^I_3, R^I_4 equal to or different from each other, are respectively free valence, hydrogen, -N=C$(NH_2)_2$, -CH_2-N$(CH_3)_2$;

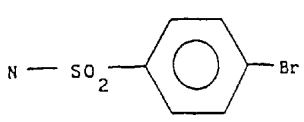
Y = S, N-R^I_6, $CR^I_7R^I_8$;

X = O, S, N-R^I_1;

R^I_2 = H, CH_3;

n = 0, 1;

Z = N-CN, N-SO_2NH_2, CH-NO_2 or



(VII$_A$)

R^I_5 = H, -NH-CH_3, NH_2;

R^I_6, R^I_7, R^I_8, R^I_1, equal to or different from each other, are hydrogen, free valence; and

component b): one or more organic compounds containing the $-ONO_2$ group, or one or more inorganic compounds containing the -NO group, or mixtures thereof, said compounds being characterized in that they are NO nitric oxide donors, i.e. when they are brought into contact in vitro with cells of the vasal endothelium or platelets, and after incubation of 5 minutes at a temperature of 37°C, are capable to release NO and to activate the cGMP synthesis (Guanosine cyclic 3',5'-(hydrogen phosphate)), as shown by the used specific tests which will be described in detail further on.

The present invention also provides a method for the treatment or prevention of ulcer and dyspepsia relapses in a patient comprising administering to the patient a combination of component a) and component b) as defined above.

In accordance with the method of the present invention, the component b) can generally be administered contemporaneously, subsequently or previously to the component a).

The present invention compositions are obtainable by directly mixing the components a) and b).

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The molar ratio between the components a) and b) can vary within wide limits, from 1 : 0.1 to 1 : 5, preferably from 1 : 0.5 to 1 : 2.

As regards the component a), the preferred (A) com-

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pounds are the following:

when R = OCH_3, R_1 = CH_3, R_2 = CH_3, R_3 = CH_3, Omeprazole residue;

as in Omeprazole, but with R = $OCHF_2$, R_1 = OCH_3, R_2 = H, Pantoprazole residue;

as in Omeprazole, but with R = H, R_2 = H, R_3 = $(CH_2)_3$-OCH_3, Rabeprazole residue;

as in Rabeprazole, but with R_3 = CH_2-CF_3, Lansoprazole residue;

in component a) the preferred compounds of formula (B) are the following:

when in formula (B) X = N-R^I_1 with R^I_1 free valence, Y = N-R^I_6 with R^I_6 = H, R^I_3 = H, R^I_4 is free valence and forms with R^I_1 a double bond, R^I_2 = CH_3, n = 1, R^I_5 = -NH-CH_3, Z = N-CN, Cimetidine residue;

when X = N-R^I_1 with R^I_1 free valence, Y = S,

R^I_3 = -N=$C(NH_2)_2$, R^I_4 is free valence and forms with R^I_1 a double bond, R^I_2 = H, n = 1 R^I_5 = H, Z = (VII_A), Ebrotidine residue;

as in Ebrotidine but with n = 0, R^I_5 = NH_2 and Z = N-SO_2NH_2, Famotidine residue;

as in Ebrotidine but with R^I_3 = -CH_2-$N(CH_3)_2$, R^I_5 = -NH-CH_3 and Z = CH-NO_2, Nizatidine residue;

as in Nizatidine, but with X = oxygen, Y = $CR^I_7R^I_8$ with R^I_7 hydrogen and R^I_8 free valence, R^I_4 is a free valence and forms

with R^I_9 a double bond, Ranitidine residue.

In the preparation of the invention compositions also the isomers of one or more compounds of each component can be used.

The components belonging to (A) and (B) classes are prepared according to methods described in "The Merck Index 12th Ed." (1996), herein incorporated by reference.

Instead of the formula (A) and (B) compounds of component a) the corresponding salts with organic or inorganic salts, obtainable by reactions known to the skilled in the

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art, can be used. Examples of usable inorganic ions are the following: hydrochlorides, nitrates, sulphates, phosphates, etc.; among the organic ones maleates, oxalates, acetates, succinates, etc. can be mentioned. Compositions containing nitrates are preferred.

The salts with the preferred compounds of the component a) are those corresponding to the preferred compounds of formula (A) or (B).

In the compositions according to the present invention salts of the compound of the above formulas contain at least one anion mole/compound mole. Preferably the ratio between the anion and compound moles is unitary. Salts having a higher molar ratio are obtained when in the molecule other basic enough aminic groups to be salified are present.

For example the salts of the class (A) and (B) compound with nitric acid are prepared according to the following methods.

When the substance to be salified is available as free base or as a corresponding salt soluble in an organic solvent, which preferably does not contain hydroxyl groups, for example acetonitrile, ethyl acetate, tetrahydrofuran, etc., the salt is prepared by dissolving the substance in the solvent at a concentration preferably equal or higher than 10% w/v, by adding the amount of concentrated nitric acid cor-

responding to the moles of salifiable aminic groups present in the compound. The nitric acid is preferably diluted in the same solvent. Preferably during and after the addition the mixture is cooled to temperatures in the range 20°C-0°C. The product is generally recovered by filtration and washed with the solvent.

When on the contrary the substance is not very soluble, or it is available as a not very soluble salt in the above mentioned solvents, the corresponding mixtures with hydroxylated solvents may be used. Examples of such solvents are methyl alcohol, ethyl alcohol and water. Precipitation can be quickened by diluting then the so obtained mixture, after the addition of nitric acid, with an apolar solvent.

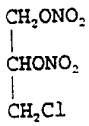
When the starting product is salified with hydrochloric acid, it is possible to prepare the nitric acid salt directly adding silver nitrate to the solution. After filtering silver chloride, the solution is concentrated and treated as above indicated to recover the nitrate salt.

When the starting product is a salt, it is also possible to liberate the corresponding base by a treatment with a sodium or potassium bicarbonate or carbonate saturated solution, or with a sodium or potassium hydroxide diluted solution. The base is then extracted by a suitable organic solvent (for example halogenated solvents, esters, ethers), which is then dried. The organic solution is evaporated and

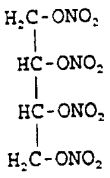
then one proceeds according to the preceding preparation methods, by dissolving the base in acetonitrile or in the other above mentioned solvents.

For the component b), the organic compounds containing the $-ONO_2$ groups which can be used are, as an example, the following, which are reported in The Merck Index 11th Ed. - 1989 and prepared by the known methods, for instance those mentioned in the same reference, herein incorporated by reference:

chlonitrate (3-chloro-1,2-propanediol dinitrate) (Merck No. 2390) having the formula $C_3H_5ClN_2O_6$ and structural formula

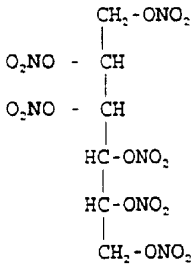


erythrityltetranitrate (1,2,3,4 butantetroltetranitrate) (Merck No. 3622) having the formula $C_4H_6N_4O_{12}$ and structural formula

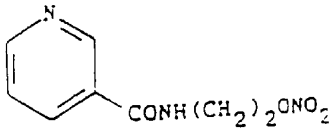


mannitol hexanitrate (Merck No. 5630) having the formula

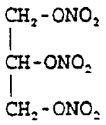
$C_6H_9N_6O_{18}$ and structural formula



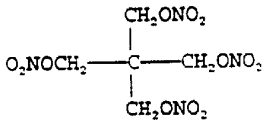
nicorandyl (N-[2-(nitroxy)ethyl]-3-pyridine-carboxamide) (Merck No. 6431) having the formula $C_9H_9N_3O_4$ and structural formula



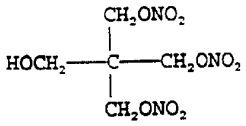
nitroglycerin (1,2,3 propanetriol trinitrate) (Merck No. 6528) having the formula $C_3H_5N_3O_9$ and structural formula



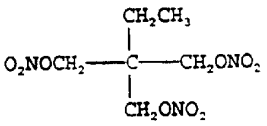
pentaerythritoltetranitrate (2,2-bis [(nitroxy)-methyl]-1,3-propanedioldinitrate) (Merck No. 7066) having the formula $C_5H_8N_4O_{12}$ and structural formula



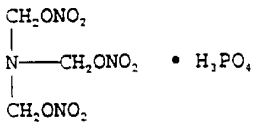
pentrinitrol (2,2-bis[(nitroxy)methyl]-1,3-propanediolmono-nitrate) (Merck No. 7094) having the formula $C_5H_9N_3O_{10}$ and structural formula



propatylnitrate (2-ethyl-2-[(nitroxy)methyl]-1,3-propane-dioldinitrate) (Merck No. 7821) having the formula $C_6H_{11}N_3O_9$ and structural formula



trolnitratephosphate (2,2',2"-nitryltrisethanoltrinitrate phosphate) (1:2 salt) (Merck No. 9682) having the formula $C_6H_{18}N_4O_{17}P_2$ and structural formula



Other compounds containing the $-ONO_2$ group which can be used are prostglandin nitroderivatives described in the PCT/EP Application 98/03645 in the Applicant's name. This patent application is herein incorporated by reference both for compounds and preparation processes.

Among the inorganic compounds containing the -NO group can be mentioned:

- nitrate salts of alkaline, earth-alkaline or III group metals, for example with aluminum, sodium and potassium nitrates are preferred;
- nitroprussiate salts, such as for example: sodiumnitroprussiate (pentakis (cyano-C)nitrosylferrate(2-)disodium) (Merck No. 8600), having the formula $Na_2[Fe(CN)_5NO]$.

The invention components b) containing the $-ONO_2$ groups or the -NO group which produce the invention results, as already said, must meet the test in vitro described in detail hereinunder.

Specifically the test relates to the nitric oxide generation from the NO-donors described in the present invention, among which, for instance nitroglicerin, nicorandyl, nitroprussiate, etc., when they are put in the presence of

endothelial cells (method a) or platelets (method b):

a) Endothelial cells

Cells of the human umbilical vein, spread on plate, with a 10^3 cells/plate density have been incubated with scalar concentrations of NO-donor (1-100 μg/ml) for 5 minutes. The incubation medium (physiologic solvent, for example Tyrode) has been then analyzed to determine the capability to generate NO, by:

1) the nitric oxide disclosure by chemiluminiscence;
2) cGMP determination (cyclic GMP No. 2715 of the above mentioned Merck).

As regards the chemiluminiscence analysis, an amount equivalent to 100 μl was injected in the reaction chamber of a chemiluminiscence analyzer containing glacial acetic acid and potassium iodide. Nitrites/nitrates present in the medium under these conditions are converted into NO which is then determined after its reaction with ozone, with consequent light generation. As it usually occurs in the devices measuring the chemiluminiscence, the produced luminiscence is directly proportional to the generated NO levels and can be measured by the suitable photomultiplier unit of a chemiluminiscence analyzer.

The photomultiplier converts the incident light into electric voltage, which is then quantitatively re-

corded. On the basis of a calibration curve, prepared with scalar nitrite concentrations, it was possible to quantitatively determine the generated NO concentration. For example, from the incubation of 100 μM of nicorandyl, an amount equal to about 10 μM of NO was generated.

As regards the cGMP determination, a portion of the incubation medium (equal to 100 μl) was centrifuged at 1000 revolutions per 20 seconds. The supernatant was discharged and the sediment treated with iced phosphate buffer (pH 7,4). The cGMP level produced were tested, by specific immuno-enzymatic reactants. From such experiments it resulted that, under these experimental conditions, the incubation with one of the various tested NO-donors caused a significant cGMP increase with respect to the values obtained in absence of a NO donor. For example, after incubation with 100 μM of sodium nitroprussiate, an increase of about 20 times the value obtained with the incubation of only the vehicle without NO donor was recorded.

b) Platelets

Washed human platelets, prepared analogously with what described by Radomski et al, (Br.J. Pharmacol. 92, 639-1987), were used. 0.4 ml aliquots were incubated with scalar NO-donor concentrations (1-100 μg/ml) for 5 mi-

nutes. The incubation medium (e.g. Tyrode) was then analyzed to determine the capability to generate NO, by determination of nitric oxide by chemiluminiscence and cGMP, with the modalities described in the previous paragraph, for the analyses carried out on the endothelial cells. As to the determination by chemiluminiscence, also in this case, on the basis of a calibration curve, prepared with scalar nitrite concentrations, it was possible to quantitatively determine the generated NO concentration. For example, after incubation of 100 μM of nicorandyl, an amount equal to 35 μM of NO was generated.

As regards the cGMP determination, also in these experimental conditions it resulted that the incubation with one of the various NO-donors tested caused a cGMP significant increase with respect to the values obtained in absence of a NO-donor. For example, after incubation with 100 μM of sodium nitroprussiate, an increase of about 30 times the value obtained with the incubation of only the vehicle without NO-donor was recorded.

In conclusion, from said tests it results that all the NO-donors according to the present invention, after incubation with endothelial cells or platelets for 5 minutes, are capable to generate NO, and to activate the cGMP synthesis

in a concentration-depending way, as determined by the used specific tests.

It has now surprisingly been found that the present invention compositions allow to improve, compared with the known above mentioned combinations, the total pharmaco-toxicological behaviour of the compounds forming the component a), increasing the therapeutic efficacy and their general and local tolerability in the ulcer and gastric dyspepsia treatment, with improved gastroprotective activity.

The present invention compositions are formulated in the correspnding pharmaceutical compositions according to well known techniques in the field together with the conventional excipients; see for example the volume "Remington's **Pharmaceutical Sciences 15a Ed."**

The administering of the present invention compositions can be carried out by oral, parenteral or transdermic way. The (A) and (B) compound doses of component a) are the conventional ones for these compounds.

Furthermore, the present invention provides compositions obtainable by combining the pharmaceutical compositions according to the present invention with conventional gastroprotective agents. As examples, prostaglandins, bismuth salts, active antibiotics towards pathogenic microorganisms

AUSTRALIAN PATENT OFFICE

in the gastrointestinal mucosa can be mentioned.

It has surprisingly been found that the gastroprotective activity of the invention compositions is very high. This makes it possible to avoid the undesired effects of known gastroprotectives when they are used in combination with compounds or formulations of the invention compounds. It has indeed been found that the amount of the known gastroprotective agents, in the combination of the invention, is lower compared with those known and does not cause undesirable side effects. The skilled in the field is able to easily determine the maximum amount of conventional gastroprotective agents to be combined with the invention pharmaceutical compositions, since this corresponds to the absence of typical side effects of the known gastroprotective agents. In any case the amount of conventional gastoprotective agents to be used in the combination is lower than that used in combinations described in the art.

The following examples have the purpose to illlustrate the invention and must not be considered as limitative of the same.

EXAMPLE 1

Pharmaceutical composition.

Mixture formed by:

Component a) cimetidine 50 g.

componente b) KNO_3 20 g.

Amounts of this mixture corresponding to 70 mg/kg, or multiples, to be supplied to animals, are then weighed.

Pharmacological Tests

EXAMPLE 2

Acute toxicity

To a group of 10 rats weighing 20 g each a single dose equal to 280 mg/kg of the Example 1 composition was supplied by oral way in a carboxymethylcellulose aqueous suspension 2% w/v.

The animals are kept under obsevation for 14 days. In no one of the group animals the toxic syntom presence was noticed.

EXAMPLE 3

Anti-ulcer Activity

The anti-ulcer activity is evaluated according to the experimental model described in the paper of A. Robert et Al. "Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl and thermal injury" Gastroenterology 77, 433-43 1979.

To 3 groups of 10 rats each, kept with empty stomach since the previous night, 15 minutes before the supply of absolute ethanol (1 ml), by oral way are supplied:

- 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 50 mg/Kg of cimetidine in 5 ml/Kg of carboxymethylcel-

lulose aqueous suspension 2%.

- 70 mg/Kg of the Example 1 composition in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.

One hour later the animals are sacrificed and the gastric lesion incidence is evaluated. The results are reported in Table 1 and they show that the combination cimetidine and potassium nitrate shows an improved gastroprotective activity with respect to cimetidine.

TABLE I

Treatment	Gastric Damage (%)
Vehicle	100
Cimetidine 50mg/Kg	100
Composition Ex. 1 70 mg/Kg	60

A reference herein to a prior art document is not an admission that the document forms part of the common general knowledge in the art in Australia or in any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprising" is used in the sense of "including", i.e. the features specified may be associated with further features in various embodiments of the invention.

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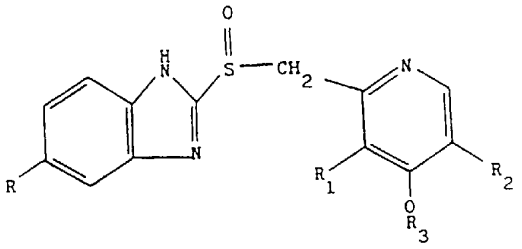
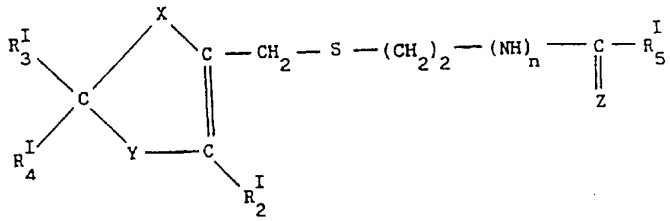
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Pharmaceutical compositions comprising the following:
component a): one or more components selected from the following classes:



(A)



(B)

wherein in the (A) formula

R = H, OCH_3, $OCHF_2$;

R_1 = CH_3, OCH_3;

R_2 = H, CH_3;

R_3 = CH_3, CH_2-CF_3, $(CH_2)_3$-OCH_3;

in the (B) class compounds:

R^I_3, R^I_4 equal to or different from each other, are re-

AUSTRALIAN PATENT OFFICE

spectively free valence, hydrogen, $-N=C(NH_2)_2$,

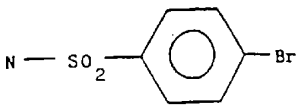
$-CH_2-N(CH_3)_2$; Y = S, $N-R^I_6$, $CR^I_7R^I_8$;

X = O, S, $N-R^I_1$;

R^I_2 = H, CH_3;

n = 0, 1;

Z = N-CN, $N-SO_2NH_2$, $CH-NO_2$ or



(VII_A)

R^I_5 = H, $-NH-CH_3$, NH_2;

R^I_6, R^I_7, R^I_8, R^I_1, equal to or different from each other, are hydrogen, free valence; and

component b): one or more organic compounds containing the $-ONO_2$ group, or one or more inorganic compounds containing the -NO group, or mixtures thereof, said compounds being characterized in that they are NO nitric oxide donors, i.e. when they are brought into contact in vitro with cells of the vasal endothelium or platelets, and after incubation of 5 minutes at a temperature of 37°C, are capable to release NO and to activate

AUSTRALIAN PATENT OFFICE

the cGMP synthesis (Guanosine cyclic 3' , 5' - (hydrogen phosphate)).

2. Pharmaceutical compositions according to claim 1, wherein the molar ratio between the components a) and b) varies from 1 : 0.1 to 1 : 5.

3. Pharmaceutical compositions according to claim 1, wherein the molar ratio between the components a) and b) varies from 1 : 0.5 to 1 : 2.

4. Pharmaceutical compositions according to any one of claims 1-3 wherein in component a) the compounds are the following:

- formula (A):

  R = OCH_3, R_1 = CH_3, R_2 = CH_3, R_3 = CH_3, Omeprazole residue;

  as in Omeprazole, but with R = $OCHF_2$, R_1 = OCH_3, R_2 = H, Pantoprazole residue;

  as in Omeprazole, but with R = H, R_2 = H, R_3 = $(CH_2)_3$-OCH_3, Rabeprazole residue;

  as in Rabeprazole, but with R_3 = CH_2-CF_3, Lansoprazole residue;

- formula (B):

  X = N-R^I_1 with R^I_1 free valence, Y = N-R^I_6 with R^I_6 = H, R^I_3 = H, R^I_4 is free valence and forms with R^I_1 a double bond, R^I_2 = CH_3, n = 1, R^I_5 = -NH-CH_3, Z = N-CN, Cimetidine residue;

  when in the formula (B) X = N-R^I_1 with R^I_1 free valence, Y = S, R^I_3 = -N=$C(NH_2)_2$, R^I_4 is free valence and forms with R^I_1 a double bond, R^I_2 = H, n = 1 R^I_5 = H, Z = (VII_A), Ebrotidine residue;

  as in Ebrotidine but with n = 0, R^I_5 = NH_2 and Z = N-SO_2NH_2, Famotidine residue;

  as in Ebrotidine but with R^I_3 = -CH_2-$N(CH_3)_2$, R^I_5 = -NH-CH_3 and Z = CH-NO_2, Nizatidine residue;

  as in Nizatidine, but with X = oxygen, Y = $CR^I_7R^I_8$ with R^I_7 hydrogen and R^I_8 free valence, R^I_4 is a free valence and forms with R^I_8 a double bond, Ranitidine residue.

Pharmaceutical compositions according to any one of

AUSTRALIAN PATENT OFFICE

claims 1-4, wherein the isomers of one or more compounds of each component are used.

6. Pharmaceutical compositions according to any one of claims 1-5, wherein instead of the compounds of formula (A) and (B) of component a) the corresponding organic or inorganic acid salts can be used.

7. Pharmaceutical compositions according to claim 6 containing nitrate salts.

8. Pharmaceutical compositions according to claim 6, containing the corresponding salts of the compounds of formula (A) or of the compounds of formula (B) as defined in claim 4.

9. Pharmaceutical compositions according to any one of claims 6-8, wherein the salts contain at least one anion mole/compound mole.

10. Pharmaceutical compositions according to any one of claims 1-9, wherein the organic compounds containing the $-ONO_2$ groups usable in component b) are selected from the following ones:
clonitrate, erytrityltetranitrate, mannitol hexanitrate, nicorandyl, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol, propatylnitrate trolnitratephosphate, prostaglandin nitroderivatives.

11. Pharmaceutical compositions according to any one of claims 1-9 wherein the inorganic compounds containing the -NO group of component b) are selected from the following: nitrate salts of alkaline, earth-alkaline or III group metals, and nitroprussiate salts.

12. Pharmaceutical compositions according to claim 11 wherein the nitrate salts are sodium and potassium nitrate.

13. Pharmaceutical compositions according to any one of the previous claims formulated for the oral, parenteral, transdermic administering.

14. Use of the pharmaceutical compositions according to any one of claims 1-13, to prepare medicaments for the therapy and prevention of the ulcer and dyspepsia

AUSTRALIAN PATENT OFFICE

relapses.

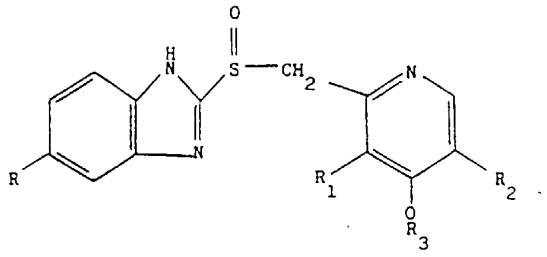
15. Use according to claim 14 wherein the (A) and (B) compound doses of component a) are those used in therapy for said compounds.

16. Pharmaceutical compositions obtainable by combining the compositions according to any one of claims 1-13 with conventional gastroprotective agents.

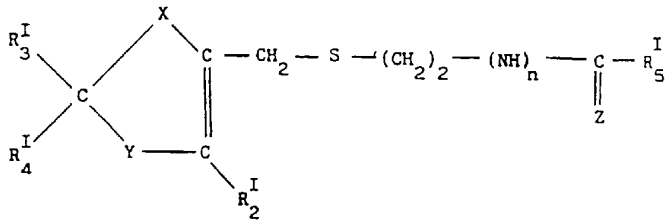
17. Compositions according to claim 16 wherein the conventional gastroprotective agents are selected from prostaglandins, bismuth salts and antibiotics.

18. Use of pharmaceutical compositions according to claim 16 or 17 to prepare medicaments for the therapy and prevention of the ulcer and dyspepsia relapses.

19. A method for the treatment or prevention of ulcer and dyspepsia relapses in a patient comprising administering to the patient a combination of:
component a): one or more components selected from the following classes.



(A)



(B)

wherein in the (A) formula

R = H, OCH_3, $OCHF_2$;

R_1 = CH_3, OCH_3;

R_2 = H, CH_3;

R_3 = CH_3, CH_2-CF_3, $(CH_2)_3$-OCH_3;

AUSTRALIAN PATENT OFFICE

in the (B) class compounds:

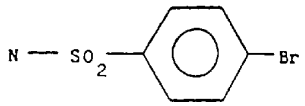
R^I_3, R^I_4 equal to or different from each other, are respectively free valence, hydrogen, $-N{=}{=}C(NH_2)_2$, $-CH_2-N(CH_3)_2$; Y = S, $N-R^I_6$, $CR^I_7R^I_8$;

X = O, S, $N-R^I_1$;

R^I_2 = H, CH_3;

n = 0, 1;

Z = N-CN, $N-SO_2NH_2$, $CH-NO_2$ or



(VII_A)

R^I_5 = H, $-NH-CH_3$, NH_2;

R^I_6, R^I_7, R^I_8, R^I_1, equal to or different from each other, are hydrogen, free valence; and

component b): one or more organic compounds containing the $-ONO_2$ group, or one or more inorganic compounds containing the -NO group, or mixtures thereof, said compounds being characterized in that they are NO nitric oxide donors, i.e. when they are brought into contact in vitro with cells of the vasal endothelium or platelets, and after incubation of 5 minutes at a temperature of 37°C, are capable to release NO and to activate the cGMP synthesis (Guanosine cyclic 3', 5'-(hydrogen phosphate)).

20. Method according to claim 19, wherein the component b) is administered contemporaneously, subsequently or previously to component a).

21. Method according to claim 19 or claim 20, wherein the molar ratio between the components a) and b) varies from 1 : 0.1 to 1 : 5.

22. Method according to claim 19 or claim 20 wherein the

AUSTRALIAN PATENT OFFICE

molar ratio between the components a) and b) varies from 1 : 0.5 to 1 : 2.

23. Method according to any one of claims 19 to 22 wherein in component a) the compounds are the following:

- formula (A):

  $R = OCH_3$, $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, Omeprazole residue;

  as in Omeprazole, but with $R = OCHF_2$, $R_1 = OCH_3$, $R_2 = H$, Pantoprazole residue;

  as in Omeprazole, but with $R = H$, $R_2 = H$, $R_3 = (CH_2)_3\text{-}OCH_3$, Rabeprazole residue;

  as in Rabeprazole, but with $R_3 = CH_2\text{-}CF_3$, Lansoprazole residue;

- formula (B):

  $X = N\text{-}R^I_1$ with R^I_1 free valence, $Y = N\text{-}R^I_6$ with $R^I_6 = H$, $R^I_3 = H$, R^I_4 is free valence and forms with R^I_1 a double bond, $R^I_2 = CH_3$, $n = 1$, $R^I_5 = \text{-}NH\text{-}CH_3$, $Z = N\text{-}CN$, Cimetidine residue;

  when in the formula (B) $X = N\text{-}R^I_1$ with R^I_1 free valence, $Y = S$, $R^I_3 = \text{-}N{=}{=}C(NH_2)_2$, R^I_4 is free valence and forms with R^I_1 a double bond, $R^I_2 = H$, $n = 1$ $R^I_5 = H$, $Z = (VII_A)$, Ebrotidine residue;

  as in Ebrotidine but with $n = 0$, $R^I_5 = NH_2$ and $Z = N\text{-}SO_2NH_2$, Famotidine residue;

  as in Ebrotidine but with $R^I_3 = \text{-}CH_2\text{-}N(CH_3)_2$, $R^I_5 = \text{-}NH\text{-}CH_3$ and $Z = CH\text{-}NO_2$, Nizatidine residue;

  as in Nizatidine, but with X = oxygen, $Y = CR^I_7R^I_8$ with R^I_7 hydrogen and R^I_8 free valence, R^I_4 is a free valance and forms with R^I_8 a double bond, Ranitidine residue.

24. Method according to any one of claims 19 to 23 wherein the isomers of one or more compounds of each component are used.

25. Method according to any one of claims 19 to 24 wherein instead of the compounds of formula (A) and (B) of component a) the corresponding organic or inorganic acid salts can be used.

26. Method according to claim 25 wherein the salts are

AUSTRALIAN PATENT OFFICE

nitrate salts.

27. Method according to claim 25 comprising the administration of a corresponding salt of the compounds of formula (A) or of the compounds of formula (B) as defined in claim 23.

28. Method according to any one of claims 25 to 27, wherein the salts contain at least one anion mole/compound mole.

29. Method according to any one of claims 19 to 28, wherein the organic compounds containing the $-ONO_2$ groups usable in component b) are selected from the following ones: clonitrate, erytrityltetranitrate, mannitol hexanitrate, nicorandyl, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol, propatylnitrate trolnitratephosphate, prostaglandin nitroderivatives.

30. Method according to any one of claims 19 to 28 wherein the inorganic compounds containing the -NO group of component b) are selected from the following: nitrate salts of alkaline, earth-alkaline or III group metals, and nitroprussiate salts.

31. Method according to claim 30 wherein the nitrate salts are sodium and potassium nitrate.

32. Method according to any one of claims 19 to 31, wherein components a) and b) are administered orally, parenterally, or transdermally.

33. Use of the pharmaceutical compositions according to any one of claims 1 to 13 for the therapy and prevention of the ulcer and dyspepsia relapses.

34. Pharmaceutical composition substantially as herein described with reference to Example 1.

35. Method according to claim 19 substantially as herein described with reference to Example 3.

Dated this 2nd day of December 2002

NICOX S.A.

By their Patent Attorneys

GRIFFITH HACK

AUSTRALIAN PATENT OFFICE