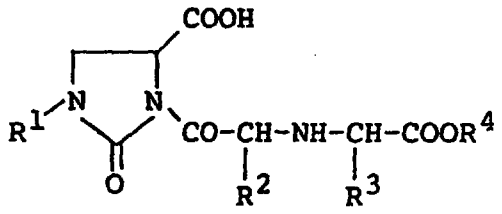
Description

This invention relates to the use of a novel agent for the prophylaxis and treatment of heart failure, more particularly, to the use of an agent for the prophylaxis and treatment of heart failure which agent is a 2-oxo-imidazolidine compound of the formula:



(I)

wherein R^1 and R^2 are the same or different and are each a lower alkyl group, R^3 is a phenyl-substituted lower alkyl group, and R^4 is hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof, and wherein said lower alkyl group contains 1 to 4 carbon atoms.

It is known that heart failure is a clinical syndrome characterised by distinctive symptoms resulting from cardiac output insufficient for needs of body organisms and is mostly induced by cardiac hypertrophy due to excessive load onto myocardium. That is, the cardiac hypertrophy induces change of myocardiac microstructure, failure of energy production mechanism with respect to myocardiac systole and increase of myocardiac oxygen consumption, which induce in turn myocardiac hyposystole (cf. "Naikagakusho" (Internal Medical Text), Vol. 2, pages 66-69, issued by Yamanaka Shoten, Feb. 5, 1982). Besides, clinically, due to myocardiac hyposystole, cardiac output is decreased and thereby input into ventricle is disturbed, which induces venous congestion and pulmonary congestion, and then, symptoms such as dyspnea and systemic edema appear.

For the treatment of the heart failure with avoiding myocardiac hyposystole, there have hitherto been used digitalis medicaments having cardiotonic activity such as digitoxin and digoxine, and xanthine medicaments such as caffeine and theophylline. However, the digitalis medicaments have some problems in applicable diseases. That is, although the digitalis medicaments are very effective for low output heart failure, i.e. in the symptoms where the cardiac output is absolutely insufficient for body's needs, they are not so effective for high output heart failure, i.e. in the symptoms where the deficiency of cardiac output is comparatively low. Moreover, contrary to most other medicaments, the digitalis medicaments have less difference between the effective dose and the dose at which they show undesirable side effects, and when the medicaments are continuously administered, there are induced so-called digitalis toxicosis symptoms such as nausea, headache, bradycardia, extrasystole and anginal symptom. Besides, xanthine medicaments have advantageously both cardiotonic and diuretic activities, but these activities are very weak, and hence, they are not so effective.

The present inventors have extensively studied to obtain a agent for the prophylaxis and treatment of the heart failure which is effective owing to different activity from the cardiotonic activity of the digitalis and xanthine medicaments, and have found that some imidazolidine compounds are effective for inhibiting or ameliorating cardiac hypertrophy and thereby are useful as an agent for the prophylaxis and treatment of heart failure, by an inhibitory activity on cardiac hypertrophy.

An object of the invention is to provide a medicament for use in the prophylaxis and treatment of heart failure. Another object of the invention is to provide an agent for the prophylaxis and treatment of heart failure.

According to the present invention there is provided the use of an agent according to formula (I) in the preparation of a pharmaceutical composition for the prophylaxis and/or treatment of heart failure.

Pharmaceutical compositions based on compounds of formula (I) are described in European Patent Publication No. EP-A-95 163, but the use is not concerned with the prophylaxis or treatment of heart failure.

The active compounds include the compounds of the formula (I) wherein R^1 is an alkyl group having 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl; R^2 is an alkyl group having 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl.; R^3 is a phenyl-substituted alkyl group having 1 to 4 carbon atoms in the alkyl moiety, such as benzyl, phenethyl, phenylpropyl, phenylbutyl.; and R^4 is hydrogen atom, or an alkyl group having 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl.

Preferred compounds are the compounds of the formula (I) wherein R^1 is methyl, R^2 is methyl, R^3 is phenethyl, and R^4 is hydrogen atom or ethyl.

The compounds (I) of this invention contain three asymmetric carbons within the molecule and hence include four diastereoisomers and eight optical isomers. This invention includes these isomers. Among these isomers, however, the compounds particularly suitable for the intended medical use are the compounds of the formula (I) wherein the carbon atoms at 4-position of the oxoimidazolidine ring and at 2-position of the amino acid moiety of the formula: -NH-CH(R^3)COOR^4 are both S-configuration. Other compounds suitable for the medical use are compounds of the formula (I) wherein the carbon atoms at 4-position of the oxoimidazolidine ring, at 2-position of the alkanoyl moiety of the formula: -COCH(R^2)- and at 2-position of the amino acid moiety of the formula: -NH-CH(R^3)COOR^4 are all S-configuration.

The 2-oxo-imidazolidine compounds (I) or a pharmaceutically acceptable salt thereof have an activity of inhibiting and ameliorating cardiac hypertrophy and an inhibitory and ameliorating activity on myocardiac hyposystole, and hence, these compounds can be used for the prophylaxis and treatment of heart failure (e.g. congestive heart failure and complementary heart failure.) and also various symptoms accompanied to heart failure, such as congestions of various organs (e.g. lung and liver.), dyspnea, pulmonary edema, systemic edema, peripheral cyanosis, paroxysmal nocturnal dyspnea and cardiac asthma in a warm-blooded animal including human being. Moreover, symptoms such as edema, pulmonary circulation disorder, hypertension and valvular disease of the heart induce cardiac hypertrophy which tends to cause heart failure, and hence, the compounds of this invention are also useful for the prophylaxis of heart failure in the patients having such symptoms as above.

For instance, when (4S)-1-methyl-3-[(2S)-2-[N((1S)-1-ethoxycarbonyl-3-phenylpropyl)amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid was orally administered to a model animal suffering from hypertension with characteristic syndrome of enlargement of heart, i.e. spontaneously hypertensive rats, at a dose of 5 mg/kg/day for 10 weeks, the compounds significantly inhibited increase of heart weight, i.e. showed significant activity of inhibiting cardiac hypertrophy. Likewise, when (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-carboxy-3-phenylpropyl)amino]-propionyl]-2-oxo-imidazolidine-4-carboxylic acid was intraperitoneally administered to the rats at a dose of 0.5 mg/kg, similar activity was obtained.

Moreover, the compounds (I) of this invention have low toxicity. For instance, when (4S)-1-methyl-3-[-(2S)-2-[N-((1S)-1-carboxy-3-phenylpropyl)amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid or (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-ethoxycarbonyl-3-phenylpropyl)amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid was orally administered to rats at a dose of 5 g/kg, even after observing for 5 days, no rat died.

The compounds (I) used as an active ingredient in this invention may be used in any form of a free acid (and/or free base) or a pharmaceutically acceptable salt thereof. The free acid (or base) can be converted into its salt by treating it with an organic or inorganic acid or alternatively with an organic or inorganic base in a usual manner. The pharmaceutically acceptable salts of the compounds (I) include organic acid addition salts (e.g. succinate, maleate, fumarate and methanesulfonate), inorganic acid addition salts (e.g. hydrochloride, hydrobromide, sulfate and phosphate.), salts with organic bases (e.g. lysine salt and ornithine salt), and salts with inorganic bases (e.g. sodium salt, potassium salt, calcium salt and magnesium salt).

The prophylactic and therapeutic agent containing as an active ingredient the compound (I) or a pharmaceutically acceptable salt thereof can be administered by oral route or by parenteral route.

The dose of the compound (I) or a pharmaceutically acceptable salt thereof may vary depending on the severity of diseases, age, weight and body conditions of the patients is usually in the range of 0.05 to 100 mg/kg/day, preferably 0.1 to 25 mg/kg/day, in case of oral administration, and in the range of 1 μg/kg/day to 2 mg/kg/day, preferably 1 μg/kg/day to 0.5 mg/kg/day, in case of parenteral administration.

The use of the compounds (I) or their pharmaceutically accetable salts may be to prepare conventional pharmaceutical preparations with the compound in admixture with conventional pharmaceutically acceptable carrier or diluent which are usually used for the pharmaceutical preparations suitable for oral or parenteral administration. The pharmaceutically acceptable carrier or diluent includes, for example, starch, lactose, glucose, potassium phosphate, corn starch, gum arabic and magnesium stearate. The pharmaceutical preparations include solid preparations such as tablets, pills, capsules and suppositories, and liquid preparations such as solutions, suspensions and emulsions. These preparations may be sterilized and may optionally contain other additives, such as stabilizers, wetting agents and emulsifiers.

The compounds (I) can be prepared by the method disclosed in European Patent Publication. No. EP-A-95163 A.

The pharmacological activities of the compounds of this invention are illustrated by the following experiments.

Experiment 1

Activity for inhibiting cardiac hypertrophy:

[Method]:

The test compound: (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-ethoxycarbonyl-3-phenylpropyl)amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid hydrochloride was dissolved in distilled pure water and orally administered to spontaneously hypertensive rats (SHR) (4 weeks old at the begining of experiment, groups of 6 rats) at a dose of 5 mg/kg/day for 10 weeks.

Twenty-four hours after the final dosing, the SHR were killed by bleeding under ether anesthesia. The weight of heart was measured and the weight of heart per 100 g of body weight (relative heart weight) was calculated. After that, the heart was used for the measurement of cross sectional area of the heart.

Method for measurement of cross sectional area of heart is as follows:

(i) After weighing the excised heart, the excised heart was immersed in 10 % neutral buffered formalin solution for about one week to fix said heart. The fixed heart was cut at a definitive region crossing the left and right ventricles to obtain a sample (thickness: about 2 mm). The sample was again immersed in a 10 % neutral buffered formalin solution overnight, treated with paraffin in a usual manner (Note 1) and then stained with hematoxyin eosine (HE).

(ii) The microscopic image of the stained sample was examined by an image analyzer (Note 2) to give the ratio of the area of stained region to the area of unstained region (the latter area being the gap produced in preparing the sample).

(iii) The real area of the sample was obtained by an image analyzer and then multiplied by the ratio obtained in the above (ii) to give the cross sectional area of the heart.

[Note 1): It is disclosed in "Byori Gijutsu Mannual" (Mannual for Pathorogical Technology) 3, Technology for Histopathorogical Preparation, ed. by Nippon Byori Gakkai, issued on March 30, 1981 by Ishiyaku Shuppan K.K.

[Note 2]: Nikon three tube color television camera and Nikon Ruzex II, manufactured by Nippon Kogaku K.K.

[Results]:

The results are shown in Table 1.

Table 1

	Relative heart weight (g)	Sectional area of heart (mm^2)
Non-administ. group	0.399 ± 0.01	66.8 ± 4.0
Test sample-administ. group	0.34 ± 0.01*	57.9 ± 2.9*
Inhibitory ratio (%)	13	13

The mark *) means that the data were significant with a level of significance of 1 %.

The inhibitory ratio was calculated by the following equation:

$$\text{Inhibitory ratio (\%)} = \frac{[\text{Value in non-administ. group}] - [\text{Value in sample-administ. group}]}{\text{Value in non-administ. group}} \times 100$$

As is clear from the above experimental results, the active compound showed 13 % inhibitory ratio in both of the relative heart weight and sectional area of the heart in comparison with the non-administration group and showed clear inhibition of cardiac hypertrophy.

Experiment 2

Activity for inhibiting cardiac hypertrophy:

[Method]:

The test compound: (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-carboxy-3-phenylpropyl)amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid hydrochloride was dissolved in distilled pure water and intraperitoneally administered to spontaneously hypertensive rats (SHR) (4 weeks old at the begining of experiment, groups of 9 rats) at a dose of 0.5 mg/kg/day for 10 weeks.

Twenty-four hours after the final dosing, the SHR were killed by bleeding under ether anesthesia. The weight of heart was measured and the weight of heart per 100 g of body weight (relative heart weight) was calculated.

[Results]:

The results are shown in Table 2.

Table 2

	Relative heart weight (g)
Non-administ. group	0.36 ± 0.013
Test sample-administ. group	0.33 ± 0.012**
Inhibitory ratio (%)	8

The mark **) means that the data were significant with a level of significance of 0.1 %.

As is clear from the above experimental results, the active compound showed 8 % inhibitory ratio of relative heart weight in comparison with the non-administration group and showed clear inhibition of cardiac hypertrophy.

The preparations of the present agent are illustrated by the following Examples.

Example 1

Tablets:

[Formulation]:

(Active ingredient) (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-ethoxycarbonyl-3-phenylpropyl)-amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid	10 mg
Lactose	86.8 mg
Polyvinylpyrrolidone	5 mg
Corn starch	37 mg
Magnesium stearate	1.2 mg
Totally	140.0 mg

[Method]:

To the active ingredient are added lactose and corn starch, and the mixture is well mixed, and thereto is added a solution of polyvinylpyrrolidone in purified water, and the mixture is well kneaded to granulate. The granules thus prepared are dried, and thereto is added magnesium stearate, and the mixture is tabletted in a usual manner to give tablets.

Example 2

Tablets:

[Formulation]:

(Active ingredient) (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-carboxy-3-phenylpropyl)-amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid	10 mg
Lactose	80 mg
Polyvinylpyrrolidone	3.3 mg
Corn starch	35.9 mg
Magnesium stearate	0.8 mg
Totally	130.0 mg

[Method]:

In the same manner as described in Example 1, the tablets are prepared.

Example 3

Injections:

[Formulation]:

(Active ingredient) (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-ethoxycarbonyl-3-phenylpropyl)-amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid	10 mg
Sodium chloride	9 mg
Distilled water for injection	q. s.
Totally	1 ml

[Method]:

The active ingredient and sodium chloride are dissolved in distilled water for injection, and the solution is filtered with a filter (pore size: 0.22 μm), and filled in ampoules and then sterilized to give injections.

Example 4

Injections:

[Formulation]:

(Active ingredient) (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-carboxy-3-phenylpropyl)-amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid	8.54 mg
Sodium chloride	9.0 mg
Sodium hydrogen carbonate	8.4 mg
Distilled water for injection	q. s.
Totally	1 ml

[Method]:

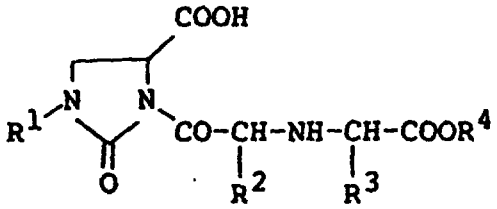
Sodium chloride is dissolved in distilled water for injection, and thereto is added the active ingredient, and the mixture is dissolved with sodium hydrogen carbonate. The solution is filterd with a filter (pore size: 0.22 μm). The solution is filled in ampoules and then sterilized to give injections.

The compositions of the present invention may be in unit dose form and each may contain from 5 to 20mg of active ingredient. The invention is also concerned with the use of a compound as defined herein in the preparation of a pharmaceutical composition of the prophylaxis and/or treatment of heart failure.

Furthermore it is to be understood that the invention includes the use of derivatives of the compound of formula (I) which are other than those wherein R^4 is hydrogen or a lower alkyl group, provided that such derivatives are convertible in the human body to provide the said composition in the free acid form, i.e. when R^4 is hydrogen.

Claims

1. The use of a compound of formula (I):



(I)

wherein R^1 and R^2 are the same or different and are each a lower alkyl group, R^3 is a phenyl-substituted lower alkyl group, and R^4 is hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition for the prophylaxis and/or treatment of heart failure, and wherein said lower alkyl group contains 1 to 4 carbon atoms.

2. The use according to claim 1, wherein the compound of the formula (I) is a compound wherein R^1 is methyl, R^2 is methyl, R^3 is phenethyl, and R^4 is hydrogen atom or ethyl, or a pharmaceutically acceptable salt thereof.

3. The use according to claim 1, wherein the compound of the formula (I) is a compound wherein the carbon atoms at 4-position of the oxoimidazolidine ring and at 2-position of the amino acid moiety of the formula: -NH-CH(R^3)COOR^4 are both S-configuration, or a pharmaceutically acceptable salt thereof.

4. The use according to claim 1, wherein the compound of the formula (I) is a compound wherein the carbon atoms at 4-position of the oxoimidazolidine ring, at 2-position of the alkanoyl moiety of the formula: -COCH(R^2)- and at 2-position of the amino acid moiety of the formula: -NH-(CR^3)COOR^4 are all S-configuration or a pharmaceutically acceptable salt thereof.

5. The use according to claim 1, wherein the compound of the formula (I) is (4S)-1-methyl-3-[(2S)-2-[N-(-(1S-1-ethoxycarbonyl-3-phenylpropyl)amino]propionyl]-2-oxo-imidazolidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof.

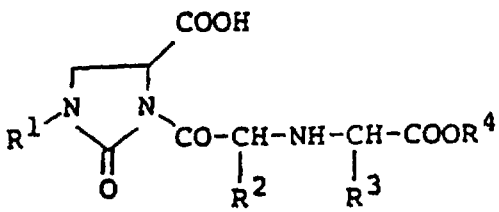
6. The use according to claim 1, wherein the compound of the formula (I) is (4S)-1-methyl-3-[(2S)-2-[N-(-(1S)-1-carboxy-3-phenylpropyl)amino]propionyl]-2-oxyimidazolidine-4-carboxylic acid, or a pharmaceutically acceptable salt thereof.

7. The use as claimed in any one of the preceding claims wherein the composition is in unit dose form which contains from 5 to 20mg of active ingredient according to formula (I).

8. The use as claimed in claim 7 wherein the composition is in the form of a tablet, pill, capsule, suppository or ampoule.

Patentansprüche

1. Verwendung einer Verbindung der Formel (I):



(I)

* C L M S *

worin R^1 und R^2 gleich oder verschieden sind und jeweils eine Niedrigalkylgruppe bedeuten, worin R^3 eine phenylsubstituierte Niedrigalkylgruppe ist, und worin R^4 ein Wasserstoffatom oder eine Niedrigalkylgruppe ist, oder ein pharmazeutisch akzeptables Salz davon, für die Herstellung einer pharmazeutischen Zusammensetzung für die Prophylaxe und/oder Behandlung von Herzinsuffizienz, und worin die Niedrigalkylgruppe 1 bis 4 Kohlenstoffatome enthält.

2. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß die Verbindung der Formel (I) eine Verbindung ist, worin R^1 Methyl ist, worin R^2 Methyl ist, worin R^3 Phenethyl ist und worin R^4 ein Wasserstoffatom oder Ethyl ist, oder daß sie ein pharmazeutisch akzeptables Salz davon ist.

3. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß die Verbindung der Formel (I) eine Verbindung ist, worin die Kohlenstoffatome an der Position 4 des Oxoimidazolidinringes und an der Position 2 des Aminosäureanteils der Formel: $-NH-CH(R^3)COOR^4$ beide S-Konfiguration aufweisen, oder daß sie ein pharmazeutisch akzeptables Salz davon ist.

4. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß die Verbindung der Formel (I) eine Verbindung ist, worin die Kohlenstoffatome an der Position 4 des Oxoimidazolidinringes, an der Position 2 des Alkanoylanteils der Formel: $-COCH(R^2)-$ und an der Position 2 des Aminosäureanteils der Formel: $-NH-(CR^3)COOR^4$ alle S-Konfiguration aufweisen, oder daß sie ein pharmazeutisch akzeptables Salz davon ist.

5. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß die Verbindung der Formel (I) (4S)-1-Methyl-3-((2S)-2-(N-((1S)-1-ethoxycarbonyl-3-phenylpropyl)- amino)propionyl)-2-oxo-imidazolidin-4-carbonsäure oder ein pharmazeutisch akzeptables Salz davon ist.

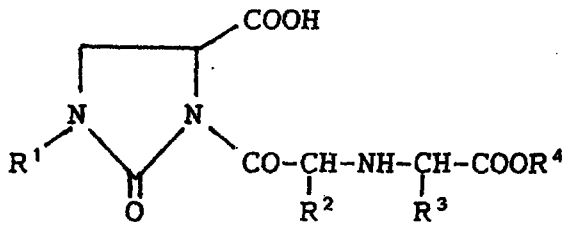
6. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß die Verbindung der Formel (I) (4S)-1-Methyl-3-((2S)-2-(N-((1S)-1-carboxy-3-phenylpropyl)- amino)propionyl)-2-oxy-imidazolidin-4-carbonsäure oder ein pharmazeutisch akzeptables Salz davon ist.

7. Verwendung nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet,** daß die Zusammensetzung in Einheitsdosierungsform vorliegt, die von 5 bis 20 mg des aktiven Bestandteils entsprechend der Formel (I) enthält.

8. Verwendung nach Anspruch 7, dadurch **gekennzeichnet,** daß die Zusammensetzung in der Form einer Tablette, einer Pille, einer Kapsel, eines Suppositoriums oder einer Ampulle vorliegt.

Revendications

1. Utilisation d'un composé de formule (I):



(I)

dans laquelle R^1 et R^2 sont identiques ou différents et sont chacun un groupe alkyle inférieur, R^3 est un groupe alkyle inférieur substitué par phényle, et R^4 est un atome d'hydrogène ou un groupe alkyle inférieur, ou d'un de ses sels pharmaceutiquement acceptables, pour la préparation d'une composition pharmaceutique pour la prophylaxie et/ou le traitement de l'insuffisance cardiaque, ledit groupe alkyle

* C L M S *

inférieur contenant 1 à 4 atomes de carbone.

2. Utilisation selon la revendication 1, dans laquelle le composé de formule (I) est un composé dans lequel R^1 est un méthyle, R^2 est un méthyle, R^3 est un phénéthyle, et R^4 est un atome d'hydrogène ou un éthyle, ou un de ses sels pharmaceutiquement acceptables.

3. Utilisation selon la revendication 1, dans laquelle le composé de formule (I) est un composé dans lequel les atomes de carbone en position 4 du cycle oxoimidazolidine et en position 2 de la partie aminoacide de formule: $-NH-CH(R^3)COOR^4$ ont tous les deux la configuration S, ou un de ses sels pharmaceutiquement acceptables.

4. Utilisation selon la revendication 1, dans laquelle le composé de formule (I) est un composé dans lequel les atomes de carbone en position 4 du cycle oxoimidazolidine, en position 2 de la partie alcanoyle de formule: $-COCH(R^2)-$ et en position 2 de la partie aminoacide de formule: $-NH-CH(R^3)-COOR^4$ ont tous la configuration S, ou un de ses sels pharmaceutiquement acceptables.

5. Utilisation selon la revendication 1, dans laquelle le composé de formule (I) est l'acide (4S)-1-méthyl-3-[(2S)-2-[N-((1S)-1-éthoxycarbonyl-3-phénylpropyl)amino]propionyl]-2-oxoimidazolidine-4-carboxylique, ou un de ses sels pharmaceutiquement acceptables.

6. Utilisation selon la revendication 1, dans laquelle le composé de formule (I) est l'acide (4S)-1-méthyl-3-[(2S)-2-[M-((1S)-1-carboxy-3-phénylpropyl)amino]propionyl]-2-oxoimidazolidine-4-carboxylique, ou un de ses sels pharmaceutiquement acceptables.

7. Utilisation telle que revendiquée dans l'une quelconque des revendications précédentes dans laquelle la composition est sous forme de doses unitaires qui contiennent 5 à 20 mg de substance active correspondant à la formule (I).

8. Utilisation telle que revendiquée dans la revendication 7, dans laquelle la composition est sous forme de comprimés, de pilules, de capsules, de suppositoires ou d'ampoules.