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(54) Titre : COMPRIME CONTENANT L'ETHYLESTER DE L'ACIDE 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL)AMINO]-PROPIONIQUEOU SES SELS

(54) Title: TABLET CONTAINING 3-[(2-{[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOLE-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-PROPIONIC ACID ETHYLESTER OR THE SALTS THEREOF

(57) Abrégé/Abstract:
The invention relates to a new tablet for the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmacologically acceptable salts thereof.

Abstract

The invention relates to a new tablet for the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmacologically acceptable salts thereof.

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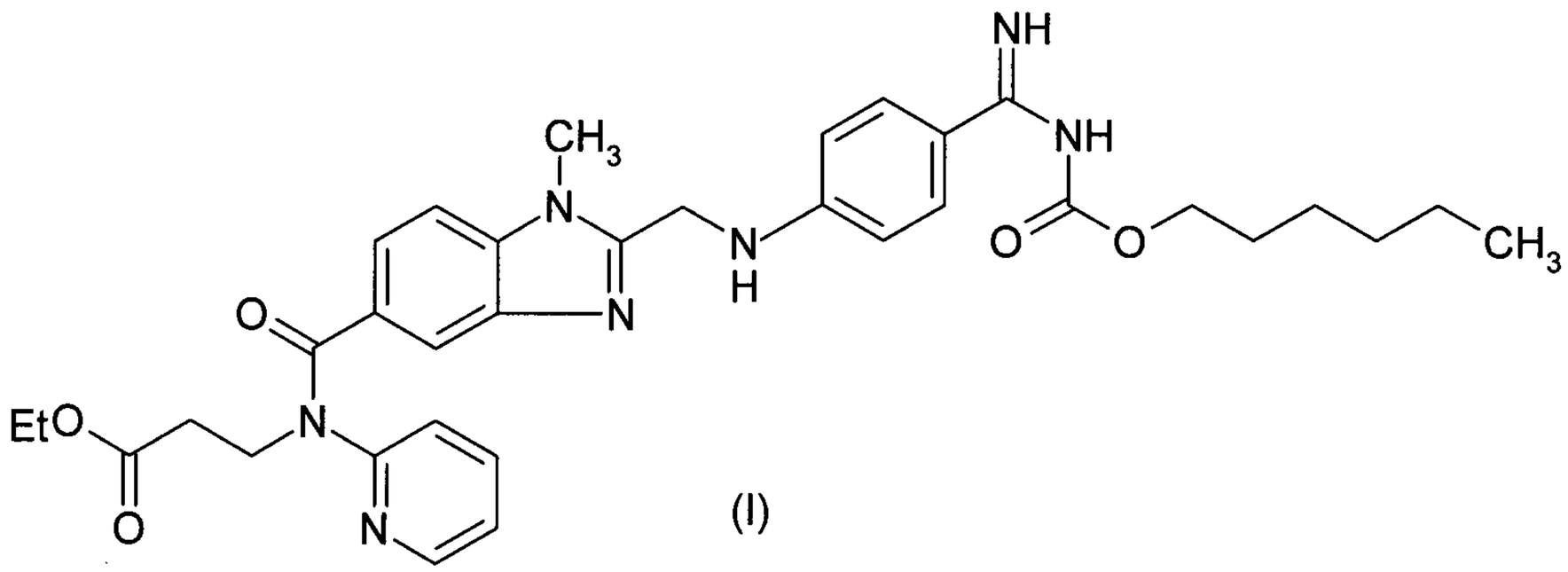
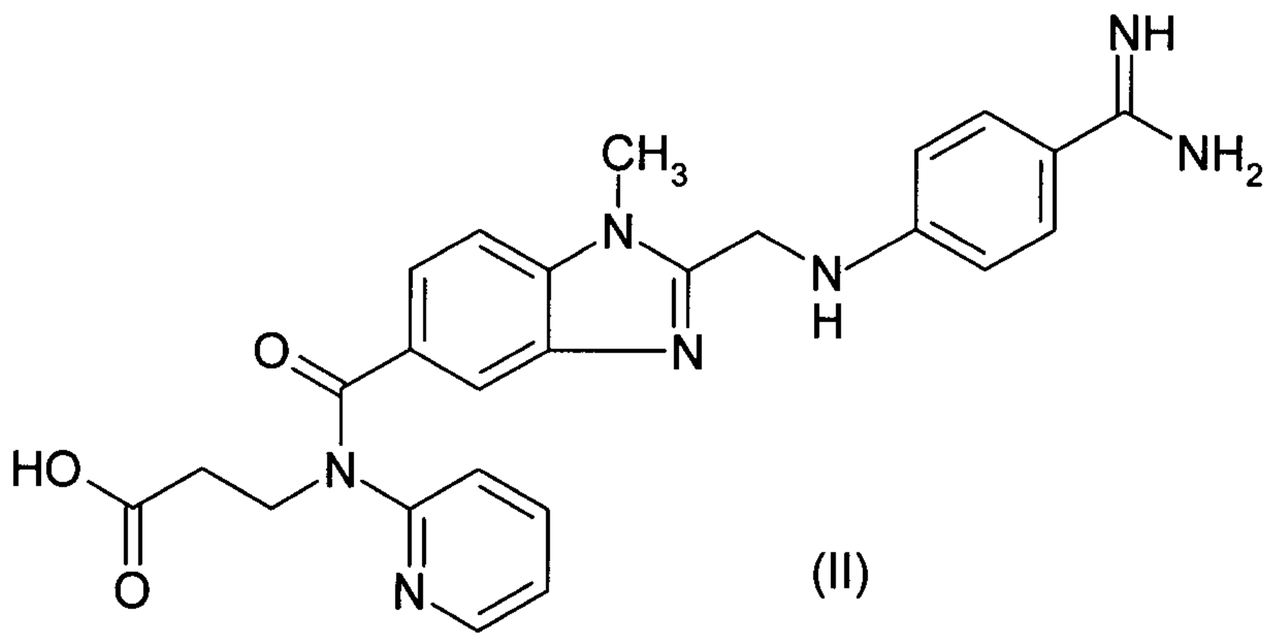
Tablet containing 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenyl-amino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid ethylester or the salts thereof

The invention relates to a tablet for the active substance ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or the pharmacologically acceptable salts thereof. This active substance with the chemical formula



(I)

is already known from WO 98/37075, in which compounds with a thrombin-inhibiting and thrombin time-prolonging activity are disclosed, under the name 1-methyl-2-[*N*-[4-(*N*-n-hexyloxycarbonylamidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-*N*-(2-pyridyl)-*N*-(2-ethoxycarbonylethyl)-amides. The compound of formula I is a double prodrug of the compound



(II)

i.e. the compound of formula I is only converted into the compound which is actually effective, namely the compound of formula II, in the body. The main range of

indications for the compound of chemical formula I is the post-operative prophylaxis of deep vein thrombosis.

The aim of the invention is to provide an improved formulation for oral use for the compound of formula I (which is also referred to hereinafter as the active substance).

Surprisingly it has now been found that the use of pharmaceutically acceptable organic acids with a solubility in water of > 1 g/250 ml at 20°C, preferably > 1 g/160 ml at 25°C, in solid oral formulations leads to a significantly improved galenic form of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate and the pharmaceutically acceptable salts thereof.

Pharmaceutically suitable acids for the purposes of this invention are for example tartaric acid, fumaric acid, succinic acid, citric acid and malic acid including the hydrates and acid salts thereof. Fumaric acid is particularly suitable for the purposes of this invention.

A preferred embodiment of the invention is a tablet.

In an exemplary embodiment, the invention relates to a tablet comprising ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof in admixture with fumaric acid, and further comprising conventional excipients and fillers.

The tablets contain 5 to 50 wt.% of active substance (based on the methanesulphonate), 5 to 50 wt.% of a pharmaceutically acceptable organic acid with a solubility in water of > 1 g/250 ml at 20°C as well as other excipients and fillers. Examples of other excipients and fillers which may be used include for example 1 to 80 wt.% of a filler, optionally up to 10 wt.% of a binder (i.e. 0 to 10 wt.% of binder), 1 to 10 wt.% of a disintegration promoter and 0.25 to 10 wt.% of a lubricant, with all the ingredients adding up to 100 wt.%.

Tablets which contain 10 to 30 wt.% active substance (based on the methanesulphonate), 10 to 40 wt.% of a pharmaceutically acceptable organic acid, 5 to 70 wt.% of a filler, 3 to 5 wt.% of a binder, 2 to 6 wt.% of a disintegration promoter and 1 to 5 wt.% of a lubricant are preferred.

Particularly preferred are tablets which contain 15 to 25 wt.% of active substance (based on the methanesulphonate), 10 to 30 wt.% of a pharmaceutically acceptable organic acid, 50 to 65 wt.% of a filler, 3 to 5 wt.% of a disintegration promoter and 1.5 to 2.5 wt.% of a lubricant.

The acid ingredient used may a pharmaceutically acceptable organic acid with a solubility in water of > 1 g / 250 ml at 20° C, such as e.g. tartaric acid, fumaric acid, succinic acid, citric acid and malic acid including the hydrates and acid salts thereof. The pharmaceutically acceptable organic acids used are preferably tartaric acid, fumaric acid, succinic acid or citric acid; fumaric acid is particularly preferred.

By the active substance is meant the compound of formula I or one of the pharmaceutically acceptable salts thereof. The methanesulphonate (mesylate) of the compound of formula I is preferred.

The fillers, binders, disintegration promoters and lubricants mentioned above are known compounds having the specified properties conventionally used in the pharmaceutical industry.

Preferred fillers which may be used are mannitol, erythritol, lactose, microcrystalline cellulose, hydroxypropylcellulose, particularly low-substituted hydroxypropylcellulose, and pregelatinised starch. It is particularly preferable to use mannitol.

The binder used may preferably be a partially or totally synthetic selected from among the polyvinylpyrrolidones (povidone) or copolymers of N-vinylpyrrolidone and vinyl acetate (copovidone) or hydroxypropylmethylcellulose.

Examples of preferred disintegration promoters include cross-linked polyvinylpyrrolidone (crospovidone), sodium starch glycolate or cross-linked cellulosecarboxymethylether sodium salt (croscarmellose sodium). Crospovidone is particularly preferred.

Preferred lubricants include for example magnesium stearate, sodium stearyl-fumarate and saccharose fatty acid esters. Magnesium stearate is particularly preferred.

The tablets may be prepared by the methods described below:

Preparation of the tablets

The tablet according to the invention may be prepared by directly mixing and compressing the ingredients or by dry granulation and compression. To prepare the tablet according to the invention the following procedure may be used, for example.

The active substance, the acid and a filler, e.g. mannitol, are premixed in an intensive mixer and then screened. The powder mixture is transferred into a gravity mixer, a disintegration promoter, e.g. crospovidone and optionally other excipients (e.g. a binder, if necessary) are added and then mixed together. After the addition of lubricants, particularly magnesium stearate and saccharose fatty acid esters, the ingredients are mixed again. The mixture of active substance and excipient thus obtained is then compressed using a suitable tablet press to produce the tablets according to the invention.

The content of active substance in the pharmaceutical composition is 5 to 50 %, preferably 10 to 30 %; the content of pharmaceutically acceptable organic acid is usually between 5 and 50 %, preferably between 10 and 40 %.

Unless otherwise stated, the percentages given are percent by weight in each case.

In the first clinical trials with conventional tablets containing the compound of formula I it had been found that highly variable plasma levels occurred, ranging to individual cases of malabsorption. The variability of the plasma level patterns is significantly lower when the compound of formula I is administered as an oral solution; no instances of malabsorption have been observed.

One advantage of the formulation according to the invention containing the compound of formula I is that it guarantees sufficient bioavailability of the active substance which is better than that obtained with a conventional pharmaceutical preparation and is largely independent of the pH of the stomach, it reduces fluctuations in the bioavailability of the active substance and prevents malabsorption. Another advantageous property of the pharmaceutical composition according to the invention is its suitability for all patients, i.e. including those whose gastric pH is raised as a result of normal physiological variability, illness or co-medication with drugs which increase the gastric pH (e.g. pantoprazole).

The dosage for oral administration is conveniently 25 to 300 mg of the active substance base (per tablet), preferably 50 to 200 mg, particularly preferably 75 to 150 mg of the active substance base, once or twice a day in each case.

The Examples that follow are intended to illustrate the invention:

Example 1

BIBR 1048 tablets 50 mg

	mg / tablet	% / tablet
mesylate of the compound of formula I[1)]	57.655	16.957
mannitol	205.145	60.337
fumaric acid	50.000	14.706
crospovidone	13.600	4.000
saccharose fatty acid ester	6.800	2.000
magnesium stearate	6.800	2.000
total	340.000	100.000

1) corresponds to 50 mg of the compound of formula I

Example 2

BIBR 1048 tablets 100 mg

	mg / tablet	% / tablet
mesylate of the compound of formula I[1)]	115.310	16.957
mannitol	410.290	60.337
fumaric acid	100.000	14.706
crospovidone	27.200	4.000
saccharose fatty acid ester	13.600	2.000
magnesium stearate	13.600	2.000
total	680.000	100.000

1) corresponds to 100 mg of the compound of formula I

Example 3

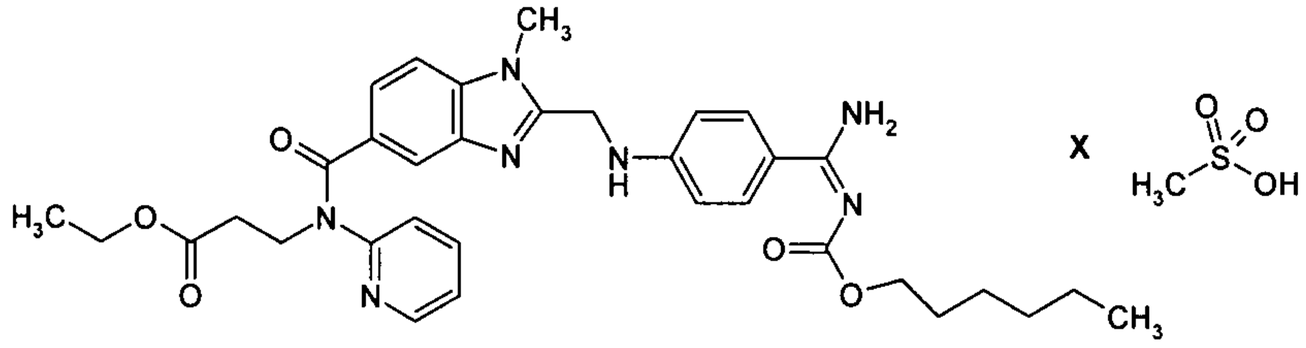
BIBR 1048 tablets 150 mg

	mg / tablet	% / tablet
mesylate of the compound of formula I[1)]	172.963	23.062
mannitol	382.037	50.938
fumaric acid	150.000	20.000
crospovidone	30.000	4.000
sodium stearyl fumarate	15.000	2.000
total	750.000	100.000

1) corresponds to 150 mg of the compound of formula I

Example 4

Preparation of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate–methanesulphonate



A solution of 5.0 mmol of methanesulphonic acid in 25 ml of ethyl acetate was added dropwise, with stirring, at ambient temperature, to a solution of 3139 mg (5.0 mmol) of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (prepared as described in WO 98/37075), in 250 ml of ethyl acetate. After a few minutes the product started to crystallise out. It was stirred for one hour at ambient temperature and for a further hour while cooling with ice, then the precipitate was suction filtered, washed with approx. 50 ml of ethyl acetate and 50 ml diethyl ether and dried at 50°C in the circulating air dryer.

Yield: 94% of theory

Melting point: 178 - 179°C

$C_{34}H_{41}N_7O_5$ x CH_4SO_3 (723.86)

Elemental analysis:								
calc.:	C	58.07%	H	6.27%	N	13.55%	S	4.43%
found:		58.11%		6.30%		13.50%		4.48%

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CLAIMS:

1. Tablet comprising ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof in admixture with fumaric acid, and further comprising conventional excipients and fillers.

2. Tablet according to claim 1, wherein the content of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or the salts thereof in the pharmaceutical composition is 5 to 50%, based on an amount of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate.

3. Tablet according to claim 1 or 2, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate is used as active substance.

4. Tablet according to any one of claims 1 to 3, wherein the content of fumaric acid is 5 to 50%.

FIG. 1

Schematic structure of the pharmaceutical composition:

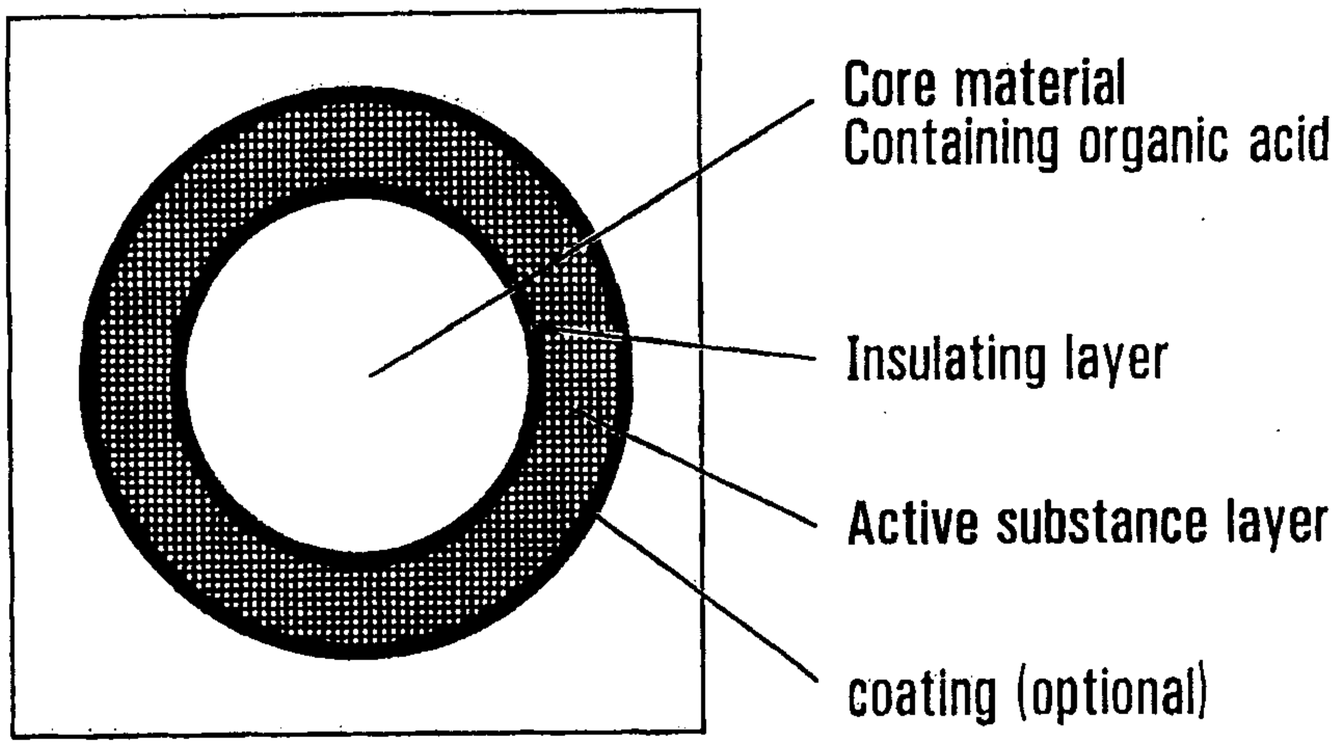

FIG. 2