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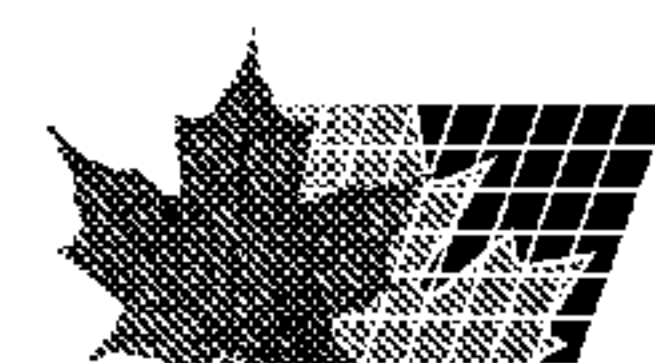
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(54) Titre : NOUVELLE FORME GALENIQUE ORALE POUR ETHYLESTER D'ACIDE 3-[(2-[[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYLE)-PHENYLAMINO]-METHYLE-1-METHYLE-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDINE-2-YLE-AMINO]PROPIONIQUE ET SES SELS
(54) Title: NOVEL ORALLY ADMINISTERED DOSAGE FORM FOR 3-[(2-[[4-(HEXYLOXYCARBONYLAMINO-IMINO-METHYL)-PHENYLAMINO]-METHYL}-1-METHYL-1H-BENZIMIDAZOL-5-CARBONYL)-PYRIDIN-2-YL-AMINO]-ETHYL PROPIONATE AND SALTS THEREOF

(57) **Abrégé/Abstract:**

The invention relates to a novel orally administered dosage form for the active substance 3-[(2-[[4-(hexyloxy carbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-ethyl propionate and pharmacologically compatible salts thereof.



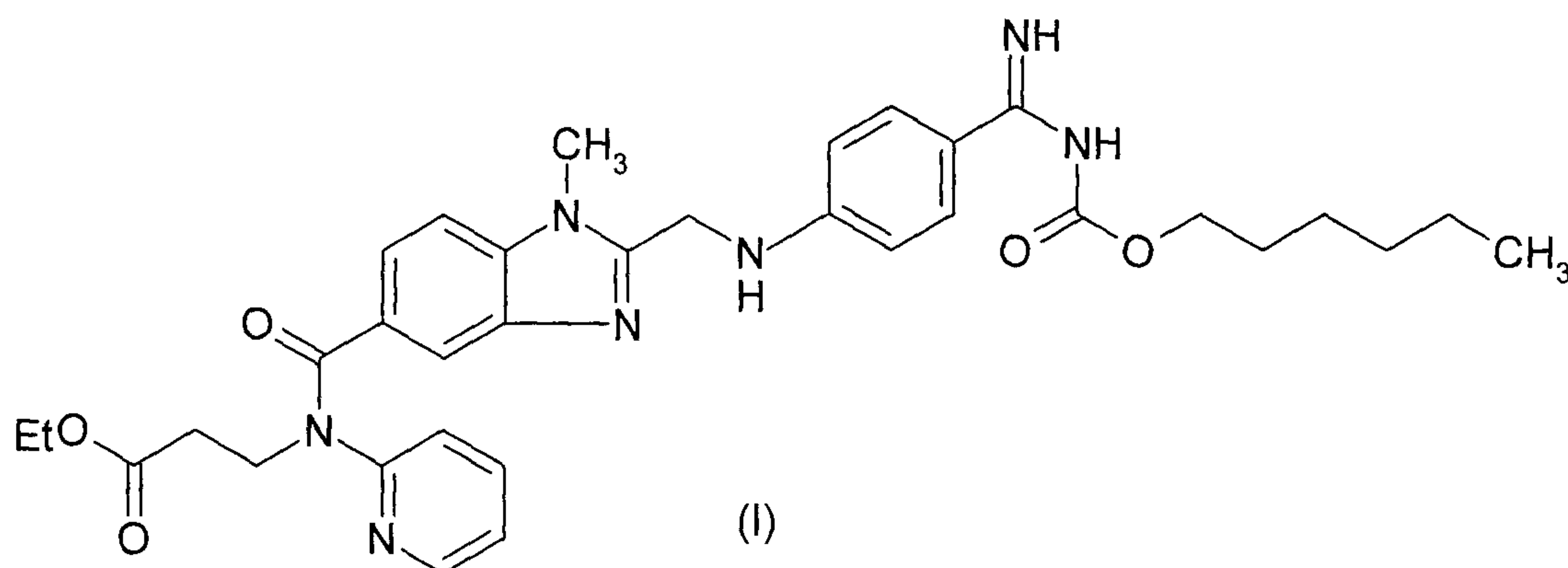
Abstract

The invention relates to a new formulation for oral administration of the active
5 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.

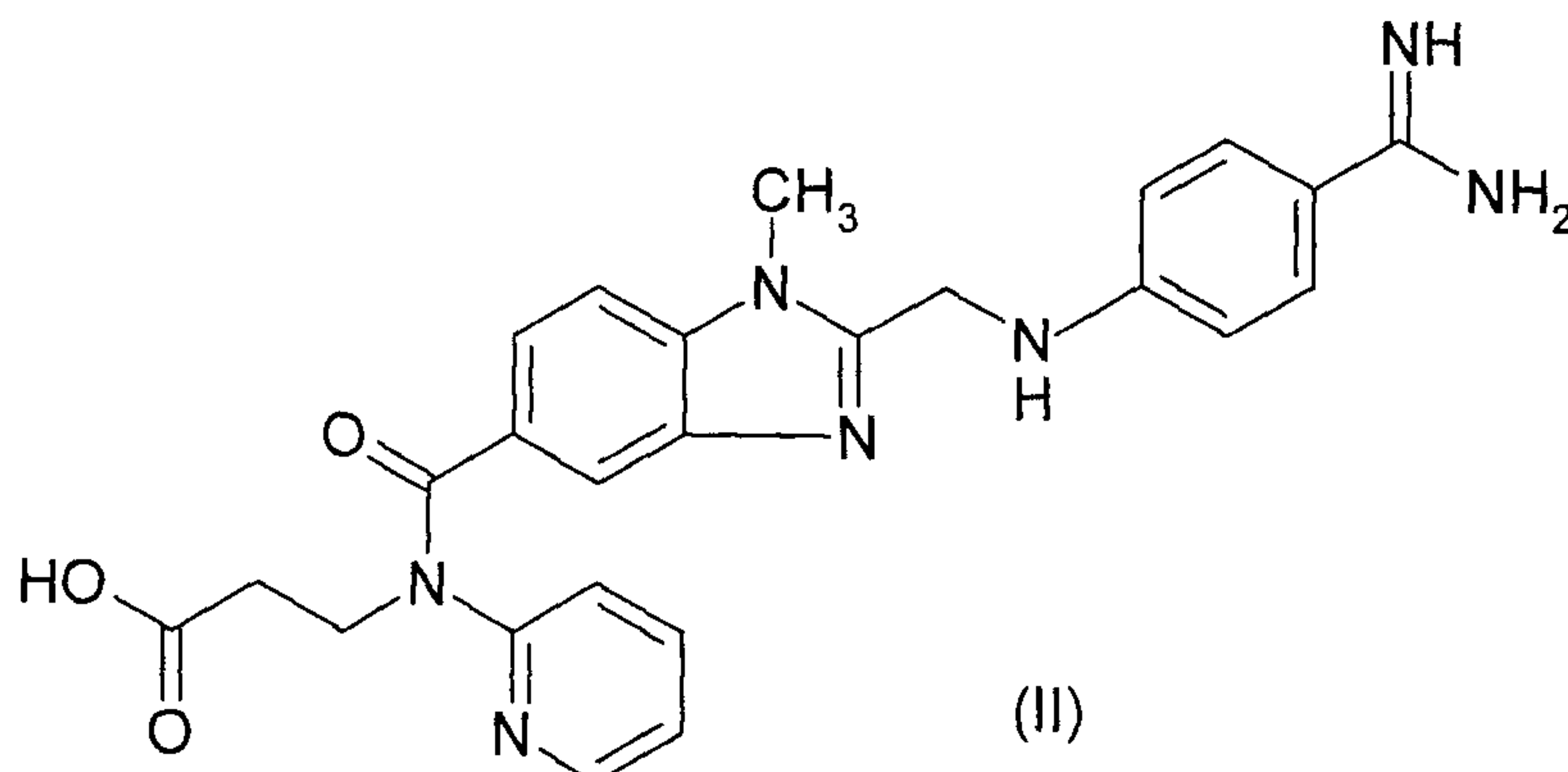
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Novel pharmaceutical composition for oral application of 3-[(2-{[4-(Hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionic acid-ethylester and the salts thereof

The invention relates to a formulation for oral administration of 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. This active substance with the chemical formula



is already known from WO 98/37075, in which compounds with a thrombin-inhibiting effect and a 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-ethoxycarbonyl-ethyl)-amide. The compound of formula I is a double prodrug of the compound



i.e. the compound of formula I is only converted into the actual effective compound, namely the compound of formula II, in the body. The main field of application of 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 the oral
5 administration of the compound of formula I and the pharmacologically acceptable salts thereof (also referred to hereinafter as the "active substance").

Surprisingly it has now been found that an anhydrous formulation which contains the active substance ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-
10 methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof in dispersed form in a lipophilic, pharmaceutically acceptable carrier system, leads to oral preparations which have significantly better properties. The carrier system may be both solid, semi-solid and liquid.

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The formulation according to the invention comprises

5 to 40 wt.% of the active substance,

55 to 95 wt.% of a pharmaceutically acceptable, lipophilic carrier system and optionally 0 to 5 wt.% of one or more stabilisers,

20 the amounts of ingredients adding up to a total of 100 wt.%.

A formulation containing stabiliser is preferred.

A preferred formulation according to the invention comprises

25 8 to 40 wt.% of the active substance,

60 to 92 wt.% of a pharmaceutically acceptable, lipophilic carrier system and optionally 1 to 4 wt.% of one or more stabilisers,

the amounts of ingredients adding up to a total of 100 wt.%.

30 A particularly preferred formulation according to the invention comprises

16 to 36 wt.% of the active substance,

61 to 81 wt.% of a pharmaceutically acceptable, lipophilic carrier system and optionally 2 to 3 wt.% of one or more stabilisers,

the amounts of ingredients adding up to a total of 100 wt.%.

The finished formulation may be packed into hard or soft capsules made for example from gelatine, hydroxypropylmethylcellulose (HPMC), Polulan, starch, modified starch, algae or other material which is broken down in the gastrointestinal tract.

5

By the active substance is meant ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof; pharmaceutically acceptable salts of ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate are preferably used. Ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate – methanesulphonate is particularly preferred. The active substance may be ground up before use. Most particularly preferred is ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate – methanesulphonate in ground form.

The pharmaceutically acceptable, lipophilic carrier systems for the purposes of the invention include

- a) microemulsion concentrates such as for example macrogol glycerol laurates according to Ph. Eur. NT 2001 and
- b) low-melting lipophilic systems comprising:
 - i) 20 to 90 wt.% (based on the finished formulation) of a lipophilic component and
 - ii) 0 to 90 wt.% (based on the finished formulation) of a surfactant compound.

Preferably microemulsion concentrates are used.

- A preferred carrier system according to b) comprises
- i) 40 to 70 wt.% (based on the finished formulation) of a lipophilic component and
 - ii) 5 to 30 wt.% (based on the finished formulation) of a surfactant compound.

A preferred embodiment of the low-melting lipophilic systems according to b) relates to those systems which have been homogenised under high pressure.

One advantage of the formulation according to the invention is that the active
5 substance is chemically and physically stabilised thereby. Additionally, the formulation is characterised by good bioavailability of the active substance.

A preferred microemulsion concentrate is Gelucire[®], while Gelucire 44/14[®] is particularly preferred, i.e. Gelucire[®] with a melting point of 44 °C and an HLB value
10 (hydrophilic/lipophilic balance value) of 14.

By Gelucire[®] is meant polyglycolised glycerides which are prepared by alcoholysis of natural oils with polyoxyethyleneglycols. They are mixtures of monoesters, diesters and/or triesters of glycerides of long-chained fatty acids with 8 to 18 carbon atoms
15 and polyethyleneglycol mono- and/or diesters of long-chained fatty acids. These preparations have a wide range of melting points between about 33 °C and 64 °C and a wide range of HLB values of between about 1 and 14. For the present invention Gelucires[®] with an HLB value of 10-14 are of particular interest.

20 By a low-melting system is meant a system with a melting point below 50 °C.

The lipophilic component (i) may consist of fats and oils such as for example hard fat (e.g. Witepsol W 45), neutral oil, olive oil, sunflower seed oil, groundnut oil, wheat germ oil and castor oil. Neutral oil is preferred.

25

The surfactant compound (ii) used may be for example lipophilic or hydrophilic emulsifiers such as perhaps mono- and di-glycerides of fatty acids with 8 to 18 carbon atoms and polysorbates (e.g. polysorbate 80 = [polyoxyethylene(20)sorbitan - monooleate), Cremophore[®] (ethoxylates of fatty alcohols or hydrogenated castor oil,
30 e.g. RH 40 (= macrogol glycerol hydroxystearate)) or tagates (polyoxyethylene-glycerol-mono-fatty acid esters, e.g. tagate S2 = polyoxyethylene(20)-glycerol-stearate).

5

The stabilisers used may be antioxidant adjuvants, such as e.g. tocopherols, butylhydroxyanisol (BHA), butylhydroxytoluene (BHT), ascorbic acid or gallic acid esters, nordihydroguaiaretic acid (NDGA) or other compounds such as e.g. flavonoids. Tocopherols, butylhydroxyanisol (BHA) and butylhydroxytoluene (BHT) are preferred according to the invention. The use of stabilisers serves to prolong the shelf life of the finished product. Tocopherol is normally used in a ratio by weight of 1 : 412 (tocopherol : active substance), while BHT is normally used in a ratio by weight of 1 : 2306 (BHT : active substance).

10 It is also advantageous to use pH stabilisers such as e.g. weak organic or inorganic bases (e.g. sodium hydrogen carbonate) as well as water-binding excipients which also act as stabilisers, (e.g. dried β -cyclodextrin; β -cyclodextrin with a water content of 4 % is preferred).

15 By a suitable choice of composition, particularly by the choice of surfactant compound and by varying the particle size of the active substance, it is readily possible for the skilled man to control the release profile of the formulation according to the invention over a wide range. Thus, depending on the desired product qualities, both instant release formulations and pharmaceutical compositions with modified release may be prepared.

The active substance dispersion may be prepared by the process described hereinafter:

25 The liquid (molten) carrier system is placed at 50 to 70°C in a reaction vessel and optionally stabilisers such as e.g. antioxidants and/or pH stabilisers as well as internal drying agents are dissolved or suspended therein. Then the active substance is incorporated with stirring and the dispersion is homogenised. The dispersion is then degassed and can then be packed into hard or soft capsules, for example. For this purpose, a quantity of dispersion corresponding to the dosage is packed into hard capsules, for example, using a standard capsule filling machine. Examples of suitable hard capsules include hard gelatine capsules or hard capsules made of hydroxypropylmethylcellulose (HPMC). The content of active substance in the

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pharmaceutical composition is 5 to 40 wt.%, preferably 8 to 36 wt.% in the solidified melt, based on the methanesulphonate of the compound of formula I.

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

- 5 Unless otherwise stated, all the amounts of active substance content specified are based on the methanesulphonate of formula I.

The dose when administered orally is conveniently 25 to 300 mg of the active substance base (per capsule), preferably 50 to 200 mg, once or twice a day in each
10 case.

Clinical trials

In the first clinical trials on test subjects with conventional tablets containing the
15 compound of formula I it was found that highly variable plasma levels occurred, ranging to individual cases of malabsorption.

Composition of the conventional tablet:

	Ingredient	mg/tablet
Core	Mesylate of the compound of formula I	57.7
	Lactose monohydrate	58.0
	Microcrystalline cellulose	48.3
	Crospovidone	3.4
	magnesium stearate	2.6
Film coating	Polyethyleneglycol 6000	0.56
	Titanium dioxide	0.80
	Talc	0.64
	hydroxypropylmethylcellulose	1.92
	iron oxide yellow	0.08
	Total	174.0

20

The variability of the plasma levels is significantly less after the administration of the compound of formula I as an orally administered acidic solution; no malabsorption was observed. However, the acidic solution has an unpleasant taste and is unstable,
25 which makes it unsuitable for commercial purposes.

Composition of the acidic solution:

Ingredient	per dose/bottle
mesylate of the compound of formula I	57.70 mg
mannitol	942.30 mg
tartaric acid	110.00 mg
purified water	99.80 g

5

Investigations have shown that the compound of formula I dissolves relatively easily in water at low pH values, whereas at pH levels above 5 it is virtually insoluble according to the definition of the European Pharmacopoeia. Therefore, pantoprazole which serves to raise the pH of the stomach was given to the test subjects in one
10 branch of treatment in the clinical trials.

For example the pharmaceutical composition according to Example 1 was tested for its bioavailability compared with the acidic solution.

15 To do this, the formulation prepared according to Example 1 containing 50 mg of active substance base per capsule (corresponding to 57.66 mg of the mesylate of the compound of formula I) was clinically tested on a total of 12 test subjects for its bioavailability. In one branch of treatment the test subjects were given the composition orally on an empty stomach without any pre-treatment. In another
20 branch of treatment the same test subjects were pre-treated with 40 mg of pantoprazole b.i.d. (= twice a day) by oral route to increase the gastric pH before oral administration of the composition; the treatment with pantoprazole was continued during the administration of the formulation according to the invention. The treatment lasted 3 days in each case.

25

The extent of absorption was determined by quantitative measurement of the excretion of the active metabolite of formula II in the urine.

8

The relative bioavailability (based on the area under the plasma concentration - time curve) was 116 % with pre-treatment with pantoprazole and 131 % without pre-treatment with pantoprazole, compared with the acidic solution (100% in each case). Thus the bioavailability of the formulation according to the invention was further
5 improved compared with the acidic solution.

The clinical trials demonstrate another advantage of the formulation according to the invention containing the compound of formula I, which consists in ensuring a sufficient bioavailability of the active substance, which is better than that of a
10 conventional pharmaceutical preparation and is also largely independent of the gastric pH, reducing fluctuations in the bioavailability of the active substance and preventing malabsorption. Another advantageous property of the pharmaceutical composition according to the invention is its suitability for all patients, i.e. including those people in whom the pH of the stomach is elevated as a result of normal
15 physiological variability, by illness or by co-medication with drugs which raise the pH of the stomach.

The Examples that follow are intended to illustrate the invention:

Example 1

Ingredient	amount/capsule (mg)	amount/capsule (mg)
active substance (mesylate of the compound of formula I)	57.66	115.32
macrogol glycerol laurate Ph. Eur.	292.34	584.68
Total	350.00	700.00

5

Example 2

Ingredient	amount/capsule (mg)	amount/capsule (mg)
active substance (mesylate of the compound of formula I)	57.66	230.64
macrogol glycerol laurate Ph. Eur.	117.2.	468.8
α -tocopherol	0.14	0.56
Total	175.00	700.00

10

Example 3

Ingredient	amount/capsule (mg)
active substance (mesylate of the compound of formula I)	115.32
butylhydroxytoluene (BHT)	0.05
macrogol glycerol laurate Ph. Eur.	234.63
Total	350.00

15

Example 4

Ingredient	amount/capsule (mg)
active substance (mesylate of the compound of formula I)	172.98
macrogol glycerol laurate Ph. Eur.	301.91
α -tocopherol	0.42
predried β -cyclodextrin with 4 % water	12.19
Total	487.50

Example 5

Ingredient	amount/capsule (mg)	amount/capsule (mg)
active substance (mesylate of the compound of formula I)	172.98	230.64
macrogol glycerol laurate Ph. Eur.	314.10	418.80
α -tocopherol	0.42	0.56
Total	487.50	650.00

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Example 6

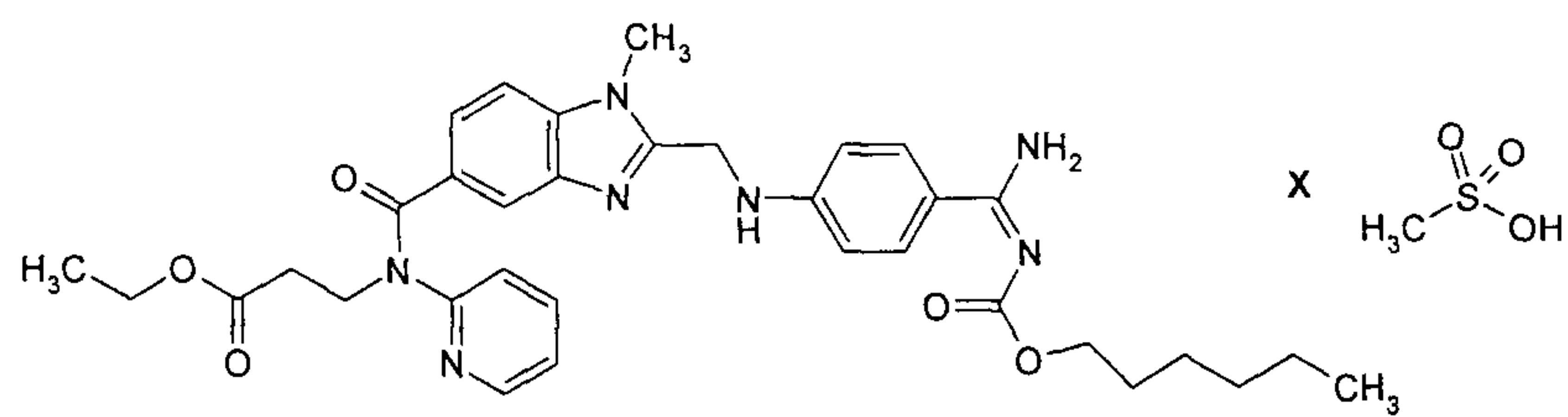
Ingredient	amount/capsule (mg)
active substance (mesylate of the compound of formula I)	57.66
neutral oil	105.60
Tween 80 (polysorbate 80)	11.74
Total	175.00

10

Example 7

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

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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

11

ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-
1H-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 began to crystallise out. It was stirred for a further hour at ambient
5 temperature and then 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 drying cupboard.

Yield: 94% of theory

Melting point: 178 - 179°C

10 $C_{34}H_{41}N_7O_5 \times CH_4SO_3$ (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%

Patent Claims:

1. Pharmaceutical composition for oral administration comprising at least
 - 5 a) ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof and
 - b) a lipophilic, pharmaceutically acceptable, liquid, solid or semi-solid carrier system.
- 10 2. Pharmaceutical composition comprising
 - 5 to 40 wt.% of ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the pharmaceutically acceptable salts thereof,
 - 15 55 to 95 wt.% of a pharmaceutically acceptable, lipophilic carrier system and optionally 0 to 5 wt.% of one or more stabilisers,
 - the amounts of ingredients adding up to a total of 100 wt.%.
3. Pharmaceutical composition according to claim 1 or 2, wherein the
 - 20 pharmaceutically suitable, lipophilic carrier system is a microemulsion concentrate.
4. Pharmaceutical composition according to claim 3, characterised in that the microemulsion concentrate is a macrogol glycerol laurate according to Ph. Eur. NT 2001.
- 25 5. Pharmaceutical composition according to claim 1 or 2, characterised in that the lipophilic carrier system is a low-melting lipophilic system comprising a lipophilic component which optionally contains one or more surfactant compounds.
- 30 6. Pharmaceutical composition according to claim 4, characterised in that the macrogol glycerol laurate is Gelucire.
7. Pharmaceutical composition according to one of claims 1 to 6, wherein the content of ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-

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methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or the salts thereof in the pharmaceutical composition is 8 to 40 % of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate methanesulphonate.

5

8. Pharmaceutical composition according to one of claims 1 to 7, characterised in that the composition is packed into hard capsules.

9. Pharmaceutical composition according to claim 8, characterised in that the hard capsules are hard gelatine capsules or hard capsules made from hydroxypropyl-methylcellulose.

10. Pharmaceutical composition according to one of claims 1 to 9, wherein ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate is used as the active substance.

11. Process for preparing a pharmaceutical composition for oral administration, comprising ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate or one of the physiologically acceptable salts thereof and a pharmaceutically acceptable, liquid, solid or semi-solid lipophilic carrier system, characterised in that the active substance is incorporated in the liquid carrier system in order to obtain a homogeneous dispersion.

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12. Process according to claim 11, characterised in that before the incorporation of the active substance, stabilisers are dissolved or suspended in the liquid carrier system melt.

13. Process according to claim 12, characterised in that the stabilisers are antioxidants and / or pH stabilisers.

30

14. Process according to one of claims 11 to 13, characterised in that the homogeneous dispersion is degassed before packing.

15. Process according to one of claims 11 to 14, characterised in that the homogeneous dispersion is packed into hard capsules.

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