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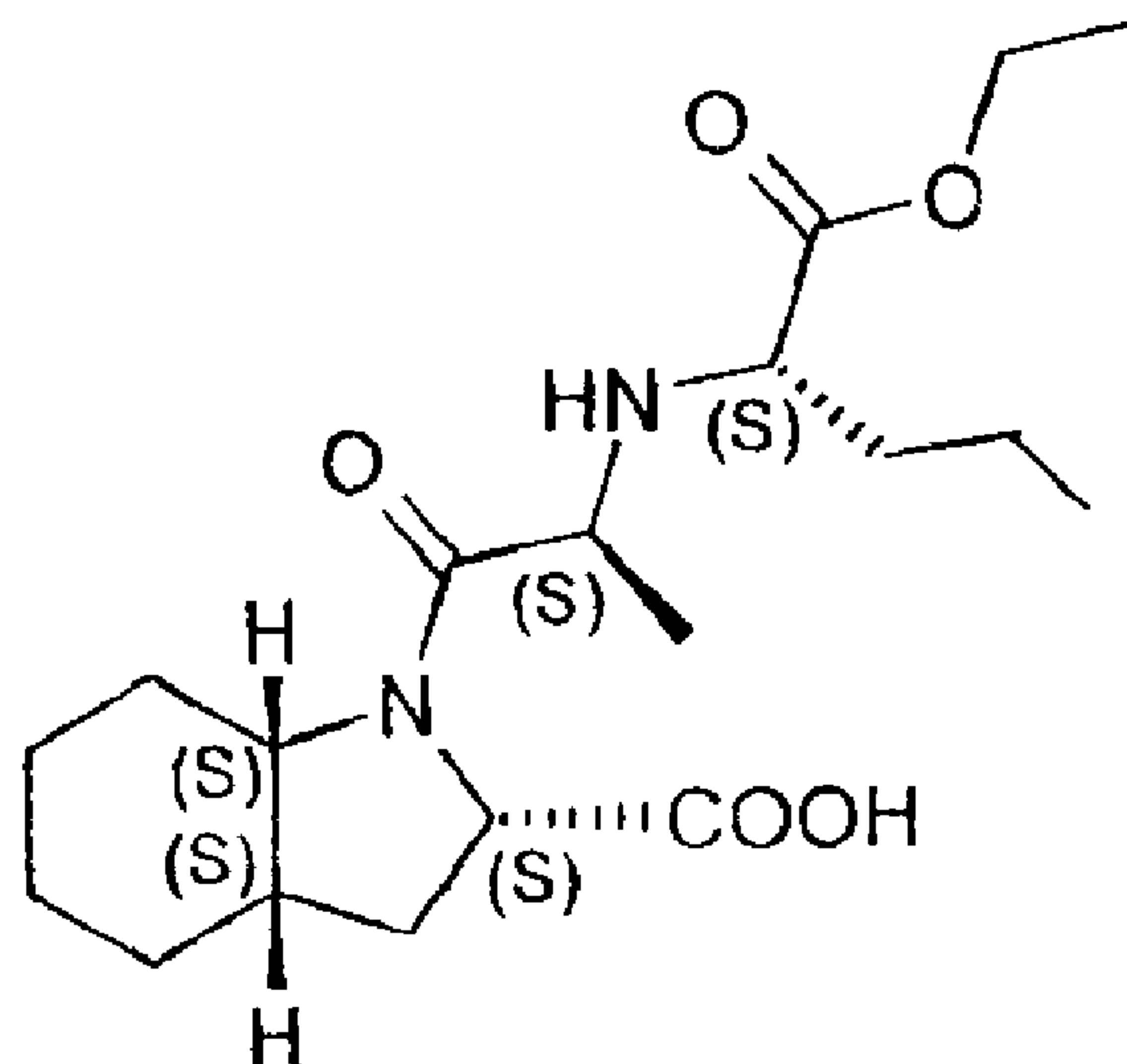
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(72) Inventeurs/Inventors:  
STRAESSLER, CHRISTOPH, CH;  
LELLEK, VIT, CH;  
FAESSLER, ROGER, CH  
(73) Propriétaire/Owner:  
LES LABORATOIRES SERVIER, FR  
(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : NOUVELLES FORMES CRISTALLINES DE PERINDOPRIL ERBUMINE  
(54) Title: NEW CRYSTALLINE FORMS OF PERINDOPRIL ERBUMINE



(57) Abrégé/Abstract:

Disclosed are two new crystalline forms,  $\delta$  and  $\epsilon$ , of perindopril erbumine.

Perindopril (2S,3aS,7aS)-1-[2-(1-ethoxycarbonyl-(S)-butylamino)-(S)-propionyl]-octahydroindole-2-carboxylic acid) has the following formula (I):



(57) **Abrégé(suite)/Abstract(continued):**

(see above formula)

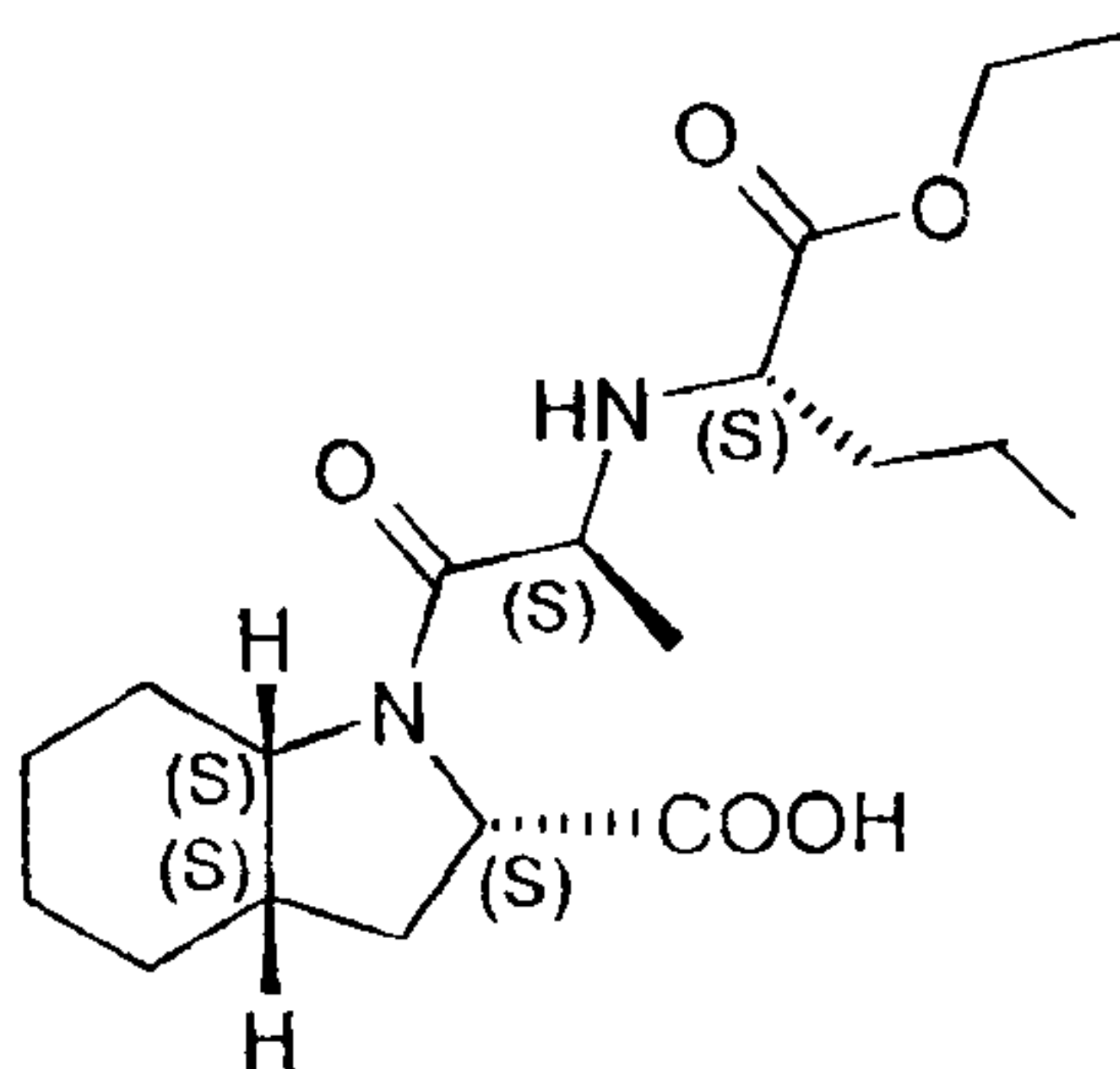
Those forms are suitable as therapeutic active substances for medicaments for the treatment of cardiovascular diseases, especially high blood pressure and heart failure. The  $\epsilon$  crystalline form is obtained in the crystallisation of perindopril erbumine. If water is then removed, and stirring is continued, the  $\epsilon$  crystalline form is converted to the  $\delta$  crystalline form. The  $\delta$  crystalline form can also be obtained by stirring the  $\alpha$  or  $\beta$  crystalline with seeding with the  $\delta$  crystalline form. The  $\epsilon$  crystalline form can also be obtained by stirring the  $\alpha$  or  $\beta$  crystalline form with seeding with the  $\epsilon$  crystalline form; or by stirring the  $\alpha$  or  $\beta$  crystalline form in tert.-butyl methyl ether and water.

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**Abstract:**

Disclosed are two new crystalline forms,  $\delta$  and  $\epsilon$ , of perindopril erbumine.

Perindopril (2S,3aS,7aS)-1-[2-(1-ethoxycarbonyl-(S)-butylamino)-(S)-propionyl]-octahydroindole-2-carboxylic acid) has the following formula (I):



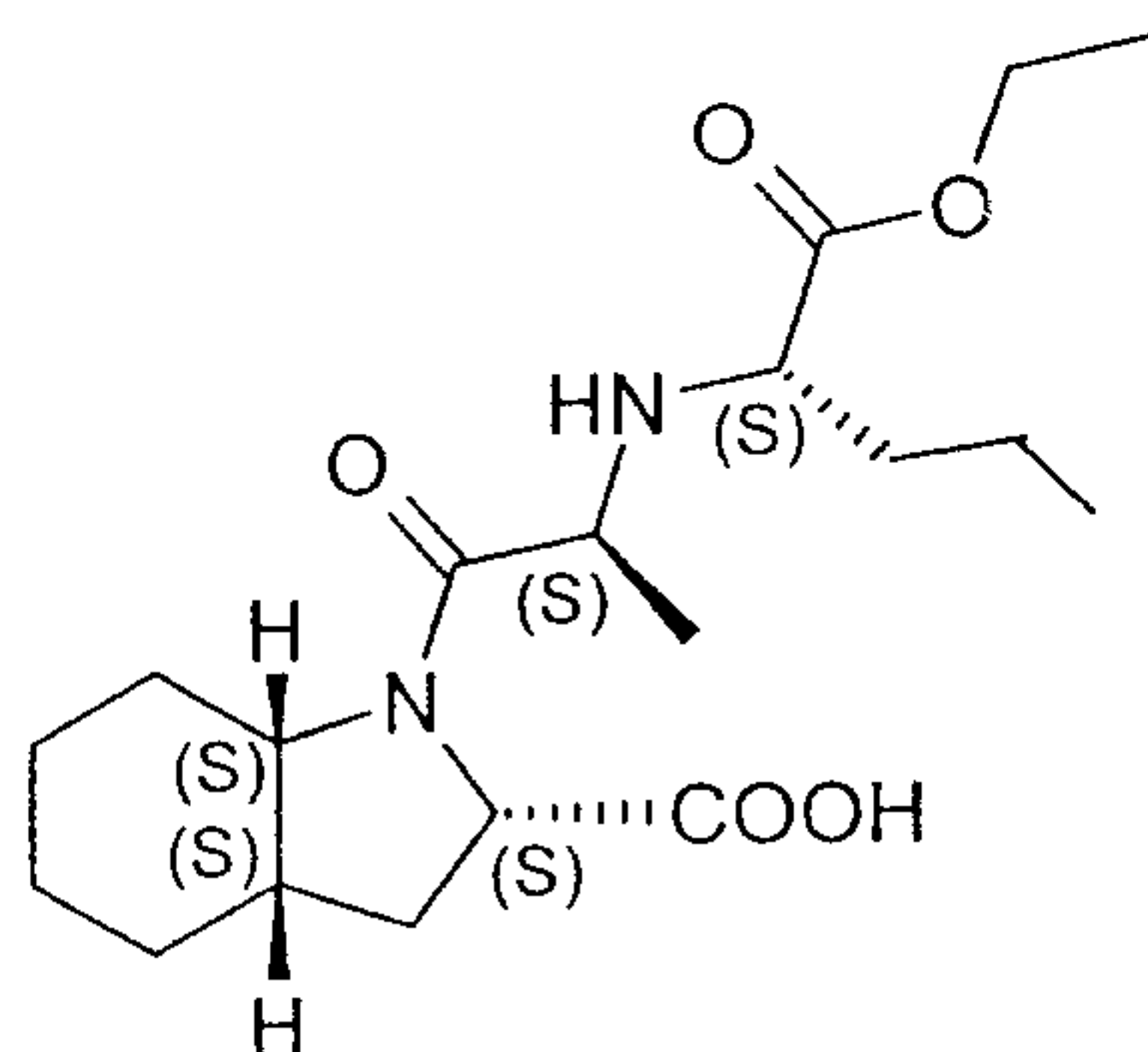
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Those forms are suitable as therapeutic active substances for medicaments for the treatment of cardiovascular diseases, especially high blood pressure and heart failure. The  $\epsilon$  crystalline form is obtained in the crystallisation of perindopril erbumine. If water is then removed, and stirring is continued, the  $\epsilon$  crystalline form is converted to the  $\delta$  crystalline form. The  $\delta$  crystalline form can also be obtained by stirring the  $\alpha$  or  $\beta$  crystalline with seeding with the  $\delta$  crystalline form. The  $\epsilon$  crystalline form can also be obtained by stirring the  $\alpha$  or  $\beta$  crystalline form with seeding with the  $\epsilon$  crystalline form; or by stirring the  $\alpha$  or  $\beta$  crystalline form in tert.-butyl methyl ether and water.

### New crystalline forms of perindopril erbumine

The present invention relates to two new crystalline forms of perindopril erbumine.

Perindopril ((2S,3aS,7aS)-1-[2-(1-ethoxycarbonyl-(S)-butylamino)-(S)-propionyl]-octahydroindole-2-carboxylic acid) has the following formula (I):



Perindopril erbumine is the tert.-butylamine salt of perindopril.

Perindopril acts as an ACE inhibitor (ACE = angiotensin-converting enzyme) and is used in the treatment of cardiovascular diseases, especially in the treatment of high blood pressure and heart failure.

Processes for the synthesis of perindopril are described in EP 49 658, US 4,508,729, EP 308 341 and US 4,914,214 and also in EP 1 256 590 and WO 01/58868.

In WO 01/87835, WO 01/87836 and WO 01/83439 there are described processes for the crystallisation of perindopril erbumine from ethyl acetate (WO 01/87835), from dichloromethane or ethyl acetate (WO 01/87836) and from chloroform (WO 01/83439), and the  $\alpha$  (WO 01/87835),  $\beta$  (WO 01/87836) and  $\gamma$  (WO 01/83439) crystalline forms obtained in those processes.

It has now been found that by crystallisation of perindopril erbumine of any crystalline form from tert.-butyl methyl ether containing from 0.9 to 2.5 % v/v water, or by transforming the  $\alpha$  or  $\beta$  crystalline form of perindopril erbumine in tert.-butyl methyl ether

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containing from 0.9 to 2.5 % v/v water, two further crystalline forms,  $\delta$  and  $\epsilon$ , can be obtained depending on the precise conditions. Those new  $\delta$  and  $\epsilon$  crystalline forms are characterised by the following X-ray diffraction data (see Tables 1 and 2 below):

Table 1: X-ray diffraction data of perindopril erbumine,  $\delta$  crystalline form (relative intensities were taken from the powder diagram obtained by  $\text{CuK}\alpha$  irradiation).

Angle 2 theta ( $^{\circ}$ )	Lattice spacing d ( $\text{\AA}$ )	Relative intensity $I/I_{\text{max}}$ (%)
5.27	16.79	2
8.93	9.93	100
9.75	9.10	32
10.65	8.34	10
14.63	6.10	25
14.97	5.97	39
15.27	5.85	48
15.95	5.61	53
17.27	5.19	18
17.87	5.02	15
18.63	4.83	13
19.99	4.51	29
20.37	4.43	26
21.31	4.24	57
21.83	4.15	37
22.49	4.03	26
23.15	3.92	19
23.65	3.84	29
23.99	3.79	16
24.71	3.69	15
25.33	3.60	15

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25.75	3.55	15
26.43	3.46	21
26.77	3.42	18
28.19	3.26	24

Note: It is well known that the intensities may vary on account of texture effects.

**Table 2:** X-ray diffraction data of perindopril erbumine,  $\epsilon$  crystalline form (relative intensities were taken from the powder diagram obtained by  $\text{CuK}_\alpha$  irradiation).

Angle 2 theta ( $^\circ$ )	Lattice spacing d ( $\text{\AA}$ )	Relative intensity $I/I_{\text{max}}$ (%)
5.28	16.75	2
8.43	10.52	22
8.87	10.00	100
9.45	9.39	92
10.01	8.87	20
13.58	6.57	6
14.21	6.28	14
14.79	6.04	61
15.31	5.84	53
15.84	5.65	49
16.43	5.45	13
16.84	5.32	13
17.65	5.09	18
18.65	4.82	11
19.87	4.54	29
21.21	4.26	49
21.79	4.15	55
22.79	3.98	27

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23.52	3.86	30
24.25	3.75	25
25.83	3.54	23
26.55	3.45	25
27.25	3.37	15
28.11	3.27	27

Note: It is well known that the intensities may vary on account of texture effects.

In accordance with the invention, the  $\epsilon$  crystalline form is obtained in the crystallisation at from 30 to 45 °C, preferably from 34 to 45°C, of perindopril erbumine of any crystalline form from tert.-butyl methyl ether (MTBE) containing from 1.5 to 2.5 % v/v water; the crystallisation is advantageously carried out with stirring. If the water is then removed, advantageously by azeotropic distillation, preferably at from 35 to 37°C, and stirring is then continued for at least 15 h at from 30 to 45°C, preferably from 35 to 37°C, the  $\epsilon$  crystalline form is converted to the  $\delta$  crystalline form.

In addition, the  $\alpha$  and  $\beta$  crystalline forms of perindopril erbumine, which are already known, can be converted to the  $\delta$  crystalline form by stirring at from 33 to 38°C, preferably from 35 to 37°C, in tert.-butyl methyl ether (MTBE) containing from 0.9 to 1.4 % v/v water, preferably from 1.0 to 1.1 % v/v water, and seeding with the  $\delta$  crystalline form.

In tert.-butyl methyl ether (MTBE) containing from 0.9 to 1.4 % v/v water, preferably from 1.0 to 1.1 % v/v water, the already known  $\alpha$  and  $\beta$  forms can be converted to the  $\epsilon$  crystalline form at from 28 to 35°C, preferably from 31 to 33°C, by seeding with the  $\epsilon$  crystalline form.

Those conversions can also be carried out without seeding, but in the boundary region it cannot, of course, be predicted with certainty whether the  $\delta$  form, the  $\epsilon$  form or mixtures of those forms will be obtained.

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The conversion of the  $\alpha$  and  $\beta$  crystalline forms to the  $\epsilon$  crystalline form can also be carried out at from 35 to 38°C in tert.-butyl methyl ether (MTBE) containing from 1.5 to 2.0 % v/v water.

Both  $\delta$  and  $\epsilon$  crystalline forms of perindopril erbumine are new and the present invention relates thereto.

They can be used in accordance with the invention as therapeutic active substances and processed together with a pharmaceutically acceptable carrier material to form a medicament. The medicament can then be used in the treatment of cardiovascular diseases, especially in the treatment of high blood pressure and heart failure.

Pharmaceutically acceptable carrier materials for the preparation of medicaments are generally known and are familiar to the person skilled in the art.

Since different forms of a pharmaceutical active substance, such as, for example, new crystalline forms, generally exhibit different bioavailabilities, solubilities and dissolution rates, they may be of great advantage for the relevant patients since they may make it possible for the dose to be reduced or for the dosage intervals to be increased, and consequently for the costs of the medicament to be reduced.

The following Examples are intended to illustrate the invention but not to limit the invention in any way in its scope and its use:

The X-ray diffraction spectra were measured on a Philips ADP1700 powder diffractometer<sup>TM</sup> with a Cu irradiation of  $K_{\alpha 1} = 0.15406$  nm and  $K_{\alpha 2} = 0.15444$  and a voltage of 40 kV.

#### Example 1: $\epsilon$ crystalline form of perindopril erbumine

5.00 g of perindopril erbumine were suspended in 50 ml of MTBE and 0.95 ml of water was added. The suspension obtained was heated, with stirring, to 48°C, a clear solution being formed. The solution was cooled, with stirring, to 41°C. Seeding was carried out at

that temperature, after which crystallisation commenced. Stirring was carried out for 30 min. at from 40 to 41°C and then the mixture was cooled to 34°C in the course of 1 h. The resulting precipitate was filtered off and washed with 10 ml of MTBE. After drying, 1.85 g of perindopril erbumine of the  $\epsilon$  crystalline form were obtained.

#### Example 2: $\delta$ crystalline form of perindopril erbumine

11.09 g of perindopril erbumine were suspended in 130 ml of MTBE and 2 ml of water were added. The suspension obtained was heated, with stirring, to 51°C, a clear solution being formed. The solution was cooled to 35°C in the course of 120 min., with stirring. Seeding was carried out at 44°C, after which crystallisation commenced. At from 35 to 37°C, 50 ml of MTBE were distilled off under reduced pressure in the course of 45 min.. At the same time the water was also removed azeotropically. 50 ml of MTBE were then added again and, at from 35 to 37°C, 50 ml of MTBE were distilled off again, under reduced pressure, in the course of 60 min.. Stirring was continued at from 35 to 37°C for 15 h, and then the precipitate obtained was filtered off and washed with 10 ml of MTBE. After drying, 8.42 g of perindopril erbumine of the  $\delta$  crystalline form were obtained.

#### Example 3: Conversion of the $\alpha$ crystalline form to the $\delta$ crystalline form

8.50 g of perindopril erbumine of the  $\alpha$  crystalline form were suspended in 85 ml of MTBE and the suspension was heated, with stirring, to from 35 to 37°C. 0.85 ml of water was added thereto, followed by 0.17 g of seed crystals of the  $\delta$  crystalline form. The suspension obtained was stirred for 23 h at from 35 to 37°C and then the precipitate was filtered off. After drying, 7.00 g of the  $\delta$  crystalline form were obtained.

#### Example 4: Conversion of the $\alpha$ crystalline form to the $\epsilon$ crystalline form

21.66 g of perindopril erbumine of the  $\alpha$  crystalline form were suspended in 216 ml of MTBE and the suspension was heated, with stirring, to from 33 to 35°C. 2.16 ml of water were added thereto and the suspension obtained was stirred for 14 h at from 33 to 35°C.

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After filtering off and drying the precipitate, 18.68 g of the  $\epsilon$  crystalline form were obtained.

Example 5: Conversion of the  $\beta$  crystalline form to the  $\delta$  crystalline form

4.00 g of perindopril erbumine of the  $\beta$  crystalline form were suspended in 40 ml of MTBE and 0.36 ml of water was added. The suspension obtained was heated to from 35 to 37°C and stirred for 20 h at from 35 to 37°C. After filtering off and drying the precipitate, the  $\delta$  crystalline form was obtained.

Example 6: Conversion of the  $\alpha$  crystalline form to the  $\epsilon$  crystalline form

7.55 g of perindopril erbumine of the  $\alpha$  crystalline form were suspended in 75 ml of MTBE and the suspension was heated, with stirring, to from 35 to 37°C. 1.32 ml of water were added thereto and the suspension obtained was stirred for 20 h at from 35 to 37°C. After filtering off and drying the precipitate, 2.31 g of the  $\epsilon$  crystalline form were obtained.

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CLAIMS:

1. Process for the preparation of perindopril erbumine of the  $\delta$  crystalline form, comprising:

5 a) recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v) water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of water; or

10 b) stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form,

wherein the  $\delta$  crystalline form of perindopril erbumine exhibits the following X-ray diffraction data (measured on a powder diffractometer with  $\text{CuK}\alpha$  irradiation):

Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
5.27	16.79	2
8.93	9.93	100
9.75	9.10	32
10.65	8.34	10
14.63	6.10	25
14.97	5.97	39
15.27	5.85	48
15.95	5.61	53
17.27	5.19	18
17.87	5.02	15

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Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
18.63	4.83	13
19.99	4.51	29
20.37	4.43	26
21.31	4.24	57
21.83	4.15	37
22.49	4.03	26
23.15	3.92	19
23.65	3.84	29
23.99	3.79	16
24.71	3.69	15
25.33	3.60	15
25.75	3.55	15
26.43	3.46	21
26.77	3.42	18
28.19	3.26	24

2. Process according to claim 1, comprising recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v) water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of water.

3. Process according to claim 1, comprising stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form.

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4. A method for preparing a medicament containing the crystalline  $\delta$  form of perindopril erbumine, comprising adding the crystalline  $\delta$  form of perindopril erbumine to a pharmaceutically acceptable carrier, wherein the crystalline  $\delta$  form of perindopril erbumine is obtained from a process comprising:
- 5 a) recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v) water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of water; or
- b) stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form,

wherein the  $\delta$  crystalline form of perindopril erbumine exhibits the following X-ray diffraction data (measured on a powder diffractometer with  $\text{CuK}\alpha$  irradiation):

Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
5.27	16.79	2
8.93	9.93	100
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10.65	8.34	10
14.63	6.10	25
14.97	5.97	39
15.27	5.85	48
15.95	5.61	53
17.27	5.19	18
17.87	5.02	15

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Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
18.63	4.83	13
19.99	4.51	29
20.37	4.43	26
21.31	4.24	57
21.83	4.15	37
22.49	4.03	26
23.15	3.92	19
23.65	3.84	29
23.99	3.79	16
24.71	3.69	15
25.33	3.60	15
25.75	3.55	15
26.43	3.46	21
26.77	3.42	18
28.19	3.26	24

5. A method according to claim 4, wherein the process comprises recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v) water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of water.

6. A method according to claim 4, wherein the process comprises stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl

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methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form.

7. A method according to claim 4, 5 or 6, wherein the medicament is for use in the treatment of a cardiovascular disease.

5 8. A method according to claim 7, wherein the cardiovascular disease is high blood pressure or cardiac insufficiency.

9. Perindopril erbumine of the  $\delta$  crystalline form, prepared according to a process comprising:

10 a) recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v) water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of water; or

15 b) stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form,

wherein the  $\delta$  crystalline form of perindopril erbumine exhibits the following X-ray diffraction data (measured on a powder diffractometer with  $\text{CuK}\alpha$  irradiation):

Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
5.27	16.79	2
8.93	9.93	100
9.75	9.10	32
10.65	8.34	10
14.63	6.10	25
14.97	5.97	39

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Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
15.27	5.85	48
15.95	5.61	53
17.27	5.19	18
17.87	5.02	15
18.63	4.83	13
19.99	4.51	29
20.37	4.43	26
21.31	4.24	57
21.83	4.15	37
22.49	4.03	26
23.15	3.92	19
23.65	3.84	29
23.99	3.79	16
24.71	3.69	15
25.33	3.60	15
25.75	3.55	15
26.43	3.46	21
26.77	3.42	18
28.19	3.26	24

10. The perindopril erbumine of the  $\delta$  crystalline form of claim 9, wherein the process comprises recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v)

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water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of water.

11. The perindopril erbumine of the  $\delta$  crystalline form of claim 9, wherein the process comprises stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form.
12. A medicament comprising perindopril erbumine of the crystalline  $\delta$  form and a pharmaceutically acceptable carrier, wherein the crystalline  $\delta$  form of perindopril erbumine is obtained from a process comprising:
- 10 a) recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v) water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of water; or
- 15 b) stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form,

wherein the  $\delta$  crystalline form of perindopril erbumine exhibits the following X-ray diffraction data (measured on a powder diffractometer with  $\text{CuK}\alpha$  irradiation):

Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
5.27	16.79	2
8.93	9.93	100
9.75	9.10	32
10.65	8.34	10
14.63	6.10	25

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Angle 2 theta (°)	Lattice spacing d(Å)	Relative intensity I/I <sub>max</sub> (%)
14.97	5.97	39
15.27	5.85	48
15.95	5.61	53
17.27	5.19	18
17.87	5.02	15
18.63	4.83	13
19.99	4.51	29
20.37	4.43	26
21.31	4.24	57
21.83	4.15	37
22.49	4.03	26
23.15	3.92	19
23.65	3.84	29
23.99	3.79	16
24.71	3.69	15
25.33	3.60	15
25.75	3.55	15
26.43	3.46	21
26.77	3.42	18
28.19	3.26	24

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13. The medicament according to claim 12, wherein the process comprises recrystallizing perindopril erbumine of any crystalline form at from 30 to 45°C from tert-butyl methyl ether containing from 1.5 to 2.5% (v/v) water, and stirring the precipitate obtained for at least 15 hours at from 30 to 45°C after the removal of  
5 water.
14. The medicament according to claim 12, wherein the process comprises stirring perindopril erbumine of the  $\alpha$  or  $\beta$  crystalline form at from 33 to 38°C in tert-butyl methyl ether containing from 0.9 to 1.4% (v/v) water with seeding with the  $\delta$  crystalline form.
- 10 15. The medicament according to claim 12, 13 or 14, wherein the medicament is for use in the treatment of a cardiovascular disease.
16. The medicament according to claim 15, wherein the cardiovascular disease is high blood pressure or cardiac insufficiency.

