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(54) Title

Pharmaceutical composition containing a crystalline form of perindopril tert-butylamine salt

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(56) Related Art

CAIRA, Topics in Current Chemistry (1998) 198: 163-208

EP 0,308,341 B1

EP 0,049,658 B1

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Abstract

The invention relates to α crystalline form of perindopril tert-butylamine salt, pharmaceutical compositions containing the α crystalline form of perindopril tert-butylamine salt, and uses of the pharmaceutical compositions in treatment of cardiovascular disease.

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AUSTRALIA

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COMPLETE SPECIFICATION

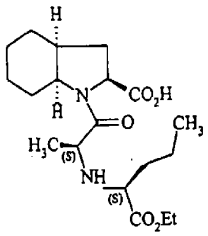
Invention Title:

A crystalline form of perindopril tert-butylamine salt

The invention is described in the following statement:

Technical Field

The present invention relates to a new α crystalline form of perindopril tert-butylamine salt of formula (I):



. $tBuNH_2$ (I),

in a pharmaceutical composition.

Background Art

Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

The principal property of these compounds is that of inhibiting angiotensin I converting enzyme (or kininase II), which prevents, on the one hand, conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular disease, more especially in arterial hypertension and heart failure.

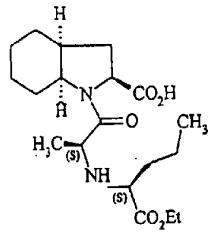
In view of the pharmaceutical value of this compound, it has been of prime importance to obtain it with excellent purity. It has also been important to be able to synthesise it by means of a process that can readily be converted to the industrial scale, especially in a form that allows rapid filtration and drying. Finally, any crystalline form should be reproducible, easily formulated and sufficiently stable to allow its storage for long periods without particular requirements for temperature, light, humidity or oxygen level.

Although there are industrial synthesis processes for perindopril, conditions for obtaining perindopril in a form that exhibits those characteristics in a reproducible manner have been difficult to achieve.

The Applicant has now found that a particular salt of perindopril, the tert-butylamine salt, can be obtained in a well defined, reproducible crystalline form that especially exhibits valuable characteristics of filtration, drying, stability and ease of formulation.

Disclosure of Invention

In a first aspect, the present invention provides an α crystalline form of the compound of formula (I):



. tBuNH$_2$ (I),

the α crystalline form characterised by the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray):

Angle 2 theta (°)	**Inter-planar distance d (Å)**	**Intensity**	**Relative intensity (%)**
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
10.947	8.08	182	4.1
13.150	6.73	82	1.9
13.687	6.46	83	1.9
14.627	6.05	582	13.2
15.412	5.74	770	17.5
16.573	5.34	1115	25.3
17.357	5.10	340	7.7
18.109	4.89	193	4.4
19.922	4.45	306	6.9

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
20.609	4.31	375	8.5
21.412	4.15	226	5.1
21.832	4.07	217	4.9
22.158	4.01	483	11
22.588	3.93	386	8.8
23.323	3.81	107	2.4
24.200	3.67	448	10.2
24.727	3.60	137	3.1
25.957	3.43	125	2.8
26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

In a second aspect, the present invention provides a process for preparation of the α crystalline form of the compound of formula (I) according to the first aspect of the present invention, comprising heating a solution of perindopril tert-butylamine salt in ethyl acetate at reflux and gradually cooling the solution until crystallisation is complete, wherein the solution at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 5 to 10°C/hour, and then cooled to ambient temperature.

In a preferred form, the concentration of the perindopril tert-butylamine salt in the ethyl acetate is from 70 to 90 g/litre.

In a preferred form, the solution of perindopril tert-butylamine salt in ethyl acetate is seeded during the cooling step at a temperature of from 76 to 65°C.

In a preferred form, the solution of the perindopril tert-butylamine salt in ethyl acetate at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 6 to 8°C/hour, and then to ambient temperature.

Preferably, the α crystalline form of the perindopril tert-butylamine salt is obtained in the form of filterable individual needles.

In a third aspect, the present invention provides a pharmaceutical composition comprising as active ingredient the α crystalline form of the compound according to the first aspect of the

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present invention, in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers.

The α crystalline form of the compound of formula (I) is preferably isolated in the form of individual needles which can be further processed before formulation into the pharmaceutical composition. Examples of such processing are well known to the art and include crushing or grinding the needle crystals to a fine powder.

Preferably, the pharmaceutical composition typically is in the form of tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, or drinkable suspensions.

More preferably, the pharmaceutical composition is in the form of a tablet.

The pharmaceutical composition typically comprises from 1 to 500 mg of the α crystalline form of the compound of formula (I). In a preferred form, the pharmaceutical composition comprises from 1 to 100 mg of the α crystalline form of the compound. In another preferred form, the pharmaceutical composition comprises from 4 to 50 mg of the α crystalline form of the compound. In another preferred form, the pharmaceutical composition comprises from 2 to 8 mg of the α crystalline form of the compound. More preferably, the pharmaceutical composition comprises 4 mg of the α crystalline form of the compound of formula (I).

The pharmaceutical composition may further comprising a diuretic. Preferably, the diuretic is indapamide.

In a fourth aspect, the present invention provides use of the pharmaceutical composition according to the third aspect of the present invention as an inhibitor of angiotensin I converting enzyme.

Preferably, the use is for treatment of cardiovascular disease.

In a fifth aspect, the present invention provides a method of treatment of cardiovascular disease comprising administering to a patient in need of such treatment an efficacious amount of the α crystalline form of compound of formula (I) according to the first aspect of the present invention.

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In a sixth aspect, the present invention provides a method of treatment of cardiovascular disease comprising administering to a patient in need of such treatment an efficacious amount of a pharmaceutical composition according to the third aspect of the present invention.

In a seventh aspect, the present invention provides use of the α crystalline form of the compound of formula (I) according to the first aspect of the present invention for the manufacture of a medicament for treatment of cardiovascular disease.

In a preferred form, the α crystalline form of the compound of formula (I) is further characterized by being in the form of individual needles. Preferably, the individual needles are about 0.2 mm long. The individual needles allow rapid and efficient filtration and drying.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia prior to development of the present invention.

In order that the present invention may be more clearly understood, preferred embodiments will be described with reference to the following examples.

Mode(s) for Carrying Out the Invention

The present invention relates to the α crystalline form of the compound of formula (I), the crystalline form being characterised by the following powder X-ray diffraction diagram, measured using a Siemens D5005 diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage of the most intense ray):

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
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18.109	4.89	193	4.4
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26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

In a preferred form, the α crystalline form of the compound of formula (I) is further characterized by being in the form of individual needles. Preferably, the individual needles are about 0.2 mm long. The individual needles allow rapid and efficient filtration and drying.

The invention relates also to a process for the preparation of the α crystalline form of the compound of formula (I), which process is characterised in that a solution of perindopril tert-butylamine salt in ethyl acetate is heated at reflux and is cooled gradually until crystallisation is complete.

In the crystallisation process according to the invention it is possible to use the compound of formula (I) obtained by any suitable process. For example, the compound of formula (I) can be obtained by the preparation process described in patent specification US 4914214 (corresponding to EP 0308341). The compound of formula (I) then undergoes the

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crystallisation process according to the present invention to produce the α crystalline form of the compound.

The concentration of the compound of formula (I) in the ethyl acetate is preferably from 70 to 90 g/litre.

Preferably, the solution of the compound of formula (I) in ethyl acetate at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 5 to 10°C/hour, preferably from 6 to 8°C/hour, and then to ambient temperature.

The solution can advantageously be seeded during the cooling step at a temperature of from 76 to 65°C.

The α crystalline form of perindopril tert-butylamine salt that is thereby obtained is in the form of individual needles about 0.2 mm long. That homogeneous crystal distribution has the advantage of allowing especially rapid and efficient filtration and drying, as well as allowing the preparation of pharmaceutical formulations having a uniform and reproducible composition, which is especially advantageous when those formulations are intended for oral administration.

The α crystalline form of the compound of formula (I) thereby obtained is sufficiently stable to allow its storage for long periods without particular requirements for temperature, light, humidity or oxygen level.

The invention relates also to pharmaceutical compositions comprising as active ingredient the α crystalline form of the compound of formula (I) together with one or more appropriate, inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions etc.

The useful dosage can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. It varies from 1 to 500 mg per day in one or more administrations. In tablet form, 4 mg is preferred.

The pharmaceutical compositions according to the invention may also comprise a diuretic such as indapamide.

The following Examples illustrate the invention but do not limit it in any way.

EXAMPLE 1: Synthesis of perindopril tert-butylamine salt

Industrial Synthesis of the tert-Butylamine Salt of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}-octahydroindole-2-carboxylic acid

Stage 1: (2S,3aS,7aS)-2-Carboxyoctahydroindole

Stage 1a: 2-Ethoxycarbonylindole

Heat 5 kg of 2-carboxyindole suspended in ethanol in the presence of sulfuric acid to boiling for 8 hours. Evaporate.

Evaporate off the ethyl acetate, take up the crystalline mass with hexane. After filtering off and drying, 5.3 kg of crystals are obtained.

Melting point: 123° to 125°C.

Microanalysis: Calculated: C % 69.83; H % 5.86; N % 7.40; Found: C % 69.56; H % 5.74; N % 7.30.

Spectrometry in the infrared: 2150 cm^{-1} (NH); 1680 cm^{-1} (carboxylic acid).

Stage 1B: (R,S)-2-Ethoxycarbonylindoline

Suspend, in a reactor, 10 kg of 2-ethoxycarbonylindoline obtained previously in 110 liters of hydrochloric ethanol. Next, add 20 kg of granulated tin. Keep stirring for approximately 2 days at ambient temperature.

Evaporate off the ethanol, take up the residue with water and add 110 liters of toluene. Stir for approximately 20 minutes. Alkalify with aqueous ammonia. Separate off the aqueous phase and extract once again with 150 liters of toluene.

Combine the toluene phases and wash them with water. Separate off the toluene phases, filter. Remove the water by distilling the water-toluene azeotrope. Cool and pass through a stream of anhydrous HCl gas.

Cool. Evaporate down and wash with pure toluene.

Weight obtained: 10.11 kg.

Yield: 84%.

Thin layer chromatography: Solvent: toluene: 10; ethyl acetate: 5; Support: Merck silica 60 F 254; Developer: UV; R_f: 0.55.

Stage 1C: (R,S)-2-Carboxyindoline

2.15 kg of (R,S)-2-ethoxycarbonylindoline dissolved in ethanol are saponified with 12.5 liters of N sodium hydroxide with stirring for 24 hours. After washing the alkaline solution, neutralize with concentrated hydrochloric acid. After filtering off, washing and drying, 1.57 kg of white crystals of the expected product are obtained.

Yield: 86%.

Melting point: 188° to 189°C.

Spectrometry in the infrared: NH_2 +: 2500-2000 cm^{-1} ; COO^- : 1620 cm^{-1}.

Stage 1D: (S)-2-Carboxyindoline

6.05 kg of (R,S)-2-carboxyindoline are added to a solution of 4.49 kg of (+)-α-methylbenzylamine in anhydrous ethanol. A white precipitated product is obtained which,

after filtering off, is digested in refluxing isopropanol. After cooling, the solid is filtered off and washed with a little isopropanol; the white crystals obtained are dried: 3.68 kg.

Rotatory power: $[\alpha]_{21}^{D}$ =-5.3 (c=1% ethanol).

(S)-2-Carboxyindoline is prepared in a quantitative yield by dissolving 1 kg of the above salt in 5 liters of water and neutralizing with an aqueous hydrochloric acid solution. This precipitate is filtered off, washed with water and dried.

Stage 1E: (2S,3aS,7aS)-2-Carboxyoctahydroindole

Place 25 kg of (S)-2-carboxyindoline, obtained previously, in 110 liters of methanol in a vessel. Keep stirred. Charge the rhodium (5% dry) catalyst into a mixer.

Start up the stirring in a hydrogenator, charge the methanolic suspension of (S)-2-carboxyindoline by passing it through the mixer and rinse the assembly with water. Heat to 60°C and pressurize with hydrogen (30 bar).

Filter off the catalyst on a single-plate filter. Collect the hydroalcoholic liquors in a reactor and evaporate the methanol off under vacuum.

After concentrating, charge approximately 300 kg of dioxane. Heat to boiling and add water until a solution is obtained. Allow to cool. Filter off and dry. 22.3 kg of crystals are obtained.

Yield: 86.1%.

Stage 2: N-[(S)-1-Carbethoxybutyl]-(S)-alanine

Stage 2A: Ethyl L-norvalinate hydrochloride

Place 35 kg of L-norvaline in approximately 300 kg of denatured ethanol in a reactor. Introduce approximately 60 kg of thionyl chloride, slowly and gradually.

After stirring for a quarter of an hour, heat to reflux for 3 hours and then evaporate off the ethanol under vacuum.

Take up the residue with 300 liters of cyclohexane and heat to boiling. Allow to cool, filter, wash with cyclohexane and dry. 52.9 kg of ethyl L-norvalinate hydrochloride are obtained, that is a 97.6% yield.

The product thus obtained is employed as such in the next stage.

Stage 2B: N-[(S)-1-carbethoxybutyl]-(S)-alanine

Place 45 kg of ethyl N-norvalinate hydrochloride obtained in the preceding stage and approximately 110 liters of water in a vessel equipped with a stirrer.

Alkalify, then pour 23 kg of pyruvic acid very gradually into the solution obtained previously and stir the reaction mixture for 30 minutes.

Place an aqueous suspension of charcoal containing 5% palladium and the alkaline solution of ethyl L-norvalinate obtained previously in a hydrogenation apparatus.

Hydrogenate under pressure (30 bar) at ambient temperature for approximately one day.

Filter under vacuum and evaporate the filtrate under reduced pressure, filter off and dry. Treat the residue obtained with ethanol; remove the insoluble material, consisting of sodium chloride, by filtration and rinse it with ethanol. Combine the ethanolic solutions; evaporate off the ethanol under reduced pressure and crystallize the residue from acetonitrile.

34.3 kg of N-[(S)-1-carbethoxybutyl]-(S)-alanine are obtained, that is a 63.9% yield.

Stage 3: tert-Butylamine salt of (2S,3aS,7aS)-1-{2-[1-ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid

Stage 3A: para-Toluenesulfonate of the benzyl ester of (2S,3aS,7aS)-2-carboxyoctahydroindole

In a 30-liter reactor, reflux 12.5 kg of (2S,3aS,7aS)-2-carboxyperhydroindole, 50 kg of para-toluenesulfonic acid and 14.2 kg of benzyl alcohol and 38.4 kg of toluene, removing the water

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formed with the aid of a continuous separator. When no more water separates out, cool, filter off the precipitate formed, and dry.

Yield: 91.3%.

Stage 3B: Benzyl ester of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid

Add approximately 3.5 kg of triethylamine to a suspension of approximately 5 kg of para-toluenesulfonate of the benzyl ester of (2S,3aS,7aS)-2-carboxyoctahydroindole in approximately 60 kg of ethyl acetate, followed by approximately 6 kg of 1-hydroxybenzotriazole, approximately 7.5 kg of the N-[(S)-1-carbethoxybutyl]-(S)-alanine obtained in stage 2 and approximately 7.0 kg of dicyclohexylcarbodiimide.

Stir, cooling slightly for approximately 3 hours, then filter off the dicyclohexylurea formed by filtration and wash the organic phase with water. The dried organic phase is evaporated to dryness.

Yield: 92.3%.

Stage 3C: (2S,3aS,7aS)-1-{2-[1-(Ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid

Dissolve, in a hydrogenator, 14 kg of benzyl ester of the (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid obtained in the preceding stage in cyclohexane.

Add the charcoal containing 5% palladium and approximately 50 liters of water. Hydrogenate at ordinary temperature and pressure until the theoretical volume of hydrogen has been absorbed. Filter, wash the insoluble material with cyclohexane, separate off the organic phase and wash the aqueous phase again with cyclohexane. Isolate the product from the aqueous phase by freeze-drying.

Stage 3D: tert-Butylamine salt of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahydroindole-2-carboxylic acid

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Place in a reactor approximately 140 liters of ethyl acetate and 10 kg of (2S,3aS,7aS)-1-{2-[1-ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}octahyd roindole-2-carboxylic acid obtained previously. Add gradually approximately 2.20 kg of tert-butylamine, heat to reflux until all has dissolved; filter. Cool, filter off and dry.

Yield: 95%.

EXAMPLE 2: α crystalline form of perindopril tert-butylamine salt

125 g of perindopril tert-butylamine salt obtained according to the process described in Example 1 above is dissolved in 1.68 litres of ethyl acetate heated at reflux.
The temperature of the solution is then brought to 60°C in the course of 2 hours 30 minutes and is then cooled to ambient temperature.
The solid obtained is collected by filtration. The resulting compound is an α crystalline form of the compound of formula (I).

The powder X-ray diffraction spectrum of the α crystalline compound was measured under the following experimental conditions:

- Siemens D5005 diffractometer, scintillation detector,
- copper anticathode (λ=1.5405 Å), voltage 40 kV, intensity mA,
- mounting θ-θ,
- measurement range: 5° to 30°,
- increment between each measurement: 0.02°,
- measurement time per step: 2 s,
- variable slits: v6,
- filter Kβ (Ni),
- no internal reference,
- zeroing procedure using the Siemens slits,
- experimental data processed using EVA software (version 5.0).

Analysis was carried out under ambient conditions.

Powder X-ray diffraction diagram:

The powder X-ray diffraction profile (diffraction angles) of the α form of perindopril tert-butylamine salt is given by the significant rays collated in the following table together with the intensity and relative intensity (expressed as a percentage of the most intense ray):

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
10.947	8.08	182	4.1
13.150	6.73	82	1.9
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25.957	3.43	125	2.8
26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

The α crystalline form of the compound of formula (I) was obtained via filtration in the form of individual needles about 0.2 mm long.

EXAMPLE 3: Pharmaceutical composition

Preparation formula for 1000 tablets each containing 4 mg of active ingredient:

Compound of Example 2 ..... 4 g

Hydroxypropylcellulose ..... 2 g

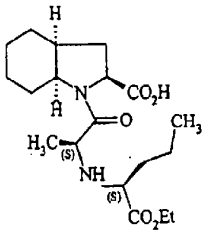
Wheat starch ..... 10 g

Lactose	100 g
Magnesium stearate	3 g
Talc	3 g

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

The claims defining the invention are as follows:

1. α crystalline form of the compound of formula (I):



. $tBuNH_2$ (I),

characterised by having the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray)

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
7.680	11.50	390	8.8
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26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

and further characterized by being in the form of individual needles.

2. The α crystalline form of the compound according to claim 1 wherein the individual needles are about 0.2 mm long.

3. The α crystalline form of the compound according to claim 1 or 2, wherein the individual needles allow rapid and efficient filtration and drying.

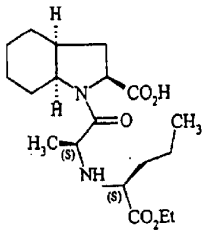
4. A process for preparation of the α crystalline form of the compound of formula (I) according to any one of claims 1 to 3, comprising heating a solution of perindopril tert-butylamine salt in ethyl acetate at reflux and gradually cooling the solution until crystallisation is complete forming individual needles, wherein the solution at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 5 to 10°C/hour, and then cooled to ambient temperature.

5. The process according to claim 4, wherein the concentration of the perindopril tert-butylamine salt in the ethyl acetate is from 70 to 90 g/litre.

6. The process according to claim 4 or 5, wherein the solution of perindopril tert-butylamine salt in ethyl acetate is seeded during the cooling step at a temperature of from 76 to 65°C.

7. The process according to any one of claims 4 to 6, wherein the solution of the perindopril tert-butylamine salt in ethyl acetate at reflux is first cooled to a temperature of from 55 to 65°C at a rate of from 6 to 8°C/hour, and then to ambient temperature.

8. A pharmaceutical composition comprising as active ingredient α crystalline form of the compound of formula (I):



. $tBuNH_2$ (I),

in combination with one or more pharmaceutically acceptable, inert, non-toxic carriers; wherein the α crystalline form of the compound of formula (I) is characterised by having the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray)

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
7.680	11.50	390	8.8
8.144	10.85	230	5.2
9.037	9.78	4410	100
10.947	8.08	182	4.1
13.150	6.73	82	1.9
13.687	6.46	83	1.9
14.627	6.05	582	13.2
15.412	5.74	770	17.5
16.573	5.34	1115	25.3
17.357	5.10	340	7.7
18.109	4.89	193	4.4

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
19.922	4.45	306	6.9
20.609	4.31	375	8.5
21.412	4.15	226	5.1
21.832	4.07	217	4.9
22.158	4.01	483	11
22.588	3.93	386	8.8
23.323	3.81	107	2.4
24.200	3.67	448	10.2
24.727	3.60	137	3.1
25.957	3.43	125	2.8
26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

and wherein the α crystalline form of compound of formula (I) has been isolated in the form of individual needles.

9. The pharmaceutical composition according to claim 8, wherein the individual needles are about 0.2 mm long.

10. The pharmaceutical composition according to claim 8 or 9, wherein the individual needles allow rapid and efficient filtration and drying.

11. The pharmaceutical composition according to any one of claims 8 to 10 in the form of tablets or dragées, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, or drinkable suspensions.

12. The pharmaceutical composition according to claim 11 in the form of a tablet.

13. The pharmaceutical composition according to any one of claims 8 to 12 comprising from 1 to 500 mg of the α crystalline form of the compound of formula (I).

14. The pharmaceutical composition according to claim 13 comprising 4 mg of the α crystalline form of the compound of formula (I).

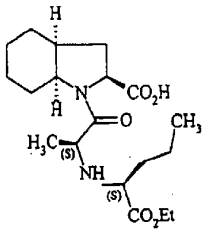
15. The pharmaceutical composition according to any one of claims 8 to 14, further comprising a diuretic.

16. The pharmaceutical composition according to claim 15, wherein the diuretic is indapamide.

17. Use of the pharmaceutical composition according to any one of claims 8 to 16 as an inhibitor of angiotensin I converting enzyme.

18. The use according to claim 17 for treatment of cardiovascular disease.

19. A method of treatment of cardiovascular disease comprising administering to a patient in need of such treatment an efficacious amount of α crystalline form of the compound of formula (I):



. $tBuNH_2$ (I),

characterised by having the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar

distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray)

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
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21.832	4.07	217	4.9
22.158	4.01	483	11
22.588	3.93	386	8.8
23.323	3.81	107	2.4
24.200	3.67	448	10.2
24.727	3.60	137	3.1
25.957	3.43	125	2.8
26.932	3.31	75	1.7
27.836	3.20	197	4.5
28.966	3.08	129	2.9
29.213	3.05	117	2.7

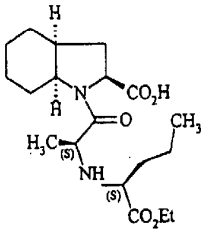
wherein the α crystalline form of the compound of formula (I) has been isolated in the form of individual needles.

20. The method of treatment according to claim 19 when the individual needles are about 0.2 mm long.

21. The method of treatment according to claim 19 or 20, wherein the individual needles allow rapid and efficient filtration and drying.

22. A method of treatment of cardiovascular disease comprising administering to a patient in need of such treatment an efficacious amount of a pharmaceutical composition according to any one of claims 8 to 16.

23. Use of the α crystalline form of the compound of formula (I):



. $tBuNH_2$ (I),

for the manufacture of a medicament for treatment of cardiovascular disease,

wherein the α crystalline form of the compound of formula (I) is characterised by having the following powder X-ray diffraction diagram, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage with respect to the most intense ray).

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28.966	3.08	129	2.9
29.213	3.05	117	2.7

and wherein the α crystalline form of the compound of formula (I) has been isolated in the form of individual needles.

24. The use according to claim 23 wherein the individual needles are about 0.2 mm long.

25. The use according to claim 23 or 24, wherein the individual needles allow rapid and efficient filtration and drying.