(12) UK Patent Application (19) GB (11) 2 395 195 (13) A

(43) Date of A Publication 19.05.2004

(21) Application No: **0226885.2**

(22) Date of Filing: **18.11.2002**

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(51) INT CL^7:
C07D 209/42 , A61K 31/404 , A61P 9/04 9/12

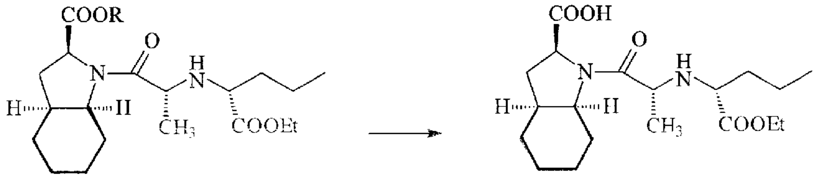
(52) UK CL (Edition W):
C2C CAA CLZ CPK C1343 C213 C247 C25Y C250 C251 C29X C29Y C30Y C32Y C322 C351 C355 C366 C367 C368 C620 C625 C638 C650 C675 C802
U1S S2415

(56) Documents Cited:
WO 2001/058868 A1 **US 4914214 A**

(58) Field of Search:
Other: **CAS ONLINE**

(54) Abstract Title: **Preparation of perindopril from carboxy-protected precursor, & perindopril monohydrates for use as angiotensin converting enzyme (ACE) inhibitors**

(57) Perindopril of formula (I), or a pharmaceutically acceptable salt thereof, may be made from a protected precursor compound of formula (II)



(II) (I)

wherein R comprises a carboxyl protecting group, by subjecting a compound of formula (II) to deprotection of the carboxylic group -COOR, in the presence of a base.

R is preferably aralkyl, such as benzyl, and the deprotection preferably comprises hydrogenolysis in the presence of a noble metal catalyst, such as palladium-on-charcoal. The base preferably is one which forms a pharmaceutically acceptable addition salt with perindopril and t-butyl amine is especially preferred, thus yielding perindopril erbumine.

A monohydrate of perindopril, or a pharmaceutically acceptable salt thereof, is also claimed and may be prepared by hydrating perindopril, or a pharmaceutically acceptable salt thereof, by way of addition of water or by drying in air. Perindopril erbumine monohydrate is a preferred compound, especially the crystalline form thereof having the X-ray diffractogram set out in figure 1. Perindopril monohydrates may be used as angiotensin converting enzyme (ACE) inhibitors.

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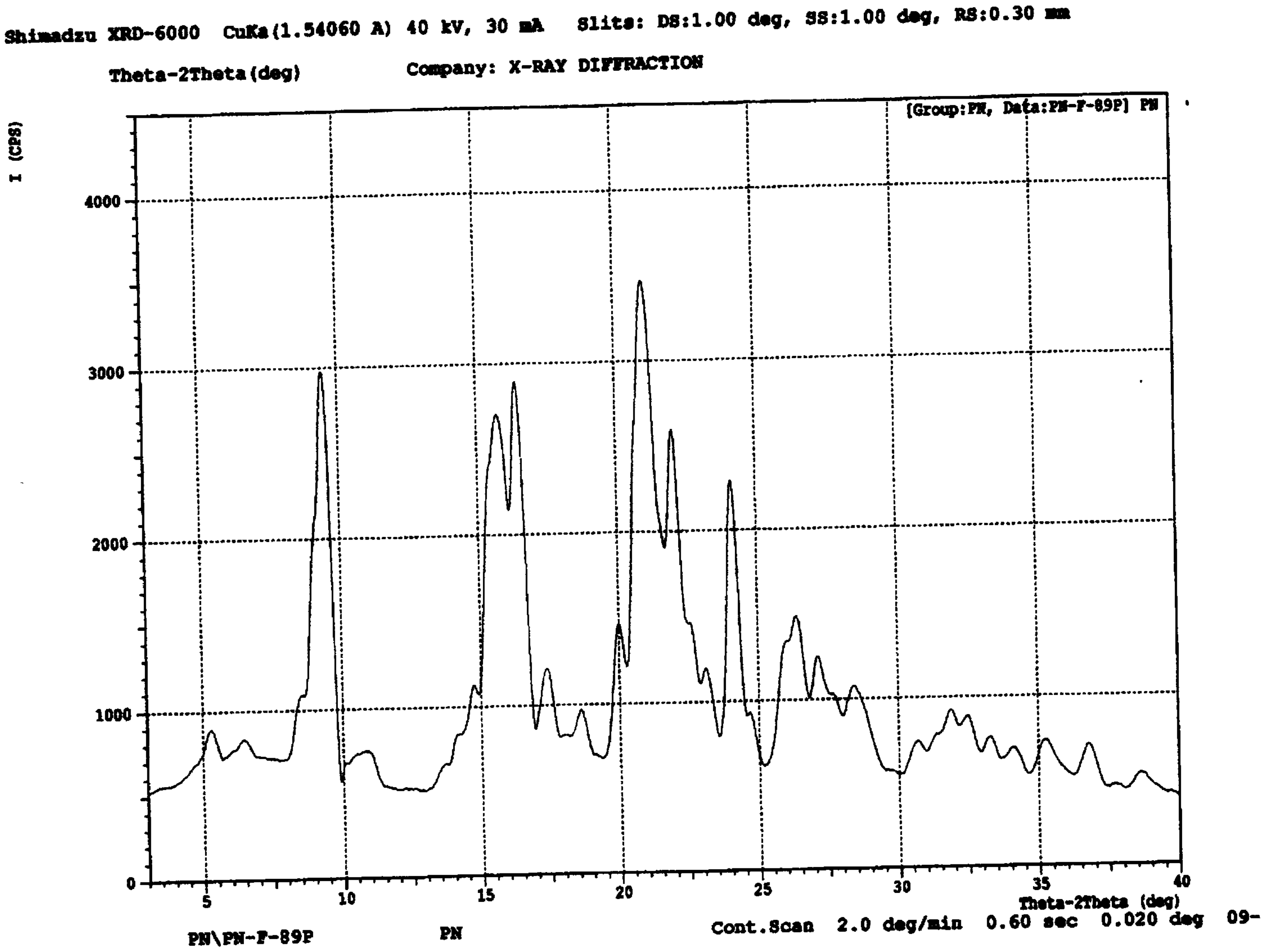
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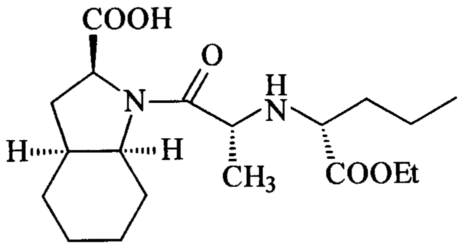
PERINDOPRIL

This invention relates to a process for preparing perindopril, or a pharmaceutically acceptable salt thereof, and a novel polymorphic form thereof.

Perindopril is the international non-proprietary name of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}-octahydroindole-2-carboxylic acid. Perindopril is known to have therapeutic application as an angiotensin – converting enzyme (ACE) inhibitor. ACE is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to angiotensin II, as well as causing the degradation of bradykinin. Angiotensin II is a vasoconstrictor which also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE has, therefore, been shown to have therapeutic utility in patients suffering from disease states such as hypertension and congestive heart failure. In addition, it has been discovered that ACE inhibitors are useful in treating cognitive disorders.

Perindopril has the following structural formula (I)



(I)

Perindopril is described in US patent no. 4508729. Preparative processes described in this US patent are carried out in an alcoholic medium, and in the presence of a neutral dehydrating agent and an organic or inorganic cyanoborohydride. Deprotection processes can be carried out where necessary, for example with reference to hydrolysis and/or hydrogenolysis.

US patent no. 4914214 describes a process for the preparation of perindopril and its t-butylamine salt. The process comprises condensation of a protected ester of (2S,3aS,7aS)-2-

carboxyperhydroindole with the (S,S) diastereoisomer of N-[(S)-1-carbethoxybutyl]-(S)-alanine, followed by deprotection employing charcoal containing 5% palladium and water. Tertiary-butylamine is then added to yield the t-butylamine salt of perindopril.

PCT patent application WO 01/87835 describes a novel crystalline form, namely α crystalline form, of the t-butylamine salt of perindopril, processes of preparing the same and pharmaceutical formulations containing the same.

PCT patent application WO 01/87836 describes a novel crystalline form, namely β crystalline form, of the t-butylamine salt of perindopril, processes of preparing the same and pharmaceutical formulations containing the same.

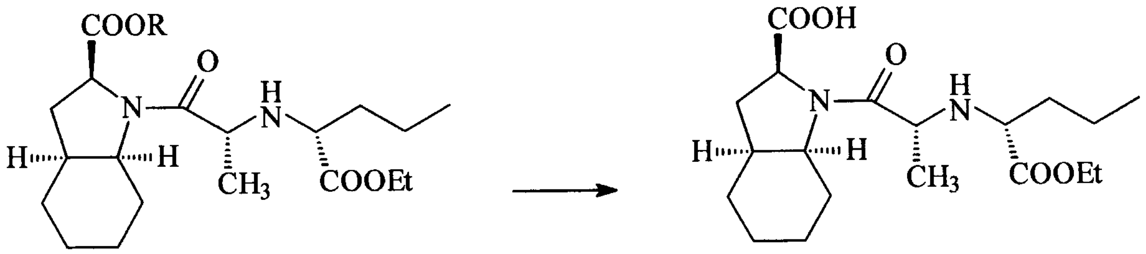
PCT patent application WO 01/87835 describes a novel crystalline form, namely γ crystalline form, of the t-butylamine salt of perindopril, processes of preparing the same and pharmaceutical formulations containing the same.

PCT patent application WO 01/58868 describes a process of preparing perindopril or pharmaceutically acceptable salts thereof, which process provides perindopril, or a salt thereof, with improved purity. More particularly, the level of known impurities associated with perindopril or a salt thereof, prepared according to PCT patent application WO 01/58868, is described as being less than 0.2 or 0.1% by weight. Intermediate process steps are carried out in the presence of 1-hydroxybenzotriazole, dicyclohexylcarbodiimide and optionally triethylamine, and at a temperature in the range of 20 to 77°C, followed by deprotection and where required salt conversion.

Prior art processes for the preparation of perindopril, or pharmaceutically acceptable salts thereof, have generally tended to be time-consuming and have often resulted in undesirable associated impurities, such as diketopiperazine analogues. There is, therefore, a need for an improved process for preparing perindopril, or pharmaceutically acceptable salts thereof, which alleviates the above mentioned problems.

We have now developed a process for preparing perindopril, or pharmaceutically acceptable salts thereof, which is advantageous in terms of a faster reaction time compared to known processes for the preparation of perindopril, or pharmaceutically acceptable salts thereof, and also in obviating the production of undesirable impurities so as to achieve a highly pure product.

In accordance with one aspect of the present invention, there is provided a process for preparing perindopril of formula (I), or a pharmaceutically acceptable salt thereof, from a protected precursor compound of formula (II)



(II) (I)

wherein R represents a carboxyl protecting group, which process comprises subjecting a compound of formula (II) to deprotection of the carboxylic group COOR attached to the heterocyclic ring, which deprotection is carried out in the presence of a base.

Typically, R can represent any suitable carboxyl protecting group that can be selectively removed by a process according to the present invention. Preferably, R can represent aralkyl, especially benzyl.

Suitably, deprotection as employed in a process according to the present invention can comprise hydrogenolysis in the presence of a noble metal catalyst, preferably palladium-on-chacoal.

The process of the present invention is advantageous in achieving a highly pure product. Perindopril, or a pharmaceutically acceptable salt thereof, prepared by a process according to the present invention is preferably more than about 99% w/w pure, and more preferably more than about 99.5% w/w pure. The purity of perindopril, or a pharmaceutically acceptable salt thereof, prepared by a process according to the present invention, can be further enhanced by an optional crystallisation step in a suitable solvent, such as ethyl acetate, isopropanol or the like, so as to obtain perindopril, or a pharmaceutically acceptable salt thereof, which is preferably about 99.8% w/w pure.

Preferably, a base employed in the process of the present invention is selected so as to provide a suitable organic ligand for forming a pharmaceutically acceptable addition salt with perindopril. In this way, it is possible to obtain a pharmaceutically acceptable salt of perindopril directly form such a reaction work-up. In a particularly preferred embodiment according to the present invention the base comprises t-butyl amine and as such a preferred process according to the present invention can provide a highly pure t-butyl amine salt of perindopril directly from the reaction process.

According to the above preferred embodiment of the present invention, there is provided a process for preparing perindopril erbumine (which is well known to those of skill in the art as being perindopril t-butylamine) from a protected precursor compound of formula (II) substantially as hereinbefore described (preferably a benzyl protected precursor compound of formula (II) where R represents benzyl), which process comprises subjecting a compound of formula (II) to deprotection (preferably hydrogenolysis in the presence of a noble metal catalyst such as palladium-on-chacoal) of the carboxylic group COOR attached to the heterocyclic ring, which deprotection is carried out in the presence of t-butylamine.

Suitably a precursor compound of formula (II) is initially dissolved in an alkanol solvent, such as isopropanol or the like, followed by addition of the base thereto. This is further followed by the deprotection of the carboxylic group COOR, suitably by the addition of palladium-on-charcoal and hydrogenation for several hours. The alkanol solvent is suitably concentrated under vacuum and replaced by a water immiscible solvent, such as ethyl acetate or the like. The resulting solids can then be cooled and filtered to yield perindopril, or a pharmaceutically acceptable salt thereof.

The process according to the present invention substantially as hereinbefore described may further comprise hydrating the resulting perindopril, or a pharmaceutically acceptable salt thereof, so as to yield a monohydrate of perindopril, or a pharmaceutically acceptable salt thereof. Hydration can be by way of the addition of water or by drying in air.

The present invention also provides a process for preparing a monohydrate of perindopril, or a pharmaceutically acceptable salt thereof, which process comprises hydrating perindopril, or a pharmaceutically acceptable salt thereof, so as to yield a monohydrate of perindopril, or a pharmaceutically acceptable salt thereof. Hydration can be by way of the addition of water or by drying in air.

In a further aspect, the invention provides a monohydrate of perindopril, or a pharmaceutically acceptable salt thereof, preferably perindopril erbumine monohydrate.

The present invention also provides perindopril erbumine monohydrate having an X-ray diffractogram, or substantially the same X-ray diffractogram, as set out in Figure 1. More particularly, perindopril erbumine monohydrate according to the present invention can be characterised as having an X-ray powder diffraction pattern with characteristic peaks (2θ): 9.5504, 14.8600, 15.7486, 16.5400, 20.0400, 21.0499, 22.0600, 24.1744, 26.3300 and 27.1600.

Further characterising data for perindopril erbumine monohydrate according to the present invention as obtained by X-ray diffraction is shown in following Table 1.

Table 1

Peak No.	2θ (deg)	d (A)	I/Il	FWHM (deg)	Intensity (Counts)	Integrated I (Counts)
1	8.6400	10.22611	10	0.57600	151	6899
2	9.5504	9.25324	73	0.50470	1090	28204
3	10.5940	8.34394	5	0.97200	79	4071
4	13.6000	6.50569	6	0.42860	91	2112
5	14.1400	6.25844	14	0.47120	215	5210
6	14.8600	5.95678	22	0.59000	332	10293
7	15.7486	5.62262	75	0.14270	1111	49244
8	16.5400	5.35533	30	0.72500	450	15749
9	17.5400	5.05220	16	0.67120	231	9128
10	18.6100	4.76406	17	0.56000	249	7981
11	20.0400	4.42722	31	0.51660	458	13471
12	21.0499	4.21704	100	0.90700	1488	63860
13	22.0600	4.02618	50	0.59480	747	23998
14	23.1600	3.83738	17	0.71720	253	12014
15	24.1744	3.67860	47	0.50030	705	17912
16	24.8000	3.58721	5	0.26000	73	1463

17	26.3300	3.38213	31	0.94000	468	19402
18	27.1600	3.28062	20	0.68500	292	9230
19	28.4444	3.13534	15	0.96890	223	11023
20	30.8000	2.90071	7	0.59340	99	3196
21	31.8000	2.81173	9	0.65600	130	4356
22	32.5600	2.74782	11	0.61340	163	4411
23	33.2400	2.69314	6	0.75000	95	3116
24	34.1800	2.62120	4	0.64000	61	2155
25	35.4728	2.52857	7	0.85430	104	4353
26	36.8838	2.43502	6	0.61900	93	2985
27	38.7340	2.32285	4	0.50800	55	1432

A monohydrate as provided by the present invention has therapeutic utility as an ACE inhibitor.

In addition, the present invention further provides a method of inhibiting ACE in a patient in need thereof comprising administering to said patient an effective ACE inhibitory amount of a monohydrate according to the present invention.

The present invention also provides use of a monohydrate according to the present invention in the manufacture of a medicament for inhibiting ACE.

A patient can be in need of treatment to inhibit ACE, for example when the patient is suffering from hypertension, chronic congestive heart failure, or the like. Inhibition of ACE reduces levels of angiotensin II and thus inhibits the vasopressor, hypertensive and hyperaldosteronemic effects caused thereby. Inhibition of ACE would also potentiate endogenous levels of bradykinin. An effective ACE inhibitory amount of a monohydrate according to the present invention is that amount which is effective in inhibiting ACE in a patient in need thereof which results, for example, in a hypotensive effect.

In effecting treatment of a patient, a monohydrate according to the present invention can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, a monohydrate according to the present invention can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated and the stage of the disease.

A monohydrate according to the present invention can be administered in the form of pharmaceutical compositions or medicaments which are prepared by combining a monohydrate according to the present invention with pharmaceutically acceptable carriers, diluents or excipients therefor, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

In another embodiment, the present invention provides pharmaceutical compositions comprising an effective ACE inhibitory amount of a monohydrate according to the present invention, together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

By "pharmaceutically acceptable" it is meant that the carrier, diluent or excipient must be compatible with a monohydrate according to the present invention, and not be deleterious to a recipient thereof.

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier, diluent or excipient may be a solid, semi-solid, or liquid material, which can serve as a vehicle or medium for the active ingredient. Suitable carriers, diluents or excipients are well known in the art. Pharmaceutical compositions according to the present invention may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solutions, suspensions or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, a monohydrate according to the present invention may be incorporated with excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups and the like.

The tablets, pills, capsules, and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose; disintegrating agents such as alginic acid, corn starch and the like; lubricants, such as magnesium stearate; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration, a monohydrate according to the present invention may be incorporated into a solution or suspension. The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; and buffers such as acetates, citrates or phosphates. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

The present invention will now be further illustrated by the following Figure and Examples, which do not limit the scope of the invention in any way.

Figure 1: X-ray diffraction pattern of perindopril erbumine monohydrate according to the present invention.

Example 1

The benzyl ester of (2S,3aS,7aS)-1-{2-[1-(ethoxycarbonyl)-(S)-butylamino]-(S)-propionyl}-octahydroindole-2-carboxylic acid, namely benzyl perindopril, (10gms) was dissolved in isopropanol (100ml). To the clear solution, t-butyl amine (2.5gms) and 10% w/w palladium on charcoal (2gms) was added. The reaction mixture was hydrogenated at a pressure of 1kg/cm^2 for 2 hours.

The reaction mass was filtered to remove the catalyst. The solvent was concentrated under vacuum and isopropanol was replaced by simultaneous addition of ethyl acetate. The solids obtained were cooled to 0°C and filtered to obtain perindopril erbumine (7.8gms).

Example 2

Perindopril erbumine (10gms) was suspended in acetone (80ml). To this was added water (0.4ml) and the contents heated to dissolve the solids and cooled to ambient. The resulting slurry was filtered to obtain perindopril erbumine monohydrate (9.4gms).

Example 3

Perindopril erbumine (20gms) was suspended in ethyl acetate (300ml). To this was added water (1.5ml) and the contents heated to dissolve the solids and cooled to 10°C. The resulting slurry was filtered to obtain perindopril erbumine monohydrate (17gms).

Example 4

Perindopril erbumine (5gms) was suspended in acetonitrile (75ml). To this was added water (0.4ml) and the contents heated to dissolve the solids and cooled to 0°C. The resulting slurry was filtered to obtain perindopril erbumine monohydrate (2.9gms).

Example 5

Perindopril erbumine (20gms) was suspended in ethyl acetate (300ml). The contents were heated to dissolve the solids and cooled to 10°C. The resulting slurry was filtered and dried in air to obtain perindopril erbumine monohydrate (17gms).

Example 6

The following tablets were prepared:

(a) Formulation I:

	Strengths		
	2 mg	**4 mg**	**8 mg**
Ingredients			
Perindopril Erbumine Monohydrate	2 mg	4 mg	8 mg
Maize starch	5 mg	10 mg	20 mg
Lactose anhydrous	12.5 mg	25.0 mg	100.0 mg
Microcrystalline cellulose	25.10 mg	50.20 mg	100.40 mg
Magnesium stearate	0.4	0.8	1.6
Total weight	45.0 mg	90.0 mg	180.0 mg

Procedure: Sift the above ingredients through respective sieves. Mix the ingredients in a suitable blender. Compress the tablets in the suitable toolings.

(b) Formulation II:

	Strengths		
	2 mg	**4 mg**	**8 mg**
Ingredients			
Perindopril Erbumine Monohydrate	2 mg	4 mg	8 mg
Maize starch	10 mg	10 mg	10 mg
Lactose anhydrous	25 mg	25.0 mg	25.0 mg
Microcrystalline cellulose	52.2 mg	49.20 mg	45.20 mg
Yellow oxide of Iron	-	1.0	-
Red oxide of Iron	-	-	1.0
Hydrogenated castor oil	0.8 mg	0.8 mg	0.8 mg
Total weight	90.0 mg	90.0 mg	90.0 mg

Procedure:

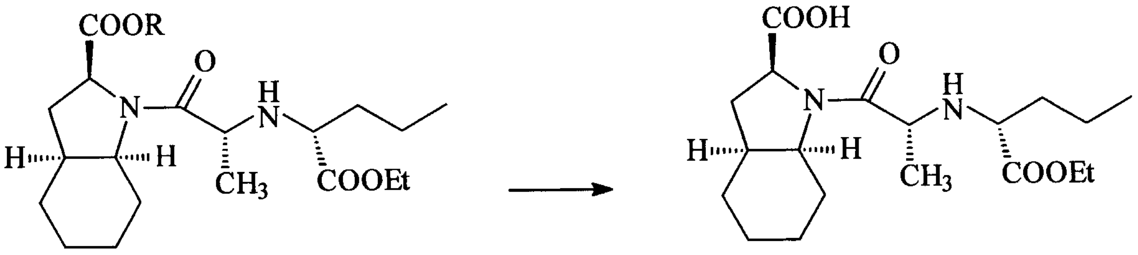
1) Dissolve Perindopril Erbumine Monohydrate in ethanol.

2) Granulate the above ingredients except Hydrogenated castor oil with the above solution. Dry the granules and size.

3) Lubricate with hydrogenated castor oil in suitable blender. Compress the granules in the suitable tooling

CLAIMS

1 A process for preparing perindopril of formula (I), or a pharmaceutically acceptable salt thereof, from a protected precursor compound of formula (II)



(II) (I)

wherein R represents a carboxyl protecting group, which process comprises subjecting a compound of formula (II) to deprotection of the carboxylic group COOR attached to the heterocyclic ring, which deprotection is carried out in the presence of a base.

2 A process according to claim 1, wherein R represents aralkyl.

3 A process according to claim 2, wherein R represents benzyl.

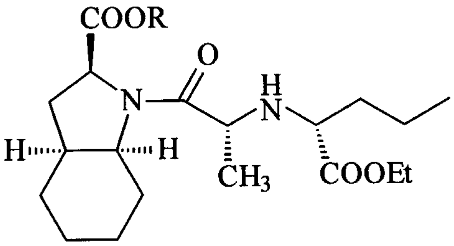
4 A process according to claim 3, wherein deprotection comprises hydrogenolysis in the presence of a noble metal catalyst.

5 A process according to claim 4, wherein the noble metal catalyst comprises palladium-on-chacoal.

6 A process according to any of claims 1 to 5, wherein said base is selected so as to provide an organic ligand for forming a pharmaceutically acceptable addition salt with perindopril.

7 A process according to claim 6, wherein said base comprises t-butyl amine.

8 A process for preparing perindopril erbumine from a protected precursor compound of formula (II)



(II)

wherein R represents a carboxyl protecting group, which process comprises subjecting a compound of formula (II) to deprotection of the carboxylic group COOR attached to the heterocyclic ring, which deprotection is carried out in the presence of t-butylamine.

9 A process according to claim 8, wherein R represents benzyl.

10 A process according to claim 8 or 9, wherein deprotection comprises hydrogenolysis in the presence of palladium-on-chacoal.

11 A process according to any of claims 1 to 10, which further comprises hydrating perindopril, or a pharmaceutically acceptable salt thereof, obtained by said process, so as to yield a monohydrate of perindopril, or a pharmaceutically acceptable salt thereof.

12 A process for preparing a monohydrate of perindopril, or a pharmaceutically acceptable salt thereof, which process comprises hydrating perindopril, or a pharmaceutically acceptable salt thereof, so as to yield a monohydrate of perindopril, or a pharmaceutically acceptable salt thereof.

13 A process according to claim 11 or 12, wherein perindopril erbumine is hydrated to yield perindopril erbumine monohydrate.

14 A monohydrate of perindopril, or a pharmaceutically acceptable salt thereof.

15 Perindopril erbumine monohydrate.

16 Perindopril erbumine monohydrate having an X-ray diffractogram, or substantially the same X-ray diffractogram, as set out in Figure 1.

17 Perindopril erbumine monohydrate characterised as having an X-ray powder diffraction pattern with characteristic peaks (2θ): 9.5504, 14.8600, 15.7486, 16.5400, 20.0400, 21.0499, 22.0600, 24.1744, 26.3300 and 27.1600.

18 A pharmaceutical composition comprising an effective ACE inhibitory amount of a monohydrate according to any of claims 14 to 17, together with one or more pharmaceutically acceptable carriers, diluents or excipients therefor.

19 Use of a monohydrate according to any of claims 14 to 17, in the manufacture of a medicament for inhibiting ACE.

20 A method of inhibiting ACE in a patient in need thereof comprising administering to said patient an effective ACE inhibitory amount of a monohydrate according to any of claims 14 to 17.

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INVESTOR IN PEOPLE

Application No: GB 0226885.2 14

Claims searched: 1-11

Examiner: Stephen Quick

Date of search: 10 March 2004

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-10	WO 01/58868 A1 (ADIR), see especially examples 2 & 3; acknowledged in this application
X	1-10	US 4914214 A (ADIR), see especially stages 3C & 3D in example; acknowledged in this application

Categories.

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art
Y	Document indicating lack of inventive step if combined with one or more other documents of same category	P	Document published on or after the declared priority date but before the filing date of this invention
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{W}:

Worldwide search of patent documents classified in the following areas of the IPC^{7}:

The following online and other databases have been used in the preparation of this search report.

CAS ONLINE