Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2151730 C 2005/01/04

(11)(21) 2 151 730

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 1994/01/07
(87) Date publication PCT/PCT Publication Date: 1994/07/21
(45) Date de délivrance/Issue Date: 2005/01/04
(85) Entrée phase nationale/National Entry: 1995/06/13
(86) N° demande PCT/PCT Application No.: DK 1994/000011
(87) N° publication PCT/PCT Publication No.: 1994/015912
(30) Priorité/Priority: 1993/01/15 (9300763.1) GB

(51) Cl.Int.^{6}/Int.Cl.^{6} C07C 401/00, A61K 31/59

(72) Inventeurs/Inventors:
HANSEN, ERIK TORNGAARD, DK;
RASTRUP ANDERSEN, NIELS SMIDT, DK;
RINGBORG, LENE HOFFMEYER, DK

(73) Propriétaire/Owner:
LEO PHARMACEUTICAL PRODUCTS LTD. A/S
(LOVENS KEMISKE FABRIK
PRODUKTIONSAKTIESELSKAB), DK

(74) Agent: BORDEN LADNER GERVAIS LLP

(54) Titre : NOUVELLE FORME CRISTALLINE D'UN ANALOGUE DE LA VITAMINE D
(54) Title: NEW CRYSTALLINE FORM OF A VITAMIN D ANALOGUE

(57) Abrégé/Abstract:
A novel form of calcipotriol, namely calcipotriol (1α, 3β, 5Z , 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol, monohydrate is provided herein. This calcipotriol is characterized by its storage stability at 40°C after 12 months, its ready wettability and wet ball milling characteristics. This product is perfectly crystalline, stable and well suited for its use in modern therapy.

ABSTRACT

A novel form of calcipotriol, namely calcipotriol (1α, 3β, 5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol, monohydrate is provided herein. This calcipotriol is characterized by its storage stability at 40°C after 12 months, its ready wettability and wet ball milling characteristics. This product is perfectly crystalline, stable and well suited for its use in modern therapy.

(a) TITLE OF THE INVENTION

New Crystalline Form of a Vitamin D Analogue

(b) TECHNICAL FIELD TO WHICH THE INVENTION RELATES

The present invention relates to calcipotriol hydrate, a new crystalline form of calcipotriol, with superior technical properties, e.g., in the manufacture of crystal suspension formulations, and with superior stability properties.

(c) BACKGROUND ART

Calcipotriol (INN) (calcipotriene (USAN), (1α, 3β, 5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol) is described in published International Patent Application No. PCT/DK86/00081, filing date 14th July 1986, Publication No. WO 87/00834.

Calcipotriol possesses a remarkable profile of biological activity which has proved very useful, e.g., in the topical treatment of psoriasis. Due to the poor stability of calcipotriol in certain solutions it is, preferred, in some formulations, in particular in creams and gels, to use crystal suspensions.

In order to prepare suitable crystal suspension formulations it is mandatory to be able to control the crystal size, this parameter being important with regard to obtaining a reproducible release of the active compound from the formulation. The crystalline bulk drug is usually subjected to micronization or to a wet milling process in order to reduce the crystal size before the final suspension formulation is prepared.

In the case of calcipotriol, a wet ball milling process has been used. However, it has turned out to be technically difficult to perform this process when using the anhydrous crystal form described in the above-referred-to WO 87/00834. These crystals are not easily wetted and during the milling process they develop a stable foam which results in difficulties in obtaining a suitable small and uniform particle size.

(d) DESCRIPTION OF THE INVENTION

It has now surprisingly been found that these technical problems can be avoided when a hitherto unknown crystalline form of calcipotriol, i.e., calcipotriol monohydrate, is used

instead of the known anhydrous form. The monohydrate is technically superior to the anhydrate; it is easily wetted; and the wet ball milling process runs smoothly. This novel product is the monohydrate of calcipotriol which is perfectly crystalline, stable and well suited for its use in modern therapy.

Thus, one broad aspect of this invention provides calcipotriol (1α, 3β, 5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol, monohydrate. This calcipotriol monohydrate is characterized by its storage stability at 40°C after 12 months, its ready wettability and wet ball milling characteristics.

A second broad aspect of this invention provides a pharmaceutical composition comprising the above-identified calcipotriol monohydrate, and a pharmaceutically-acceptable vehicle.

By a first variant of this second broad aspect of this invention, the pharmaceutical composition is a cream.

By a second variant of this second broad aspect of this invention, the pharmaceutical composition is a gel.

By a variation of this second broad aspect of this invention and the above variants thereof, the pharmaceutical composition has a content of the active component of 1-100 μg/g of the composition.

A third broad aspect of this invention provides a process of preparing calcipotriol monohydrate which comprises dissolving calcipotriol in an organic solvent, and then adding water to the resulting solution to precipitate the hydrate, the hydrate having the Formula (1α, 3β, 5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol, and being characterized by its storage stability at 40°C, its ready wettability and wet ball milling characteristics.

A fourth broad aspect of this invention provides an improvement in the preparation of a gel formulation which involves wet ball milling a calcipotriol component and adding the wet milled calcipotriol component to a gel base, the improvement comprising wet milling calcipotriol hydrate as the calcipotriol component and using the wet-milled hydrate for addition to a gel base, the hydrate having the Formula (1α, 3β, 5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol, and being characterized

by its storage stability at 40°C after 12 months, its ready wettability and wet ball milling characteristics.

Stability studies have demonstrated that calcipotriol hydrate is surprisingly stable, and this is illustrated by stability data at 40°C. The anhydrous form of calcipotriol shows a considerable degree of decomposition at this temperature and more than 30% degradation is seen after 12 months storage. In contrast, the calcipotriol hydrate of a broad aspect of the present invention, shows no degradation after 12 month storage at 40°C.

Calcipotriol monohydrate may be prepared by dissolving crystalline or non-crystalline calcipotriol in an organic solvent, e.g., ethyl acetate or acetone, followed by the addition of water and optionally a non-polar solvent, e.g., hexane.

Calcipotriol monohydrate forms part of pharmaceutical preparations for topical use, e.g., creams, ointments, solutions, lotions or gels. The concentration of the active ingredient will generally be between 1 and 100 μg/g.

The formulations prepared according to aspects of the present invention comprise the active compound in association with a pharmaceutically-acceptable vehicle and, optionally, other therapeutic ingredient(s). The vehicle(s) must be "acceptable" in the sense of being compatible with the other ingredients of the preparations and not deleterious to the recipient thereof.

Preparations suitable for topical administration include liquid or semi-liquid preparations, e.g., liniments, lotions, applicants, oil-in-water or water-in-oil emulsions, e.g., creams, ointments, pastes or gels; or solutions or suspensions.

In addition to the aforementioned ingredients, the preparations of aspects of this invention may include one or more additional ingredients, e.g., diluents, buffers, surface active agents, thickeners, lubricants, preservatives, e.g., methyl hydroxybenzoate (including anti-oxidants), emulsifying agents, and the like.

The formulations may be applied one or more times daily.

(e) AT LEAST ONE MODE FOR CARRYING OUT THE INVENTION

The invention, in its broad aspects, will now be further described in the following non-limiting Examples.

Example 1

Calcipotriol (2.5 g) was dissolved in ethyl acetate (80 ml) at 50-80°C and filtered. The solution was saturated with water, and the product was precipitated upon voluntary cooling to room temperature. The resulting slurry was cooled to 0-10°C and filtered. The filtered product was dried in vacuo to give calcipotriol hydrate (2.35 g).

IR spectroscopy KBr technique

Lines characteristic for the hydrate are 1455 (m), 1442 (m), 1330 (w), 1290 (m), 1210 (m), 1085 (m), 907 (m), 895 (m) and 573 (w) cm^{-1}, respectively.

Solid State CPMAS Cross Polarization Magic Angle Spinning

The following resonances are characteristic for calcipotriol, hydrate: 147.9, 146.5, 134.8, 130.3, 129.0, 126.5, 116.0, 109.4, 75.5, 68.2, 67.2, 56.9, 55.2, 47.8, 47.5, 42.9, 42.0, 41.3, 30.7, 28.9, 25.6, 23.1, 22.6, 19.5, 14.6, 6.2 and 1.9 ppm, respectively.

Differential Scanning Calorimetry (DSC)

On a Perkin Elmer DSC7 instrument using 20°C/min. And approx. 2 mg sample, the hydrate shows loss of water near 117°C and a melting peak near 169.7°C.

Example 2

Calcipotriol (22.7 g) was dissolved in methanol (200-250 ml), filtered and concentrated *in vacuo* tp a residue which was dissolved in ethyl acetate (200-250 ml) at 50-80°C and water (2 ml) was added. The resulting solution was seeded with calcipotriol, hydrate, and the product was precipitated upon voluntary cooling to room temperature. Hexane (100 ml) was added from a dropping funnel, the resulting slurry was cooled to 0-10°C and filtered.

The filtered product was washed with 1:1 mixture of ethyl acetate and hexane (200 ml) and dried *in vacuo* to give calcipotriol hydrate (19.7 g), shown to be identical with the product described in Example 1.

Example 3

Calcipotriol (120 mg) was dissolved in acetone (2 ml) and water (1.5-3 ml) was added. The product crystallized spontaneously and the resulting slurry was cooled to 0-

10°C and filtered. The filtered product was dried *in vacuo* to yield calcipotriol hydrate (100 mg), shown to be identical with the product of Example 1.

Example 4

Cream 50 μg/g

Calcipotriol hydrate.....	50 mg
Cetomacrogel 1000.....	30 g
Cetostearylalcohol.....	60 g
Chloroallylhexaminium chloride.....	0.5 g
Propyleneglycol.....	30 g
Disodiumhydrogenphosphate.....	2 g
Liquid paraffin.....	50 g
White soft paraffin.....	170 g
Purified water.....	up to 1000 g

Melt cetomacrogol 1000, cetostearylalcohol, liquid paraffin and white soft paraffin at 75°C. Dissolve propylene glycol in water at 75°C and mix the solution with the fatty phase. Homogenize the emulsion and cool to 30°C. Mill calcipotriol hydrate in part of the aqueous phase to a particle size predominantly below 10 μm and suspend in an aqueous solution of disodiumhydrogenphosphate and chloroallylhexaminiumchloride. Add the suspension to the emulsion and fill the cream in tubes.

Example 5

Gel 50 μg/g

Calcipotriol hydrate.....	52.2 mg
(corresponding to 50 mg anhydrous)	
CARBOMER$_{TM}$.....	7 g
Cetomacrogol 1000.....	1 g
Diazolidinyl urea.....	2 g

Dichlorobenzyl alcohol.....	1 g
Disodium edetate.....	0.5 g
Sodium hydroxide.....	3.7 g
Propylene glycol.....	30 g
Purified water.....	up to 1000 g

Dissolve cetomacrogol, diazolidinyl urea, dichlorobenzyl alcohol, disodium edetate and propylene glycol in water. Add CARBOMER$_{TM}$ and homogenize by high speed. Add sodium hydroxide dissolved in part of the water during agitation. Mill the calcipotriol hydrate in a bottle of water with glass beads until a particle size below 10 μm has been obtained. Add the calcipotriol hydrate suspension to the gel and mix for 30 minutes. Fill the gel into collapsible tubes.

Claims

1. Calcipotriol (1α, 3β, 5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol), monohydrate.

2. Calcipotriol monohydrate as claimed in claim 1 which is characterized by its storage stability at 40°C after 12 months.

3. A pharmaceutical composition comprising calcipotriol monohydrate as claimed in claim 1 or claim 2, and a pharmaceutically-acceptable vehicle.

4. Pharmaceutical composition according to claim 3, which is a cream.

5. Pharmaceutical composition according to claim 3, which is a gel.

6. Pharmaceutical composition according to any one of claims 3-5, with a content of the active component of 1-100 μg/g of the composition.

7. The process of preparing calcipotriol monohydrate which comprises dissolving calcipotriol in an organic solvent, and then adding water to the resulting solution to precipitate said hydrate, said hydrate having the Formula (1α, 3β, 5Z, 7E, 22E, 24S)-24-Cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol, and being characterized by its storage stability at 40°C after 12 months.

8. The process according to claim 7, wherein said organic solvent comprises ethyl acetate.

9. The process according to claim 7, wherein said organic solvent comprises acetone.

10. The process according to any one of claims 7 to 9, wherein a non-polar solvent is added along with water.

11. The process according to claim 10, wherein said non-polar solvent comprises hexane.

12. In the preparation of a gel formulation which involves wet ball milling a calcipotriol component and adding the wet milled calcipotriol component to a gel base, the improvement which comprises wet milling calcipotriol hydrate as said component and using said wet-milled hydrate for addition to said gel base, said hydrate having the Formula (1α, 3β, 5Z, 7E, 22E, 24S)-24-cyclopropyl-9,10-secochola-5,7,10(19), 22-tetraene-1,3,24-triol, and being characterized by its storage stability at 40°C after 12 months.