Se adjunta traducción del CPP (7 páginas) al final del presente documento.

Protocol No: 171/21

Destination: Chile

I, **MICHAEL LIGHTOWLER**, a duly appointed Notary Public of England and Wales **CERTIFY THAT** The Medicines and Healthcare Products Regulatory Agency in the United Kingdom have confirmed to me that the Certificate of a Pharmaceutical Product bearing No: PP10170212 of which the attached photostatically reproduced document is a true copy was issued by them on 10th February 2021

SIGNED AND SEALED by me at Brentwood, Essex England this Eighteenth day of February Two Thousand and Twenty One

Michael Lightowler LLB Notary Public
Cathedral Place, Brentwood, Essex CM14 4ES
t 01277 268333 - e ml@notaryservices.co.uk
Regulated through the Faculty Office of the Archbishop of Canterbury

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: Pays / Pais:	United Kingdom of Great Britain and Northern Ireland
This public document Le présent acte public / El presente documento público	
2. Has been signed by a été signé par ha sido firmado por	Michael Lightowler
3. Acting in the capacity of agissant en qualité de quien actúa en calidad de	Notary Public
4. Bears the seal / stamp of est revêtu du sceau / timbre de y está revestido del sello / timbre de	The Said Notary Public

Certified

Attesté / Certificado

5. at á / en	London	**6. the** le / el día	22 February 2021
7. by par / por	Her Majesty's Principal Secretary of State for Foreign, Commonwealth and Development Affairs		
8. Number sous no / bajo el numero	APO-2247616		
9. Seal / stamp Sceau / timbre Sello / timbre	FOREIGN, COMMONWEALTH & DEVELOPMENT OFFICE LONDON	**10. Signature** Signature Firma	A. Fraser

This Apostille is not to be used in the UK and only confirms the authenticity of the signature, seal or stamp on the attached UK public document. It does not confirm the authenticity of the underlying document. Apostilles attached to documents that have been photocopied and certified in the UK confirm the signature of the UK official who conducted the certification only. It does not authenticate either the signature on the original document or the contents of the original document in any way.

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Certificate Number: PP10170212

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY

On behalf of the Department of Health

CERTIFICATE OF A PHARMACEUTICAL PRODUCT (1)

This certificate conforms to the format recommended by the World Health Organisation
(explanatory notes are attached)

Exporting (certifying) country: **UNITED KINGDOM**

Importing (requesting) country: **CHILE**

1 Name and dosage form of the product:

A) In the United Kingdom - Rocaltrol 0.25 microgram Capsules, CAPSULE, SOFT

B) In CHILE - Rocaltrol 0.25mcg Capsules, CAPSULE, SOFT

1.1 Active ingredient(s) (2) and amount(s) (3) per unit dose:

Active Ingredient(s)	Amount per unit dose
CALCITRIOL	0.25 MCG

For complete qualitative composition including excipients, see attached. (4)

1.2 Is this product licensed to be placed on the market for use in the exporting country? (5) Yes

1.3 Is this product actually on the market in the exporting country? Yes

1.4 The product is not on the market in the exporting country because

N/A

2A.1 Product Licence/Marketing Authorisation

Number [7]: **PL 43252/0028**

Date of Issue: 07 September 2020

2A.2 The name and address of the Product Licence/Marketing Authorisation holder are:

Name: ATNAHS PHARMA UK LIMITED

Address: SOVEREIGN HOUSE, MILES GRAY ROAD, BASILDON, ESSEX, SS14 3FR, UNITED KINGDOM

2A.3 Status of the Product Licence/Marketing Authorisation holder [8]:

c) is not involved in manufacturing, packaging or labelling the dosage form but is responsible for the quality and release of the product

2A.3.1 For categories b,c and d the names and address of the manufacturing site where the dosage form is produced are [9]:

See attached page for Manufacturers/Packagers

2A.4 Is Summary Basis of Approval appended? [10] No

2A.5 Is the attached, officially approved product information complete and consonant with the licence? [11] Yes

2A.6 Applicant for certificate, if different from licence holder (name and address) [12] :

Name:

Address:

Section 2B is not included because the product named in this certificate is licensed in the UK[6]

3	Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? (14)	N/A

IF NO OR NOT APPLICABLE PROCEED TO QUESTION 4

3.1	Periodicity of routine inspections (years)	
3.2	Has the manufacturer of this type of dosage form been inspected?	
3.3	Do the facilities and operations conform to GMP as recommended by the World Health Organisation ? (15)	
4	Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product including Good Manufacturing Practice (GMP)? (16)	Yes

If No, explain

Additional Information:

NONE

Address of certifying authority:

The Medicines and Healthcare products Regulatory Agency,
10 South Colonnade, Canary Wharf, London E14 4PU, United Kingdom

Telephone Number: +44 (0) 20 3080 6593

Name of authorised person: Mahmoodullah Khan

Signature: PLEASE SEE COVER LETTER

Stamp and Date: 10 February 2021

Names and Addresses of Manufacturers/Packagers (9)

Manufacturers

Name: CATALENT GERMANY EBERBACH GMBH
Address: STEINBEISSTRASSE 2, EBERBACH, D-69412, GERMANY

Excipient	Modifier	Amount per unit dose
BUTYLHYDROXITOLUENUM		
MEDIUM CHAIN TRIGLYCERIDES		
BUTYLHYDROXYANISOLE		
YELLOW IRON OXIDE E172	shell MN	
YELLOW IRON OXIDE E172	shell MX	
KARION 83	shell MN	
KARION 83	shell MX	
TITANIUM DIOXIDE E171	shell MN	
TITANIUM DIOXIDE E171	shell MX	
GLYCEROL 85%	shell MN	
GLYCEROL 85%	shell MX	
RED IRON OXIDE E172	shell MN	
RED IRON OXIDE E172	shell MX	
GELATIN	shell MN	
GELATIN	shell MX	

Explanatory Notes

1. This certificate, which is in the form recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the UK. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

2. Whenever possible International Non-proprietary Names (Inns) or national non-proprietary names have been used.

3. The formula (complete composition) of the dosage form should be given on the certificate or be appended.

4. Details of the quantitative composition are preferred but their provision is subject to the agreement of the Marketing Authorisation holder.

5. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the Marketing Authorisation.

6. Sections 2A and 2B are mutually exclusive.

7. Indicate when applicable if the licence is provisional or the product has not yet been approved.

8. Specify whether the person responsible for placing the product on the market:

   (a) manufactures the dosage form and is responsible for the quality assurance and release of the product.
   (b) packages and/or labels a dosage form manufactured by another company but is responsible for the quality assurance and release of the product.
   (c) is not involved in manufacturing, packaging or labelling the dosage form but is responsible for the quality and release of the product.
   (d) is involved in none of the above.

9. This information is optional and can be provided only with the permission of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

   It should be noted that:

   information concerning the site of manufacture is part of the Marketing Authorisation. If the manufacturing site is changed the licence must be updated or it will cease to be valid.

   in the UK manufacture of pharmaceutical products is only permitted on licensed manufacturing sites. When the product-licence holder or applicant conforms to status (b), (c) or (d) as described in note 8 above the Manufacturing Licence holder is responsible for the manufacture of the dosage form.

10. This refers to the document prepared by some national regulatory authorities that summarises the technical basis on which the product has been licensed. The UK Medicines and Healthcare products Regulatory Agency does not prepare such a document.

11. This refers to product information approved by the Medicines and Healthcare products Regulatory Agency such as a Summary of Product Characteristics (SPC).

12. In this circumstance permission for issuing the certificate is required from the Marketing Authorisation holder. This permission must be provided to the Medicines and Healthcare products Regulatory Agency by the applicant.

13. Please indicate the reason that the applicant has provided for not requesting registration:

    (a) the product has been developed exclusively for the treatment of conditions - particularly tropical diseases - not endemic in the UK.
    (b) the product has been reformulated with a view to improving its stability under tropical conditions.
    (c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the UK.
    (d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient.
    (e) this type of product does not require a Marketing Authorisation in the UK.
    (f) any other reason.

14. "Yes" means the Medicines and Healthcare products Regulatory Agency arranges periodic inspections of the manufacturing plant in which the dosage form is produced. "No" means that manufacture is taking place in a country other than the UK and inspections are not carried out by any Regulatory Authority. "Not applicable" means that manufacture is taking place in a country other than the UK and inspection is conducted under the aegis of the country of manufacture.

15. The requirements of good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardisation (WHO Technical Report Series No. 822, 1992, Annex 1).

16. This section is to be completed when the product-licence holder or applicant conforms to status (b), (c) or (d) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form and the extent and nature of any controls exercised over each of these parties.

Certificate Number: PP101702

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

1 NAME OF THE MEDICINAL PRODUCT

Rocaltrol 0.25 microgram Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains either 0.25 or 0.5 microgram of calcitriol.

Excipient(s) with known effect

Each 0.25 microgram capsule contains 2.87 – 4.37 mg sorbitol.
Each 0.5 microgram capsule contains 2.87 – 4.36 mg sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsules.

Rocaltrol 0.25 microgram capsules: One length brown-orange to red-orange opaque and the other white to grey-yellow or grey-orange opaque.

Rocaltrol 0.5 microgram capsules: Both lengths brown-orange to red-orange opaque.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocaltrol is indicated for the correction of the abnormalities of calcium and phosphate metabolism in patients with renal osteodystrophy.

Rocaltrol is also indicated for the treatment of established post-menopausal osteoporosis.

4.2 Posology and method of administration

The dose of Rocaltrol should be carefully adjusted for each patient according to the biological response so as to avoid hypercalcaemia.

The effectiveness of treatment depends in part on an adequate daily intake of calcium, which should be augmented by dietary changes or supplements if necessary. The capsules should be swallowed with a little water.

Posology

Adults

Renal Osteodystrophy

The initial daily dose is 0.25 mcg of Rocaltrol. In patients with normal or only slightly reduced calcium levels, doses of 0.25 mcg every other day are sufficient. If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within 2 - 4 weeks, the daily dosage may be increased by 0.25 mcg at 2 - 4 week intervals. During this period, serum calcium levels should be determined at least twice weekly. Should the serum calcium levels rise to 1 mg/100ml (250 µmol/l) above normal (9 to 11 mg/100 ml or 2250 – 2750 µmol/l), or serum creatinine rises to > 120 µmol/l, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues. Most patients respond to between 0.5 mcg and 1.0 mcg daily. See section 4.5 for details of dose adjustments related to drug interactions.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

An oral Rocaltrol pulse therapy with an initial dosage of 0.1 mcg/kg/week split into two or three equal doses given at the end of the dialysis has been shown to be effective in patients with osteodystrophy refractory to continuous therapy. A maximum total cumulative dosage of 12 mcg per week should not be exceeded.

Post-menopausal Osteoporosis
The recommended dose of Rocaltrol is 0.25 mcg twice daily.

Serum calcium and creatinine levels should be determined at 1, 3 and 6 months and at 6 monthly intervals thereafter.

Elderly
Clinical experience with Rocaltrol in elderly patients indicates that the dosage recommended for use in younger adults may be given without apparent ill-consequence.

Paediatric Population
The safety and efficacy of calcitriol capsules in children have not been sufficiently investigated to enable dosing recommendations. Limited data are available for the use of calcitriol capsules in paediatric patients.

Method of administration
Rocaltrol capsules are for oral administration only.

4.3 Contraindications
Rocaltrol is contraindicated:

- in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the excipients listed in section 6.1
- in all diseases associated with hypercalcaemia
- in patients with evidence of metastatic calcification
- if there is evidence of vitamin D toxicity.

4.4 Special warnings and precautions for use
There is a close correlation between treatment with calcitriol and the development of hypercalcaemia.

All other vitamin D compounds and their derivatives, including proprietary compounds or foodstuffs which may be "fortified" with vitamin D, should be withheld during treatment with Rocaltrol.

An abrupt increase in calcium intake as a result of changes in diet (e.g. increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcaemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognise the symptoms of hypercalcaemia.

As soon as the serum calcium levels rise to 1 mg/100 ml (250 µmol/l) above normal (9-11 mg/100 ml or 2250-2750 µmol/l), or serum creatinine rises to >120 µmol/l, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues (see section 4.2).

Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphataemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. In such cases, the plasma phosphate level should be maintained at the normal level (2-5 mg/100 ml or 0.65-1.62 mmol/l) by the oral administration of appropriate phosphate-binding agents and low phosphate diet.

The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2.

Patients with vitamin D-resistant rickets (familial hypophosphataemia) who are being treated with Rocaltrol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by Rocaltrol should be taken into account since this effect may modify the need for phosphate supplementation.

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with Rocaltrol, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from a long acting vitamin D preparation (e.g. ergocalciferol (vitamin D_2) or colecalciferol) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value, thereby increasing the risk of hypercalcaemia (see section 4.9).

Patients with normal renal function who are taking Rocaltrol should avoid dehydration. Adequate fluid intake should be maintained.

In patients with normal renal function, chronic hypercalcaemia may be associated with an increase in serum creatinine.

Rocaltrol capsules contain sorbitol

Rocaltrol contains 2.87 – 4.37 mg sorbitol in each 0.25 microgram capsule.
Rocaltrol contains 2.87 – 4.36 mg sorbitol in each 0.5 microgram capsule.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be considered.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

Dietary instructions, especially concerning calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcaemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias (see section 4.4).

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Laboratory Abnormalities
In patients with normal renal function, chronic hypercalcaemia may be associated with a blood creatinine increase.

Post Marketing
The number of adverse effects reported from clinical use of Rocaltrol over a period of 15 years in all indications is very low with each individual effect, including hypercalcaemia, occurring at a rate of 0.001 % or less.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Treatment of asymptomatic hypercalcaemia (see section 4.2).

Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with Rocaltrol may give rise to similar symptoms. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2 / dl^2. A high calcium level in the dialysate may contribute to the development of hypercalcaemia.

Acute symptoms of vitamin D intoxication: anorexia, headache, vomiting, constipation.

Chronic symptoms: dystrophy (weakness, loss of weight), sensory disturbances, possibly fever with thirst, polyuria, dehydration, apathy, arrested growth and urinary tract infections. Hypercalcaemia ensues, with metastatic calcification of the renal cortex, myocardium, lungs and pancreas.

The following measures should be considered in treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote faecal excretion. Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

Hypercalcaemia at higher levels (>3.2 mmol/L) may lead to renal insufficiency particularly if blood phosphate levels are normal or elevated due to impaired renal function.

Should hypercalcaemia occur following prolonged treatment, Rocaltrol should be discontinued until plasma calcium levels have returned to normal. A low-calcium diet will speed this reversal. Rocaltrol can then be restarted at a lower dose or given in the same dose but at less frequent intervals than previously.

In patients treated by intermittent haemodialysis, a low concentration of calcium in the dialysate may also be used. However, a high concentration of calcium in the dialysate may contribute to the development of hypercalcaemia.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues
ATC code: A11CC04

Calcitriol is the most active known form of vitamin D_3 in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol. In physiological amounts it augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation. The defective production of calcitriol in chronic renal failure contributes to the abnormalities of mineral metabolism found in that disorder.

The biological effects of calcitriol are mediated by the vitamin D receptor, a nuclear hormone receptor expressed in most cell types and functioning as a ligand-activated transcription factor that binds to DNA sites to modify the expression of target genes.

Rocaltrol is a synthetic preparation of calcitriol. Oral administration of Rocaltrol to patients with chronic renal failure compensates for impaired endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30 ml/min. Consequently, intestinal malabsorption of calcium and phosphate and the resulting hypocalcaemia are improved, thereby reversing the signs and symptoms of bone disease.
In patients with established post-menopausal osteoporosis, Rocaltrol increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.

The onset and reversal of the effects of Rocaltrol are more rapid than those of other compounds with vitamin D activity and adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily.

5.2 Pharmacokinetic properties

Absorption
Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1µg Rocaltrol in healthy subjects were found within 2-6 hours.

After a single oral dose of 0.5 mcg Rocaltrol in healthy subjects, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4 pg/ml to 60.0 ± 4.4 pg/ml after two hours, and then fell to 53.0 ± 6.9 after four hours, to 50.0 ± 7.0 after eight hours, to 44 ± 4.6 after twelve hours and to 41.5 ± 5.1 pg/ml after 24 hours.

Distribution
During transport in the blood at physiological concentrations, calcitriol is mostly bound to a specific vitamin D binding protein (DBP), but also, to a lesser degree, to lipoproteins and albumin. At higher blood calcitriol concentrations, DBP appears to become saturated, and increased binding to lipoproteins and albumin occurs.

Biotransformation
Calcitriol is hydroxylated and oxidised in the kidney and in the liver by a specific cytochrome P450 enzyme: CYP24A1.

Several metabolites with different degrees of vitamin D activity have been identified.

Elimination
The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours. However, the pharmacological effect of a single dose of calcitriol lasts at least 4 days. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range and up to 165 µg single oral dose. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

5.3 Preclinical safety data
Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20 ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80 ng/kg/day (8 times the usual human dosage) for up to 6 months produced moderate adverse effects; changes seen appeared to be primarily the result of prolonged hypercalcaemia.

Reproductive toxicity studies in rats indicated that oral doses up to 300 ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, multiple foetal abnormalities were observed in two litters at an oral maternally toxic dose of 300 ng/kg/day and one litter at 80 ng/kg/day, but not at 20 ng/kg/day (twice the usual human dose). Although there were no statistically significant differences between treated groups and controls in the numbers of litters or foetuses showing abnormalities, the possibility that these findings were due to calcitriol administration could not be discounted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Content
Butylhydroxyanisole E320
Butylhydroxytoluene E321
Medium-chain triglycerides

Shell
Gelatin
Glycerol
Karion 83 (Sorbitol E420, Mannitol E421, Hydrogenated hydrolysed starch)
Titanium dioxide E171
Iron oxide red E172
Iron oxide yellow E172

6.2 Incompatibilities
None.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package and keep the blisters in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container
PVC opaque blisters containing 100 capsules (5 strips of 20 capsules).

6.6 Special precautions for disposal
Not applicable.

Certificate Number: PP101702

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

7 MARKETING AUTHORISATION HOLDER

Atnahs Pharma UK Limited

Sovereign House

Miles Gray Road

Basildon

Essex

SS14 3FR

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 43252/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 January 2003

10 DATE OF REVISION OF THE TEXT

23/12/2020

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Magnesium-containing drugs (e.g. antacids) may cause hypermagnesaemia and should therefore not be taken during therapy with Rocaltrol by patients on chronic renal dialysis.
Since Rocaltrol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration (normal values: 2-5 mg/100 ml, or 0.65-1.62 mmol/l).

Patients with vitamin D-resistant rickets (familial hypophosphataemia) should continue their oral phosphate therapy. However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Bile acid sequestrants including cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Rocaltrol during pregnancy has not been established.

Supravalvular aortic stenosis has been produced in foetuses by near-fatal oral doses of vitamin D in pregnant rabbits. There is no evidence to suggest that vitamin D is teratogenic in humans even at very high doses. Rocaltrol should be used during pregnancy only if the benefits outweigh the potential risk to the foetus.

Breast-feeding
It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcaemia in the mother and for adverse reactions from Rocaltrol in nursing infants, mothers may breastfeed while taking Rocaltrol, provided that the serum calcium levels of the mother and infant are monitored.

4.7 Effects on ability to drive and use machines

On the basis of the pharmacodynamic profile of reported adverse events, this product is presumed to be safe or unlikely to adversely affect such activities.

4.8 Undesirable effects

The adverse reactions listed below reflect the experience from investigational studies of Rocaltrol, and the post-marketing experience.
The most commonly reported adverse reaction was hypercalcaemia.

The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Table 1 Summary of ADRs Occurring in Patients Receiving Rocaltrol® (calcitriol)

System Organ Class	Very common	Common	Uncommon	Not known
Immune System Disorders				Hypersensitivity, Urticaria
Metabolism and Nutrition Disorders	Hypercalcaemia		Decreased appetite	Polydipsia, Dehydration, Weight decreased
Psychiatric Disorders				Apathy, Psychiatric disturbances
Nervous System Disorders		Headache		Muscular weakness, Sensory disturbance, Somnolence
Cardiac Disorders				Cardiac arrhythmias
Gastrointestinal Disorders		Abdominal pain, Nausea	Vomiting	Constipation, Abdominal pain upper, Paralytic ileus
Skin and subcutaneous tissue disorders		Rash		Erythema, Pruritus
Musculoskeletal and Connective Tissue Disorders				Growth retardation
Renal and Urinary Disorders		Urinary tract infection		Polyuria, Nocturia
General disorders and administration site conditions				Calcinosis, Pyrexia, Thirst
Investigations			Blood creatinine increased	

Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcaemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcaemia) (see sections 4.2 and 4.4). Occasional acute symptoms include decreased appetite, headache, nausea, vomiting, abdominal pain or abdominal pain upper and constipation.

Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalisation of elevated serum calcium within a few days of treatment withdrawal, i.e. much faster than in treatment with vitamin D_3 preparations.

Chronic effects may include muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation and urinary tract infections.

In concurrent hypercalcaemia and hyperphosphataemia of > 6 mg/100 ml or > 1.9 mmol/l, calcinosis may occur; this can be seen radiographically.

Hypersensitivity reactions including rash, erythema, pruritus and urticaria may occur in susceptible individuals.

TRADUCCION REALIZADA POR Q.F MARIA SOLEDAD RIOS T

04-04.2021

ML
Servicios Notariales

Protocolo N°171/21
Destino: Chile

Yo, MICHAEL LIGHTOWLER, un notario público debidamente registrado en Inglaterra y Gales, CERTIFICO que Medicines and Healthcare Products Regulatory Agency en el Reino Unido me ha confirmado que el Certificado de Producto Farmacéutico N° PP10170212 de la cual el documento adjunto reproducido fotostáticamente es una copia verdadera que fue emitida por ellos en 10 de febrero de 2021

Firmado y sellado por mi en Brentwood, Essex England este día diceiocho de febrero de dos mil veintiuno.

(Firma)

APOSTILLA (Convenio de La Haya del 5 de Octubre de 1961)	
1. País: REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE	
El presente documento público	
2. Ha sido firmado por: Michael Lightowler	
3.quien actúa en calidad de Notario público	
4. y está revestido del sello/timbre de El mencionado notario público	
Certificado	
5. en Londres	**6. el** 22 febrero 2021
7. por Her Majesty´s Principal Secretary of State for Foreign, Commonwealth and Development Affairs	
8. Número APO-2247616	
9. Sello/timbre	**10. Firma** D.Brigden

Certificado número: PP10170212

AGENCIA REGULATORIA DE MEDICAMENTOS Y PRODUCTOS PARA EL CUIDADO DE LA SALUD

En representación del Departamento de Salud

CERTIFICADO DE UN PRODUCTO FARMACÉUTICO (1)

Este certificado conforma el formato recomendado por la Organización Mundial de la Salud
(Se adjuntan notas aclaratorias)

País exportador(que certifica): REINO UNIDO

País importador (que solicita): CHILE

1 Nombre y forma farmacéutica del producto:

A) En el Reino Unido-Rocaltrol 0,25 microgramos cápsulas, CÁPSULAS BLANDAS

B) En CHILE- Rocaltrol 0,25 microgramos cápsulas, CÁPSULAS BLANDAS

1.1 Ingrediente()s activo(s)(2) y cantidad(es) (3)por unidad de dosis:

Ingrediente Activo	**Cantidad por unidad de dosis**
CALCITRIOL	0,25 mcg

Para composición cualitativa completa, incluyendo excipientes, ver adjunto. (4)

1.2 ¿Está este producto autorizado para ser colocado en el mercado para uso en el país exportador?(5)

SI

1.3 ¿Está este producto actualmente en el mercado del país exportador?

SI

1.4 El producto no está en el mercado del país exportador debido a

N/A

(Excluyendo información adicional)

2A.1 Autorización del producto/Autorización de comercialización

Número(7): PL 43252/0028

Fecha de emisión: 07 septiembre 2020

2A.2 El nombre y dirección del titular de la autorización del producto/autorización de comercialización es:

Nombre: ATNAHS PHARMA UK LIMITED

Dirección: Sovereign House, Miles Gray Road, Basildon, Essex, SS14 3FR, REINO UNIDO

2A.3 Estado del titular de la autorización del producto/autorización de comercialización (8):

c) no está involucrado en la fabricación, envasado o etiquetado de la forma farmacéutica pero es responsable por la calidad y liberación del producto.

2A.3.1 Para las categorías b, c y d, los nombres y direcciones de los sitios de manufactura donde se fabrica la forma farmacéutica.(9)

Ver página adjunta para fabricantes/empacadores

2A.4 ¿Se adjunta el resumen básico de la aprobación? (10)

NO

2A.5 ¿La información adjunta del producto y oficialmente aprobada está completa y en consonancia con la licencia?

SI

2A.6 Solicitante del certificado, si es diferente del titular de la licencia (nombre y dirección).(12)

Nombre:

Dirección:

Sección 2B no está incluida debido a que el producto nominado en este certificado está autorizado en el RU(6)

(excluyendo la información adicional)

3. ¿Organiza la autoridad regulatoria inspecciones periódicas de la planta de manufactura en la cual la forma farmacéutica es producida?(14)

SI LA RESPUESTA ES NO O NO APLICABLE, PROCEDER A LA PREGUNTA 4

3.1 Periodicidad de las inspecciones de rutina (años)

3.2 ¿El fabricante de esta forma farmacéutica ha sido inspeccionado?

3.3 ¿Las instalaciones y operaciones cumplen con las BPM según lo recomendado por la Organización Mundial de la Salud? (15)

4 La información presentada por el solicitante satisface a la autoridad certificadora en todos los aspectos de la fabricación del producto incluyendo las Buenas Prácticas de Manufactura (BPM)? (16)

Si la respuesta es no, explique

Información adicional

NINGUNA

Dirección de la Autoridad Certificadora

La Agencia Reguladora de Medicamentos y productos para el Cuidado de la Salud

10 South Colonnade, Canary Wharf, London E14 4PU, Reino unido

Número de teléfono: +44(0)20 3080 6593

Nombre de la persona autorizada: Mahmoodullah Khan

Firma: FAVOR VER LA CARTA DE PRESENTACIÓN

Timbre y Fecha: 10 de febrero de 2021

Nombres y direcciones de fabricantes /empacadores (9)

Fabricantes

Nombre: CATALENT GERMANY EBERBACH GMBH

Dirección: STEINBEISSTRASSE 2, EBERBACH, D-69412, ALEMANIA

Excipiente	Modificadores
Butilhidroxitolueno	
Cadena media de triglicéridos	
Butilhidroxianisol	
Oxido de fierro amarillo E172	cápsula MN
Oxido de fierro amarillo E172	cápsula MX
Karion 83	cápsula MN
Karion 83	cápsula MX
Dióxido de titanio E171	cápsula MN
Dióxido de titanio E171	cápsula MX
Glicerol 85%	cápsula MN
Glicerol 85%	cápsula MX
Óxido de hierro rojo E172	cápsula MN
Óxido de hierro rojo E172	cápsula MX
Gelatina	cápsula MN
Gelatina	cápsula MX

Certificado Número PP101170212

Notas explicativas

1. Este certificado. El cuale s recomendado por la OMS, establece el estado del producto farmacéutico y del solicitante del certificado en el TU. Este es para un único producto solamente ya que las características e información n aprobada para diferentes formas farmacéuticas y diferentes presentaciones puede variar.

2. Cuando sea posible Denominaciones internacionales sin propietario (INNa) o denominaciones nacionales sin propietario han sido usadas.

3. La fórmula (composición completa) de la forma farmacéutica debería ser dada en el certificado o ser adjuntada.

4. Detalles de la composición cuantitativa son preferidos pero su provisión está sujeta al acuerdo del titular de la autorización de comercialización.

5. Cuando sea aplicable, adjuntar detalles de cualquier restricción aplicada a la venta, distribución o administración del producto que está especificado en la autorización de comercialización

6. Las secciones 2A y 2B son mutuamente excluyentes

7. Indicar cuando sea aplicable, si la autorización es provisional o si el producto no ha sido aún aprobado

8. Especificar si la persona responsable de colocar el producto en el mercado:
(a) fabrica la forma farmacéutica y es responsable de asegurar la calidad y liberar el producto
(b) Empaca y/o etiqueta la forma farmacéutica fabricada por otra compañía pero es responsable de asegurar la calidad y de liberar el producto
(c) No está involucrado en la fabricación , empaque o etiquetado de la forma farmacéutica pero es responsable de la calidad y liberación del producto
(d) No está involucrado en ninguna de las anteriores

9. Esta información es opcional y puede ser provista solamente con la autorización del titular de la autorización del producto o, en el caso de productos no registrados, del solicitante. La no completitud de esta sección indica que la parte interesada no ha autorizado la inclusión de esta información.

10. Esto se refiere al documento preparado por algunas autoridades regulatorias nacionales que resumen las bases técnicas sobre las cuales el producto ha sido autorizado. La Agencia Regulatoria de Medicamentos y Productos para el cuidado de la Salud no prepara tal documento.

11. Esto se refiere a la información del producto aprobada por la Agencia Regulatoria de Medicamentos y Productos para el cuidado de la Salud como Resumen de características del producto.

12. En esta circunstancias un permiso para emitir el certificado es requerido a partir del titular de la autorización de comercialización. Este permiso debe ser provisto a la Agencia Regulatoria de Medicamentos y Productos para el cuidado de la Salud por el solicitante.

13. Por favor indicar la razón que el solicitante ha provisto para no solicitar el registro:
a) el producto ha sido desarrollado exclusivamente para el tratamiento de condiciones - particularmente enfermedades tropicales. No endémicas en RU.
b) el producto ha sido reformulado con vista a mejorar su estabilidad bajo condiciones tropicales
c) el producto ha sido reformulado para excluir excipientes no aprobados para uso en medicamentos en el RU
d) el producto ha sido reformulado cumplir un limite de dosificación diferente para un ingrediente activo
e) este tipo de producto no requiere autorización de comercialización en el RU
f) cualquier otra razón

14. "Si" significa que la Agencia Regulatoria de Medicamentos y Productos para el cuidado de la Salud organiza inspecciones periódicas de la planta de fabricación en la cual el producto es producido. "No" significa que la fabricación está tomando lugar en un país diferente del RU y las inspecciones no son llevadas a cabo por ninguna autoridad regulatoria. "No aplicable" significa que la fabricación está tomado lugar en un país distinto que el RU y la inspección es conducida bajo la égida del país de manufactura.

15. Los requerimientos de Buenas Prácticas de Manufactura y Control de Calidad de Medicamentosa que se refiere el certificado son aquellas incluidas en el trigésimo segundo informe del Comité de Expertos sobre Especificaciones de preparaciones farmacéuticas (OMS Informe Técnico Series N° 823, 1992, Anexo 1). Recomendaciones específicamente aplicables a productos biológicos han sido formuladas por el Comité de Expertos de la OMS sobre Estandarización Biológica (OMS Informe Técnico Series N° 822, 1992, Anexo 1).

16. Esta sección es para ser completada cuando el titular de la autorización del producto o solicitante conforma el estatus (b), (c) o (d) según se describe en la nota 8 arriba. Esto es de particular importancia cuando contratantes extranjeros están involucrados en la fabricación del producto. En estas circunstancias el solicitante debe proveer a la autoridad certificadora con la información para identificar a las partes contratantes responsables de cada etapa de manufactura del producto terminado y la extensión y naturaleza de cualquier control ejercido sobre cada una de las partes.