Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Calcifediol Faes 72 microgram soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 72 micrograms of calcifediol as calcifediol monohydrate.

Excipients with known effect:
Each soft capsule contains 1 mg of ethanol, 10 mg of sorbitol as sorbitol liquid (non-crystallising) (E 420) and 0.2 mg of Allura red (E 129).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule.
Pink oval soft gelatin capsule with a longitudinal joint. Dimensions: 11 mm by 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of vitamin D deficiency (i.e., 25(OH)D levels < 25 nmol/L) in adults

Prevention of vitamin D deficiency in adults with identified risks (see section 5.1).

As adjuvant for the specific treatment of osteoporosis in adult patients with vitamin D deficiency or at risk of vitamin D deficiency.

4.2 Posology and method of administration

Posology
The dose, frequency and duration of the treatment will be determined by the prescriber taking into account the plasma levels of 25(OH)D, type and condition of the patient and other comorbidities such as obesity, malabsorption syndrome, treatment with corticosteroids.

- Treatment of vitamin D deficiency and prevention of vitamin D deficiency in patients with identified risks: one capsule (75 microgram of calcifediol monohydrate) once a week.
- As adjuvant for the specific treatment of osteoporosis: one capsule (75 microgram of calcifediol monohydrate) once a week.

Calcifediol Faes should not be administered with a daily frequency.

Serum concentrations of 25(OH)D should be monitored after initiation of the treatment, usually after 3-4 months and the treatment should be re-evaluated accordingly.

The patient's dietary habits should be carefully evaluated and artificially added vitamin D content of certain food types should be taken into consideration. In applicable cases, national posology recommendations in treatment of vitamin D deficiency and prevention can be considered.

Renal Impairment

Use of Calcifediol Faes in patients with chronic kidney disease should be accompanied by periodic monitoring of serum calcium and phosphorus, and hypercalcemia prevention (see section 4.4).

Hepatic Impairment
No dosage adjustment is required for hepatic impaired patients.

Elderly population
No dosage adjustment is required for elderly patients.

Paediatric population
The safety and efficacy of [nationally to be completed] in children and adolescent have not yet been established. No data are available.

Method of administration
Oral administration.
Calcifediol soft gelatin capsules can be administered with or without a meal, swallowed whole and could be taken with water, milk or juice.

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
- Hypercalcemia (serum calcium > 2.6 mmol/L) or hypercalciuria
- Calcium lithiasis
- Hypervitaminosis D

4.4 Special warnings and precautions for use

Hypercalcemia and hyperphosphatemia
To obtain an adequate clinical response to oral administration of calcifediol monohydrate, an appropriate dietary calcium intake is also required. Therefore, to control the therapeutic effects, the following parameters should be monitored, in addition to 25(OH)D: serum calcium, phosphorus and alkaline phosphatase as well as urinary calcium and phosphorus in 24 hours. A decrease in serum levels of alkaline phosphatase normally precedes the onset of hypercalcemia. Once parameters are stabilized and the patient is under maintenance treatment, the above-mentioned determinations should be performed regularly, especially for serum levels of 25(OH)D and calcium.

Renal impairment:
To be administered with caution. Use of this drug in patients with chronic kidney disease should be accompanied by periodic monitoring of serum calcium and phosphorus, and hypercalcemia prevention. Transformation to calcitriol takes place in the kidney; thus, in case of severe renal impairment (creatinine clearance of less than 30 mL/min) a very significant reduction in the pharmacological effects may occur.

Heart failure:
Special caution is required. The patient's serum calcium should be monitored constantly, especially in patients on digitalis, because hypercalcemia may occur and arrhythmias appear. Twice-a- week determinations are recommended at the beginning of treatment.

Hypoparathyroidism:
1-alpha-hydroxylase is activated by parathyroid hormone. As a result, in case of parathyroid insufficiency the activity of calcifediol may decrease.

Prolonged immobilization:
In patients with prolonged immobilization, it may be necessary to reduce the dose in order to avoid hypercalcemia.

Sarcoidosis, tuberculosis, or other granulomatous diseases:
To be administered with caution since these conditions lead to a greater sensitivity to the effect of calcifediol monohydrate as well as to an increase of the risk of adverse effects at doses lower than the recommended dose. It is necessary to monitor serum and urinary calcium concentrations in these patients.

Interference with laboratory tests:

Patients should be warned that this drug contains a component that can alter the results of laboratory tests:
Determination of cholesterol: calcifediol may interfere with Zlatkis-Zak method, leading to false increases in serum cholesterol levels.

Warnings on excipients
This medicine contains 1 mg of alcohol (ethanol) in each soft capsule. The amount in one capsule of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains 10 mg of sorbitol as sorbitol liquid (non-crystallising) in each soft capsule.
This medicine contains Allura red (E 129) which may cause allergic reactions.

International Units (IU) should not be used for determination of the dose of calcifediol as this could lead to overdosing. Instead, the dosing recommendation in section 4.2 should be followed.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs that might increase 25(OH)D levels:

- Cytochrome P-450 enzymes inhibitors: Drugs that inhibit cytochrome P-450 (e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may inhibit CYP27B1 (also known as 1α-hydroxylase), which metabolizes calcifediol to its active form (1,25-dihydroxyvitamin D3), and CYP24A1, which metabolizes both calcifediol and calcitriol to inactive metabolites, thereby altering serum calcifediol concentrations.
- Isoniazid may increase 25(OH)D levels due to inhibition of its metabolic activation.

Drugs that might decrease 25(OH)D levels:

- Phenytoin, phenobarbital, primidone, carbamazepine, diphenylhydantoin and other enzyme inducers (such as glucocorticoids, antineoplastic drugs, and antiretrovirals): enzyme inducers may reduce plasma concentrations of calcifediol and inhibit its effects by inducing its hepatic metabolism. For this reason, it is generally recommended to monitor plasma 25-OH-D levels when calcifediol is administered with antiepileptics that are CYP3A4 inducers in order to consider supplementation.
- Drugs that decrease the absorption of calcifediol such as cholestyramine, colestipol or orlistat, which can result in decreased effects. It is recommended to space doses of these medicines and calcifediol monohydrate at least 2 hours.
- Paraffin and mineral oil: Due to liposolubility of calcifediol, the product can dissolve in paraffin and intestinal absorption may decrease. Using other types of laxatives or at least spacing doses is recommended.
- Rifampicin may reduce the effectiveness of calcifediol due to induction of hepatic enzymes.

Drugs that might alter calcium/phosphate levels.

- Thiazide diuretics: Co-administration of a thiazide diuretic (hydrochlorothiazide) with calcifediol monohydrate in patients with hypoparathyroidism may lead to hypercalcemia, which may be temporary or require the interruption of the treatment with calcifediol monohydrate.
- Some antibiotics, such as penicillin, neomycin and chloramphenicol can increase calcium absorption.
- Phosphate-binding agents such as magnesium salts: Since calcifediol monohydrate has an effect on phosphate transport in the intestine, kidney and bone, hypermagnesemia may occur. The dosage of agents that bind to phosphate shall be adjusted according to phosphate concentrations in serum.
- Verapamil: Some studies show potential inhibition of antianginal action, due to antagonism of their actions.
- Vitamin D: Co-administration of any vitamin D analogue should be avoided as additive effects and hypercalcemia can occur.
- Calcium supplements: Uncontrolled intake of additional preparations containing calcium should be avoided.
- Corticosteroids: They counteract the effects of vitamin D analogue drugs such as calcifediol.

Cardiac glycosides: Calcifediol can cause hypercalcemia, which can, in turn, enhance the inotropic effects of digoxin and its toxicity, producing cardiac arrhythmias.

Interaction with food and drinks
Food supplemented with vitamin D should be taken into account, since additive effects may occur.

4.6 Fertility, pregnancy and lactation

Pregnancy

The dose of this medicinal product is not recommended during pregnancy and breast-feeding. The recommended daily intake level for vitamin D3 (cholecalciferol, the precursor of calcifediol), during pregnancy and lactation follows national guidelines and is around 600 I.U. (corresponding to 15 microgram cholecalciferol) and should not exceed 2000 I.U. (corresponding to 50 microgram cholecalciferol).
There is no or limited amount of data from the use of calcifediol (syn. calcidiol, the metabolite of cholecalciferol) in pregnant women. Calcifediol monohydrate should not be used during pregnancy unless the clinical condition of the woman requires treatment with calcifediol and the potential benefits to the mother outweigh the potential risks to the fetus.
Studies in animals have shown reproductive toxicity (see section 5.3).
There is no indication that calcifediol monohydrate is teratogenic in humans at therapeutic doses. Overdose of calcifediol monohydrate has to be avoided during pregnancy, as prolonged hypercalcaemia can lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

Breast-feeding
Calcifediol is excreted into breast milk. A risk to the newborn/child cannot be excluded. This should be considered when giving additional vitamin D to the breastfed child.

Fertility
It is unknown whether calcifediol has an effect on human fertility. Studies in rats have not shown impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Calcifediol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Frequencies are assigned as follows: 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) and not known (cannot be estimated from the available data).

The adverse effects related to this vitamin D analogue are associated to increased levels of calcium when an excessive intake of this medicine may occur i.e., associated with overdose or prolonged treatment. The doses of calcifediol monohydrate required for hypervitaminosis vary considerably from one subject to another. The adverse reactions due to increased levels of calcium can occur initially or at a later stage (see section 4.9 Overdose).

The immune system
Unknown frequency (cannot be calculated from the available data): Hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, rash, localised oedema / local swelling, and erythema).

Metabolism and nutrition disorders:
Unknown frequency (cannot be calculated from the available data): Hypercalcaemia and hypercalciuria.

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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms:
Administration of calcifediol monohydrate in high doses or for long periods of time may cause hypercalcemia, hypercalciuria, hyperphosphatemia and renal failure. As early symptoms of overdose, weakness, fatigue, drowsiness, headache, anorexia, dry

mouth, metallic taste, nausea, vomiting, abdominal cramps, polyuria, polydipsia, nocturia, constipation or diarrhoea, dizziness, tinnitus, ataxia, rash, hypotonia (especially in children), muscle or bone pain and irritability may appear.

Among later symptoms of hypercalcemia, the following are included: runny nose, itching, decreased libido, nephrocalcinosis, renal failure, osteoporosis in adults, growth retardation in children, weight loss, anaemia, conjunctivitis with calcification, photophobia, pancreatitis, elevated blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, increased transaminases (SGOT and SGPT), hyperthermia, generalized vascular calcification, convulsions, soft tissue calcification. Rarely, patients may develop hypertension or psychotic symptoms; serum alkaline phosphatase may decrease; electrolyte imbalances together with moderate acidosis can lead to cardiac arrhythmias.

In the most serious cases, where serum calcium exceeds 3 mmol/L, syncope, metabolic acidosis and coma may happen. Although symptoms of overdose are usually reversible an overdose might lead to kidney or heart failure.

It is accepted that serum levels of 25-OH-cholecalciferol above 375 nmol/L may be associated with an increased incidence of adverse effects.
Increased calcium, phosphate, albumin, and urea nitrogen in blood as well as cholesterol and blood transaminases are typical of this kind of overdose.

Treatment:
Treatment of Calcifediol Faes overdose consists of:

1. Withdrawal of treatment (with Calcifediol Faes) and with any calcium supplement being administered.
2. Follow a diet low in calcium. Administration of large volumes of liquids, both orally and parenterally, is advisable to increase calcium excretion. If necessary, administer steroids and induced forced diuresis with loop diuretics such as furosemide.
3. If intake has occurred in the previous 2 hours, gastric emptying and forced emesis are advisable. If calcifediol monohydrate has already passed through the stomach, a laxative (paraffin or mineral oil) can be administered. If calcifediol monohydrate has already been absorbed, hemodialysis or peritoneal dialysis with a dialysis solution free of calcium can be performed.

Hypercalcemia derived from prolonged administration of calcifediol persists for approximately 4 weeks after discontinuation of treatment. Signs and symptoms of hypercalcemia are usually reversible. However, calcification due to long-term hypercalcemia can cause serious kidney or heart failure and death.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vitamin D and analogues, ATC code: A11CC06

Mechanism of action
Vitamin D has two main forms: D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is synthesized in the skin by exposure to sunlight (ultraviolet radiation) and, to a lesser extent, is obtained from the diet. Vitamin D3 (or cholecalciferol) must undergo a two-step metabolic process to be active; the first step occurs in the microsomal fraction of the liver where Vitamin D3 is hydroxylated at position 25 giving rise to 25-hydroxycholecalciferol, calcifediol or calcidiol. The second step takes place in the kidney where 1,25-dihydroxycholecalciferol or calcitriol is formed due to the activity of enzyme 25-hydroxycholecalciferol 1alpha-hydroxylase. The conversion to 1,25-dihydroxycholecalciferol in the kidneys is regulated, among others, by its own concentration, by parathyroid hormone (PTH) and by serum calcium and phosphate concentration. Other metabolites with unknown function exist. 1,25-dihydroxycholecalciferol is transported from the kidney to target tissues (intestine, bone and parathyroid gland, among others) by binding to specific plasma proteins.

Pharmacodynamic effects
Active vitamin D increases absorption of calcium and phosphorus in the intestine and improves normal bone formation and mineralization and acts on different levels:
Intestine: Vitamin D enhances absorption of calcium and phosphorus in the small intestine.
Bone: calcitriol enhances bone formation by increasing levels of calcium and phosphate and stimulates action of osteoblasts.
Kidney: calcitriol enhances tubular reabsorption of calcium.
Parathyroid glands: vitamin D inhibits the secretion of parathyroid hormone.

Clinical efficacy and safety

The efficacy and safety of calcifediol monohydrate 75, 100 and 125 micrograms soft capsules were evaluated in a randomized, double-blind, double dummy, controlled, multicenter, dose-ranging phase II/III study in general population with serum 25(OH)D levels <50 nmol/L. Based on 25(OH)D baseline levels at Visit 1, subjects were allocated to Cohort 1 (25(OH)D: >10 to <20 ng/mL) or to Cohort 2 (25(OH)D: ≤ 10 ng/mL). Subjects of Cohort 1 were randomized to be treated with Placebo, calcifediol monohydrate 75 mcg/week or calcifediol monohydrate 100 mcg/week. Subjects of Cohort 2 were randomized to be treated with Placebo, calcifediol monohydrate 100 mcg/week or calcifediol monohydrate 125 mcg/week.

674 subjects were randomized and 636 completed the main phase of the study (4 months): 376 subjects in cohort 1 and 260 subjects in cohort 2.

The percentage of responders in cohort 1 (25(OH)D: >10 to <20 ng/mL) and cohort 2 (25(OH)D: ≤ 10 ng/mL) at 16 weeks (primary endpoint) is presented in the following tables.

Response Rates at Visit 4 (16 weeks) – Cohort 1 (N = 388)

25-OH-D level	Placebo (N = 73)	Calcifediol monohydrate 75 mcg (N = 156)	Calcifediol monohydrate 100 mcg (N = 159)
≥ 30 ng/mL, *n* (%)	8 (11.0%)	116 (74.4%)	143 (89.9%)
≥ 20 ng/mL, *n* (%)	37 (50.7%)	146 (93.6%)	157 (98.7%)

Response Rates at Visit 4 (16 weeks) – Cohort 2 (N =269)

25-OH-D level	Placebo (N = 55)	Calcifediol monohydrate 100 mcg (N = 104)	Calcifediol monohydrate 125 mcg (N = 110)
≥ 30 ng/mL, *n* (%)	0 (0.0%)	51 (49.0%)	84 (76.4%)
≥ 20 ng/mL, *n* (%)	4 (7.3%)	96 (92.3%)	101 (91.8%)

Superiority of calcifediol groups vs. placebo was shown in both cohorts for both thresholds (20 and 30 ng/mL) at 16 weeks (primary endpoint) ($p < 0.0001$ for each hypothesis). In addition, superiority was shown for the higher calcifediol dose vs. the lower calcifediol dose in both cohorts for a 25(OH)D response level of ≥ 30 ng/mL ($P = 0.0002$ for Cohort 1 and $P < 0.0001$ for Cohort 2).

The highest levels of 25(OH)D with calcifediol monohydrate 75, 100 and 125 micrograms soft capsules were achieved after 6 months of treatment, indicating that there is no cumulative effect.

The treatment with the three tested doses of calcifediol monohydrate 75 mcg, 100 mcg and 125 mcg was safe and well tolerated by the subjects during the 52-week treatment period, being comparable to placebo.

5.2 Pharmacokinetic properties

Absorption

Calcifediol is well absorbed in the intestine, approximately 75-80% is absorbed through this process.

Following oral administration of calcifediol, the maximum serum concentration of 25-OH-cholecalciferol is reached after 4 hours approximately.

Distribution

Calcifediol circulates in the blood bound to a specific α-globulin (DBP). Is stored in adipose tissue and muscle for prolonged periods. Storage in adipose tissue is lower than for vitamin D, due to its lower lipophilicity.

Metabolism and Biotransformation

Production of calcitriol from calcifediol is catalysed by the 1-alpha-hydroxylase enzyme, CYP27B1, located in the kidney and in all vitamin D-responsive tissues. CYP24A1, located in these tissues, catabolises both calcifediol and calcitriol to inactive metabolites.

Elimination

Calcifediol half-life is around 12 to 21 days and it is primarily excreted in the bile.

5.3 Preclinical safety data

Repeat-dose toxicity
Effects in non-clinical repeat-dose toxicity studies with calcifediol were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating such toxicity is only likely to occur in chronic overdosage where hypercalcaemia could result.

Genotoxicity and carcinogenicity
No carcinogenicity and genotoxicity studies have been conducted with calcifediol. However, carcinogenic or mutagenic effects have not been reported with vitamin D3.

Reproductive toxicity
Embryo-foetal-development studies in rabbits have shown that oral administration of calcifediol during organogenesis induces teratogenicity only at doses well above the maximum human equivalent dose (MHED). In rats, no effects in embryo-foetal studies have been observed at doses clearly superior the MHED.
Calcifediol has not been shown to have effects on fertility in rats at doses considered sufficiently in excess of the MHED.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous
Medium chain triglycerides
Gelatin
Glycerol
Sorbitol, liquid (non-crystallising) (E 420)
Titanium dioxide (E 171)
Allura red (E 129)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

This medicine is packed in PVC/PVDC//Alu blisters containing 4, 12, 16, 24 or 48 capsules. Blisters are packed in a cardboard box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Leioa

48940 Bizkaia

8 MARKETING AUTHORISATION NUMBER

PA0864/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd August 2024

10 DATE OF REVISION OF THE TEXT

September 2024