# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Cadelius 600 mg / 2000 IU orodispersible tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 1500 mg calcium carbonate (equivalent to 600 mg calcium) and 2,000 IU (50 micrograms) cholecalciferol (vitamin $D_3$).

Excipients with known effect
Each orodispersible tablet contains 44.32 mg lactose (as lactose monohydrate), 8.67 mg aspartame (E951), 7.6 mg sucrose and 1.5 mg partially hydrogenated soybean oil.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Orodispersible tablet.

Round and flat, white or almost white, orodispersible tablet with a diameter of 19 mm.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cadeliusis indicated in adults for treatment of calcium and vitamin D deficiency.

### 4.2 Posology and method of administration

Posology
*Adults and elderly*
One orodispersible tablet daily (corresponding to 600 mg of calcium and 2,000 IU of vitamin D3).
Alternatively, national posology recommendations in treatment of vitamin D deficiency can be followed.
After first month, lower doses may be considered, dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment.
The dose of vitamin D depends on the severity of the disease, desirable serum levels of 25-hydroxycholecalciferol (25(OH)D) and patient´s response to treatment.
The amount of calcium in Cadelius is less than the usually recommended daily intake. Cadelius is therefore to be used primarily by patients with need of vitamin D substitution but with a dietary intake of calcium of 500–1,000 mg daily.
Patient's dietary intake of calcium should be estimated by their prescriber. Mono preparation is necessary for dose adjustment

*Paediatric population*
Cadelius is contraindicated for use in children and adolescents aged 0 – 18 years (see section 4.3).

*Dosage in renal impairment*
Cadelius should be used with caution in patients with impairment of renal function (see section 4.4).
Cadelius is contraindicated for use in patients with severe renal impairment (see section 4.3 and 4.4).

Method of administration
Oral use.

Tablets should be sucked and not swallowed whole. They should be taken preferably after meals.

**4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Any disease and/or condition resulting in hypercalcaemia or hypercalciuria (e.g. myeloma, bone metastases, primary hyperparathyroidism, prolonged immobilisation accompanied by hypercalciuria and/or hypercalcaemia).
- Nephrolithiasis.
- Nephrocalcinosis.
- Hypervitaminosis D.
- Severe renal impairment or renal failure. (See section 4.4)
- Pregnancy.
- Pediatric population
- Allergy to peanut or soya.

**4.4 Special warnings and precautions for use**

Cadelius should be prescribed with caution to patients suffering from sarcoidosis due to risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to calcium content in serum and urine.

During long-term treatment, calcium serum levels should be supervised and renal function should be monitored by measurements of serum creatinine. Monitoring is especially important in patients on concomitant treatment with cardiac glycosides or thiazide diuretics (see section 4.5) and in patients with a high tendency to calculus formation. In case of hypercalciuria (exceeding 300 mg or 7.5 mmol/24 hours) or signs of impaired renal function the dose should be reduced or the treatment discontinued.

Vitamin D should be used with caution in patients with renal function impairment and its effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally, and other forms of vitamin D should be used (see sections 4.3 and 4.8).

Cadelius orodispersible tablets should be used cautiously in immobilised patients with osteoporosis due to increased risk of hypercalcaemia.

The content in vitamin D (2,000 IU) within Cadelius should be considered when prescribing other medicinal products or food supplements containing vitamin D.

Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Co-administration with tetracyclines or quinolones is usually not recommended and should be done with caution (see section 4.5).

The calcium and alkali intake from other sources (food, dietary supplements and other drugs) should be taken into consideration when prescribing Cadelius. If high doses of calcium are taken concomitantly with absorbable alkali agents (like carbonates) this could lead to milk-alkali syndrome (Burnett-Syndrome), i.e. hypercalcaemia, metabolic alkalosis, renal failure and soft tissue calcification. High doses of calcium or vitamin D should only be given under close medical supervision. In these cases, frequent monitoring of the calcium level in the serum and urine is necessary.

<u>Warnings on excipients</u>
This medicinal product may be harmful to people with phenylketonuria, since it contains aspartame, source of phenylalanine.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine, since it contains lactose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine, since it contains sucrose.

Patients allergic to peanuts or soya must not use this medicine, since it contains soya oil (see section 4.3).

Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

**4.5 Interaction with other medicinal products and other forms of interaction**

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium levels should be regularly monitored during concomitant use of thiazide diuretics (see section 4.4).

Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin $D_3$ since its metabolism increases.

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of Cadelius.

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium and vitamin D. Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels (see section 4.4).

The efficacy of levothyroxine can be reduced by the concurrent use of calcium, due to decreased levothyroxine absorption. Administration of calcium and levothyroxine should be separated by at least four hours.

If a bisphosphonate is used concomitantly, it should be administered at least three hours before the intake of Cadelius, since gastrointestinal absorption may be reduced.

Calcium salts may decrease the absorption of iron, zinc or strontium ranelate. Consequently, these should be taken with a 2-hour difference from the intake of Cadelius.

Calcium may also reduce absorption of sodium fluoride, and such preparation should be administered at least three hours before the intake of Cadelius.

Simultaneous treatment with orlistat, ion-exchange resins such as colestyramine, or laxatives such as paraffin oil, may reduce the gastrointestinal absorption of vitamin D. Therefore, a time interval as long as possible between the intakes is recommended.

Calcium carbonate may interfere with the absorption of concomitantly administered tetracyclines. For this reason, medicinal products containing tetracyclines should be administered at least two hours before or four to six hours after oral intake of calcium (see section 4.4).

The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken two hours before or six hours after intake of calcium (see section 4.4).

Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. Patients should not take calcium products within two hours after eating food high in oxalic and/or phytic acid.

**4.6 Fertility, pregnancy and lactation**

Pregnancy
Studies in animals have shown reproductive toxicity of high doses of vitamin D (see section 5.3). In pregnant women, overdoses of calcium and vitamin D should be avoided as permanent hypercalcaemia has been related to adverse effects on the developing foetus.

Cadelius should not be used during pregnancy.

Breastfeeding
Cadelius can be used during breast-feeding. Calcium and vitamin $D_3$ pass into breast milk. This should be considered when giving additional vitamin D to the child. Due to the high vitamin D3 content of Cadelius a risk to the infant cannot be excluded. Such supplementation does not replace the administration of vitamin D in newborns.
A decision must be made whether to discontinue breast-feeding or to discontinue Cadelius therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Alternatively, treatment may be switched to other calcium and vitamin D3 containing medicinal products containing vitamin D3 in lower strength.

Fertility
Calcium and vitamin D have no noxious effects on fertility at the recommended dosages (see section 5.3).

**4.7 Effects on ability to drive and use machines**

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

**4.8 Undesirable effects**

Frequency 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) and not known (cannot be estimated from available data).

| **MedDRa system/organ classification** | **MedDRa frequency convention** | | |
|---|---|---|---|
| | **Uncommon** | **Rare** | **Not known** |
| Immune system disorders | | | hypersensitivity reactions such as angioedema or laryngeal edema. |
| Metabolism and nutrition disorders | hypercalcaemia; hypercalciuria. | | |
| Gastrointestinal disorders | | constipation; flatulence; nausea; abdominal pain; diarrhoea; abdominal distension. | |
| Skin and subcutaneous tissue disorders | | pruritus; rash; urticaria. | |

Other special population(s)
Patients with mild to moderate renal impairment: potential risk of hyperphosphatemia, nephrolithiasis and nephrocalcinosis (see sections 4.3 and 4.4).

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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

**4.9 Overdose**

Overdose can lead to hypervitaminosis and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and, in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

Treatment of hypercalcaemia: the treatment with calcium and vitamin D must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, and cardiac glycosides must also be discontinued. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: calcium, combinations with vitamin D and/or other drugs, ATC code: A12AX.

Cadelius is a fixed combination of calcium and vitamin D3. Vitamin D3 is involved in calcium-phosphorus metabolism. It allows the active absorption of calcium and phosphorus from the intestine and their uptake by bone. Supplementation with calcium and vitamin D3 corrects vitamin D and calcium deficiency.

**5.2 Pharmacokinetic properties**

Absorption
*Calcium*
The amount of calcium absorbed through the gastrointestinal tract is approximately 30 % of the ingested dose.

*Cholecalciferol*
Vitamin D is absorbed in the small intestine.

Distribution and biotransformation
*Calcium*
99 % of the calcium in the body is concentrated in the mineral component of bones and teeth. The remaining 1 % is present in the intra- and extracellular fluids. About 50 % of the total blood-calcium content is in the physiologically active ionised form with approximately 10 % being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin. The bioavailability of calcium can be slightly increased by concomitant intake of food.

*Cholecalciferol*
Cholecalciferol and its metabolites circulate in blood bound to a specific globulin. Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25-dihydroxycholecalciferol. 1,25-dihydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Not metabolised vitamin D is stored in adipose and muscle tissues.

Elimination
*Calcium*
Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

*Cholecalciferol*
Vitamin D is excreted in faeces and urine.

**5.3 Preclinical safety data**

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies treated with Vitamin D (4-15 times the human dose).

There is no further relevant information on the safety assessment in addition to what is stated in other parts of this summary of product characteristics.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Maltodextrin
Anhydrous citric acid (E330)
Low-substituted hydroxypropyl cellulose (E463)
Lactose monohydrate
Stearic acid Aspartame (E951)
Sucrose
Gelatin
Orange flavouring agent (containing flavouring preparations, natural flavouring substances, maltodextrin and dextrin)
Maize starch
Partially hydrogenated soybean oil
all-rac-α-tocopherol (E307)
Silicon dioxide

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years.
Cadelius should be used within 30 days after the container is opened.

**6.4 Special precautions for storage**

No special storage conditions.

Store in the original package in order to protect from light. Keep container tightly closed in order to protect from moisture.

**6.5 Nature and contents of container**

High density polyethylene bottle closed with a polyethylene cap which contains a silica gel tab as desiccant.

Contents of container
30 orodispersible tablets.
Multipacks contain 60 (2 packs of 30) orodispersible tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

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

**7 MARKETING AUTHORISATION HOLDER**

Italfarmaco S.A.
C/ San Rafael 3
Pol. Ind. Alcobendas
Madrid
28108
Spain

**8 MARKETING AUTHORISATION NUMBER**

PA2102/002/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25th August 2020

**10 DATE OF REVISION OF THE TEXT**

May 2023