# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Colecalciferol Aristo 20,000 IU soft capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:
500 microgram colecalciferol (vitamin $D_3$ equivalent to 20,000 IU).

Excipients with known effect:
Each capsule contains 16.5 milligrams of sorbitol.

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Soft capsule

Light yellow coloured clear transparent round shaped gelatin capsule.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Initial treatment of symptomatic vitamin D deficiency in adults.

### 4.2 Posology and method of administration

Posology

Recommended dose: One capsule (20,000 IU) weekly.
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/or the patient´s response to treatment.

Alternatively, national posology recommendations in treatment of vitamin D deficiency can be followed.

Special populations:

*Dosage in hepatic impairment*
No dose adjustment is required.

*Dosage in renal impairment*
Colecalciferol Aristo Capsulesmust not be used in patients with severe renal impairment (see section 4.3).

*Paediatric population*
Colecalciferol Aristo Capsules are not recommended.

Method of administration

*Oral*

The capsules should be swallowed whole (not chewed) with water.

Patients should be advised to take Colecalciferol Aristo Capsules preferably with meal (see section 5.2 Pharmacokinetic properties -"Absorption").

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Diseases or conditions resulting in hypercalcemia and / or hypercalciuria.
- Pseudohypoparathyroidism.
- Hypervitaminosis D.
- Nephrolithiasis.
- Nephrocalcinosis.
- Severe renal impairment.

**4.4 Special warnings and precautions for use**

Colecalciferol Aristo Capsules should be used with caution in patients with impaired renal function, impaired renal calcium and phosphate excretion, a tendency to form calcium-containing kidney stones (calculi), treatment with benzothiadiazine derivatives and in immobilized patients with caution (risk of hypercalcemia, hypercalciuria). In these patients, the calcium levels in plasma and urine are monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol may not be metabolised normally and Colecalciferol Aristo Capsules are contraindicated (see section 4.3).

The active metabolite of vitamin $D_3$ (1, 25-dihydroxycholecalciferol) may affect the phosphate balance. Therefore, in conditions with increased phosphate levels, treatment with a phosphate binder may be considered. Caution should be taken in patients who are suffering from sarcoidosis or other granulomatous disorders because of the risk of increased conversion of vitamin D to its active metabolite. These patients should be monitored with regard to the calcium content in serum and urine.

During treatment with Colecalciferol Aristo Capsules in patients with renal insufficiency serum and urine levels of calcium should be monitored and the renal function monitored by measurement of serum creatinine.

Allowances should be made for vitamin D supplements from other sources. Vitamin D is fat soluble and may accumulate in the body. This may cause toxic effects in case of overdose and long term treatment with excessive doses. Recommended treatment should therefore not be exceeded.

In case of hypercalcaemia with urine calcium content levels of 7.5 mmol/24 hours (300 mg/24 hours) the treatment should be discontinued (see section 4.3).

Caution is required in patients receiving treatment for cardiovascular disease (see Section 4.5 – cardiac glycosides including digitalis or diuretics).

In patients with renal insufficiency treated with Colecalciferol Aristo Capsules close medical supervision is required to monitor the calcium and phosphate balance.

Oral administration of high-dose vitamin D (500,000 IU by single annual bolus) was reported to result in an increased risk of fractures in elderly subjects, with the greatest increase occurring during the first 3 months after dosing.

The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

Medical supervision is required whilst on treatment to prevent hypercalcaemia. In such cases, the calcium levels monitored in serum and urine (see above).

<u>Paediatric population</u>

Colecalciferol Aristo Capsules are not indicated for use in children and adolescents.

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

Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation. Concomitant use of glucocorticoids can decrease the effect of vitamin D.

Rifampicin and isoniazid (e.g. to treat tuberculosis) may reduce the effectiveness of vitamin $D_3$ due to hepatic enzyme induction.
Thiazide diuretics may result in hypercalcaemia due to the reduction of the renal calcium excretion. The calcium levels in plasma and urine should be monitored during long-term therapy.
Vitamin $D_3$ might increase the intestinal absorption of aluminium.

The toxicity effects of digitalis and other cardiac glycosides may be accentuated (risk of cardiac arrhythmias) with the oral administration of calcium combined with Vitamin D. Strict medical supervision is needed and, if necessary monitoring of ECG and calcium levels in plasma and urine.

Simultaneous treatment with ion exchange resins such as cholestyramine, colestipol hydrochloride, orlistat or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

**4.6 Fertility, pregnancy and lactation**

This formulation is not suitable for use in pregnancy or during lactation and a low strength formulation should be used.

Pregnancy

There are no or limited amount of data from the use of colecalciferol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be vitamin D deficient a higher dose may be required (up to 2000 IU/day). During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment.

Breast-feeding

Vitamin D can be prescribed while the patient is breast-feeding if necessary. This supplementation does not replace the administration of vitamin D in the neonate. Overdose in infants induced by nursing mothers has not been observed; however, when prescribing additional vitamin D to a breast-fed child the practitioner should consider the dose of any additional vitamin D given to the mother as vitamin D and its metabolites are excreted in breast milk.

Fertility

Normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility.

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

Colecalciferol Aristo Capsules have no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**

The frequency of possible side effects listed below are defined as:

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)

Metabolism and nutrition disorders:

Uncommon: Hypercalcaemia and hypercalciuria.

Gastrointestinal disorders:

Not known: Constipation, flatulence, nausea, abdominal pain, diarrhoea.

Skin and subcutaneous disorders:

Rare: Pruritus, rash and urticaria.

Dependent on dose and duration of treatment of serious and persistent hypercalcemia with its acute (heart rhythm disturbances, nausea, vomiting, psychiatric symptoms, loss of consciousness) and chronic (increased urination, increased thirst, loss of appetite, weight loss, kidney stones, kidney calcification, calcification may occur in tissues outside the bone) episodes occur.

Very rarely fatality has been described (see 4.4 Special warnings and precautions for use and 4.9 overdose).

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 HPRAPharmacovigilance, Website: www.hpra.ie.

**4.9 Overdose**

Symptoms of overdose

Ergocalciferol (vitamin D2) and colecalciferol (vitamin D3) have only a relatively narrow therapeutic index. In adults with normal function of the parathyroid glands, the threshold for vitamin D intoxication is 40,000 to 100,000 IU per day for 1 to 2 months. Infants and young children can react to much lower concentrations. Therefore, vitamin D should always be taken under medical supervision.

Acute or chronic overdose of vitamin D can cause hypercalcaemia. Symptoms of hypercalcemia are tiredness, headache, muscle and joint pain, muscle weakness, psychiatric symptoms (e.g., euphoria, dazedness, and disturbed consciousness), nausea, vomiting, lack of appetite, weight loss, thirst, polyuria, formation of renal calculi, nephrocalcinosis, extraosseous calcification and kidney failure, changes in ECG, arrhythmias, and pancreatitis. In isolated cases their course has been described as fatal. Chronic overdoses can lead to vascular and organ calcification as a result of hypercalcaemia.

Overdose in pregnancy:
Massive doses during pregnancy have been related to the occurrence of aortic stenosis syndrome and idiopathic hypercalcaemia in newborns. In addition, anomalies of the face, physical and mental retardation, strabism, enamel defects, craniosynostosis, supervalvular aortic stenosis, pulmonary stenosis, inguinal hernia, cryptorchidism in male progeny, as well as premature development of secondary sex characteristics in female progeny have been reported. See section 4.6.

However, several case reports are available of normal children born to mothers with hypoparathyroidism, receiving very high doses.

Therapeutic measures in overdose

A specific antidote does not exist. As a first measure the vitamin D preparation should be discontinued; normalization of hypercalcemia due to vitamin D intoxication takes several weeks. Graded according to the degree of hypercalcemia, the treatment is directed to symptoms. Rehydration and treatment with diuretics, e.g. furosemide to ensure adequate diuresis. In hypercalcemia biphosphonates or calcitonin and corticosteroids may be given. If a massive dose has been ingested ventricular emptying may be considered, together with administration of carbon.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Vitamin D and analogues, ATC code: A11CC05

Mechanism of action

In its biologically active form vitamin D3 stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue.

Pharmacodynamic effects
In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroids is inhibited directly by the biologically active form of vitamin D3. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active vitamin $D_3$.

**5.2 Pharmacokinetic properties**

Absorption
At alimentary doses vitamin $D_3$ is almost completely absorbed. Vitamin $D_3$ is absorbed together with fat and administration with the major meal of the day might therefore facilitate absorption.

Distribution
Vitamin $D_3$ is stored in the fatty tissue and its biological half-life is approx. 50 days. After a single dose of vitamin $D_3$ maximum serum concentrations of the active metabolite 25-hydroxycholecalciferol are reached after about a week.

Biotransformation
It is hydroxylated in the liver to form 25-hydroxycolecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25 dihydroxycolecalciferol (calcitriol).

Elimination
25-Hydroxycholecalciferol is then slowly eliminated with an apparent half-life in serum of about 50 days, due to the slow elimination of the parent compound. 25-Hydroxycholecalciferol is metabolised to the active metabolite 1, chol25-dihydroxycholecalciferol. After high vitamin $D_3$ doses serum 25-hydroxycholecalciferol concentrations can be increased for a month or two. Hypercalcaemia resulting from overdose can persist for several weeks. The metabolites circulate in the blood bound to a specific α - globin, Vitamin D and its metabolites are excreted mainly in the bile and faeces.

**5.3 Preclinical safety data**

Effects in non-clinical repeat-dose toxicity studies 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.
Colecalciferol has been shown to be teratogenic at high doses in animals (4-15 times the human dose). Offspring from pregnant rabbits treated with high doses of vitamin D had lesions anatomically similar to supravalvular aortic stenosis and offspring not showing such changes show vasculotoxicity similar to that of adults following acute vitamin D toxicity. Colecalciferol is also foetotoxic in mice with fewer and smaller offspring from pregnant mice receiving medium and high dose Vitamin D.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Capsule content:
Medium chain triglycerides
all-rac-α-Tocopheryl acetate

Capsule Shell:
Gelatin
Glycerol
Sorbitol liquid partially dehydrated (E420)
Purified water

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

36 months.

**6.4 Special precautions for storage**

Store below 25°C.

**6.5 Nature and contents of container**

Aluminium PVCPVDC Blisters
Pack sizes: 4 capsules/6 capsules/14 capsules/50 capsules
Pack sizes: 56 (4 x 14) capsules (hospital pack)

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

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

**7 MARKETING AUTHORISATION HOLDER**

Aristo Pharma GmbH
Wallenroder Str. 8-10
13435 Berlin
Germany

**8 MARKETING AUTHORISATION NUMBER**

PA1983/002/001

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

Date of first authorisation: 23rd February 2018
Date of last renewal: 18th October 2022

**10 DATE OF REVISION OF THE TEXT**

July 2023