SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tridolio 24.000 IE zachte capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

600 micrograms Cholecalciferol (vitamin D3), equivalent to 24 000 IU

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Soft capsule.

The capsule is a clear, light yellow, oval-shaped soft capsule. It contains a clear, light yellow, oily liquid. Capsule dimensions are 9 mm x 6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of vitamin D deficiency in adolescents and adults (serum 25(OH)D <25 nmol/l (<10 ng/mL)).
- Prevention of vitamin D deficiency in adolescents and adults at high risk of vitamin D deficiency.
- As an adjunct to specific therapy for osteoporosis in adult patients with vitamin D deficiency or at risk of vitamin D deficiency.

4.2 Posology and method of administration

Posology
The dosage should be determined individually, depending on the amount of vitamin D supplementation required. Before starting the vitamin D therapy, the patient's dietary habits should be carefully evaluated and artificially added vitamin D content of certain food types should be taken into consideration.

Adults:
Treatment of vitamin D deficiency in adolescents and adults (serum 25(OH)D < 25 nmol/l (<10 ng/mL)).
24 000 IU (1 capsule) per month up to 24 000 IU (1 capsule) per week. Maximum cumulative dose of 96 000 IU/month.

After the first month, a lower dose should be considered depending on the desired serum levels of 25-hydroxycolecalciferol (25 (OH) D), the severity of the disorder and the response of the patient on treatment.

Prevention of vitamin D deficiency in adolescents and adults at high risk of vitamin D deficiency.
24 000 IU (1 capsule) per month.

As an adjunct to specific therapy for osteoporosis in adult patients with vitamin D deficiency or at risk of vitamin D deficiency.
24 000 IU (1 capsule) per month.

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

Hepatic impairment
No dose adjustment is necessary for patients with hepatic impairment.

Renal impairment
In severe renal impairment the dosage must be determined individually by the treating physician dependent upon desirable serum levels of 25-hydroxycholecalciferol (25(OH)D), the severity of the disease and the patient's response to the treatment (see section 4.4).

Paediatric population
Tridolio should not be used in children under 12 years. The strength of 24 000 IU soft capsules is not suitable for the use in children up to 12 years because studies on the safe use of very high doses in children are too limited. However, cholecalciferol products with a lower strength than 24 000 IU are available on the market. The posology does not need to be adapted for adolescents (12 – ≤18 years).

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1
- Diseases/conditions associated hypercalcaemia and / or hypercalciuria.
- Calcium nephrolithiasis, nephrocalcinosis,
- D- hypervitaminosis

4.4 Special warnings and precautions for use

Monitoring calcium
During the initial and long-term treatment, serum calcium level and renal function should be monitored by measuring the serum creatinine level. Monitoring is especially important for elderly patients who concomitantly take cardiac glycosides or diuretics (see section 4.5), and in the case of hyperphosphataemia, as well as for patients with an increased risk of lithiasis. In case of signs of impaired renal function the dose should be reduced or the treatment discontinued.

Pseudohypoparathyroidism
Cholecalciferol is not recommended if pseudohypoparathyroidism is present (the need for vitamin D may be reduced by the sometimes normal sensitivity to vitamin D, with a risk of long-term overdose). In such cases, more manageable vitamin D derivatives are available.

Renal impairment
Cholecalciferol should be used with caution in patients with renal impairment and the 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 impairment, vitamin D in the form of cholecalciferol is not metabolised normally (see section 4.2).

Sarcoidosis
Cholecalciferol should be used with caution in patients with sarcoidosis due to risk of increased metabolism of vitamin D into its active form. Serum and urine calcium levels should be regularly monitored in these patients.

Concomitant use of multivitamin products
The content of vitamin D in this medicinal product should be considered when prescribing other vitamin D metabolites and analogues, as well as food supplements containing vitamin D. Additional doses of vitamin D should be taken under closed medical supervision.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per capsule. That is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

Thiazide diuretics
Thiazide diuretics reduce the excretion of calcium with urine. Regular monitoring of the serum calcium level is necessary in the case of concomitant use with thiazide diuretics or with calcium containing products taken in large doses because of the increased risk of hypercalcaemia.

Glucocorticoids
Systematic corticosteroids inhibit the absorption of calcium. Long-term use of corticosteroids may offset the effect of vitamin D.

Digitalis and other cardiac glycosides
In cases of treatment with drugs containing digitalis and other cardiac glycosides, the administration of vitamin D may increase the risk of digitalis toxicity (arrhythmia). Strict medical supervision is needed and, if necessary monitoring of ECG and calcium.

Resins and laxatives
Simultaneous treatment with ion exchange resins (e.g. colestyramine), or laxatives (like paraffin oil) may impair the absorption of vitamin D. Orlistat may potentially impair the absorption of vitamin D as it is fat-soluble, do not take vitamin D within 2 hours (before or after) any orlistat and vitamin D analogue administration.

Actinomycin and imidazole
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.

Phenytoin or barbiturates
Anticonvulsants like phenytoin and barbiturates (e.g. primidone) may reduce the effect of vitamin D due to the activation of the microsomal enzyme system.

Magnesium
Products containing magnesium (like antacids) may not be taken during long-terms high dose vitamin D treatment because of the risk of hypermagnesiaemia.

Phosphor
Products containing phosphor used in large doses, given concomitantly may increase the risk of hyperphosphataemia.

Concomitant use of anti-resorptive products for osteoporosis
Medicinal products having effect through the inhibition of bone resorption decrease the calcium amounts derived from bone. In order to avoid this, as well as concomitantly to treatment with medicines enhancing bone development, it is necessary to take vitamin D and ensure proper calcium levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of cholecalciferol in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3).

Vitamin D deficiency is harmful for mother and child. However, overdose of vitamin D must be avoided during pregnancy, as prolonged hypercalcaemia may lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.
Where there is a vitamin D deficiency the recommended dose is dependent on national guidelines, however, the maximum recommended dose during pregnancy is 4 000 IU/day vitamin D3. Tridolio 24 000 IU soft capsules is not recommended during pregnancy.

Breast-feeding

Vitamin D and its metabolites pass into breast milk. Tridolio 24 000 IU soft capsules should not be used during breastfeeding. If treatment with vitamin D is clinically indicated during breastfeeding, this should be considered when giving additional vitamin D to the child.

Fertility

There are no data on the effect of cholecalciferol on fertility. However, 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

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

4.8 Undesirable effects

The undesirable effects are classified below by System Organ Class *and frequency, 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 available data).*

SYSTEM ORGAN CLASS	**Preferred MedDRA Terms** *Frequencies*		
	Uncommon	Rare	not known
Immune system disorders			Hypersensitivity reactions such as angio-oedema or laryngeal oedema
Metabolism and nutrition disorders	Hypercalcaemia Hypercalciuria		
Skin and subcutaneous disorders		Pruritus Rash Urticaria	

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 listed in Appendix V.

4.9 Overdose

Overdose of the product may cause hypervitaminosis, hypercalcaemia and hyperphosphatemia. Symptoms of hypercalcaemia: anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, confusion, polydipsia, polyuria, bone pain, calcification in the kidneys, kidney stones, vertigo, and cardiac arrhythmia in severe cases. Hypercalcaemia in extreme cases may lead to coma or even death. Persistently high levels of calcium may cause irreversible renal impairment and soft tissue calcification.

Treatment of hypercalcaemia: treatment with vitamin D (and calcium) should be discontinued. At the same time, the use of thiazide diuretics, lithium, vitamin D and A as well as cardiac glycosides should also be discontinued. In the case of patients with impaired consciousness gastric emptying is also necessary. Rehydration and mono- or combined therapy with loop diuretics, bisphosphonates, calcitonin and corticosteroids may be used depending on the severity of the overdose. Serum electrolyte levels, renal function and diuresis should be monitored. In severe cases ECG and central venous pressure monitoring may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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 D. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active vitamin D.

5.2 Pharmacokinetic properties

Absorption
Fat-soluble vitamin D3 is absorbed through the small intestine in the presence of bile acids with the help of micellum and gets into the blood through lymphatic circulation.

Distribution
Following absorption, vitamin D3 enters the blood as part of chylomicrons. Vitamin D3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D3 at these sites for later release into the circulation. Circulating vitamin D3 is bound to vitamin D-binding protein.

Biotransformation
Vitamin D3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D3 undergoes glucuronidation prior to elimination.

Elimination
Vitamin D and its metabolites are excreted in faeces and urine.

Special population
A defect in the metabolism and excretion of vitamin D has been described in patients with chronic renal failure.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. There is no further information of relevance to the safety assessment in addition to what is stated in other parts of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill
Medium-chain Triglycerides
Butylhydroxytoluene (E 321)

Capsule shell
Disodium phosphate (E 339)
Modified starch (E 1440)
Carrageenan (E 407)
Glycerol (E 422)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Opaque, white PVC/PVdC film blister packs with aluminium foil.
Pack sizes: 4, 6, 8, 12 soft capsules

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

ZWITTER PHARMACEUTICALS LTD
34-36 Pentelis Avenue
15234 Chalandri, Athene
Griekenland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 131396

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 17 september 2024

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 7: 10 maart 2025.