Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

THORENS 10 000 I.U. /ml oral drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral drops, solution (50 drops) contains 10 000 I.U. colecalciferol (vitamin D_3), equivalent to 0.25 mg.
1 drop contains 200 I.U. colecalciferol (vitamin D_3), equivalent to 0.005 mg.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral drops, solution.

Clear and colorless to greenish-yellow oily solution without visible solid particles and/or precipitate

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prevention and treatment of vitamin D deficiency in adults, adolescents and children with an identified risk.
As an adjunct to specific therapy for osteoporosis in patients with vitamin D deficiency or at risk of vitamin D insufficiency.

4.2 Posology and method of administration

Posology

Adults
Preventionof vitamin D deficiency and as an adjunct to specific therapy for osteoporosis:
Recommended dose is 3-4 drops (600 I.U. - 800 I.U.) per day.

Treatment of vitamin D deficiency:
4 drops (800 I.U.) per day. Higher doses should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment. The daily dose should not exceed 4 000 I.U. (20 drops per day).

Paediatric population
Prevention:
For prevention in children (0 years to 11 years old) with an identified risk, the recommended dose is 2 drops (400 I.U.) per day.

For prevention in adolescents (12 years to 18 years old) with an identified risk, the recommended dose is 3-4 drops (600-800 I.U.) per day.

Treatment of deficiency in children and adolescents:
The dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment.
The daily dose should not exceed 1 000 I.U. per day for infants <1 year, 2 000 I.U. per day for children 1-10 years and 4 000 I.U. per day for adolescents >11 years.

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

- *Special Populations*

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

Patients with mild or moderate renal impairment: no specific adjustment is required
Colecalciferol must not be used in patients with severe renal impairment.
- *Dosage in pregnancy*
The recommended daily intake for pregnant women is 400 I.U. (2 drops), however, in women who are considered to be vitamin D3 deficient a higher dose may be required (up to 2 000 I.U. /day - 10 drops).
- *Other conditions*: in obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D3 metabolism, higher doses are required for the treatment and prevention of vitamin D3 deficiency.
Method of administration
Patients should be advised to take THORENS preferably with a meal (see section 5.2 Pharmacokinetic properties **-** "Absorption").

The product should be shaken before use.

THORENS has a taste of olive oil. THORENS can be taken as is or to facilitate the intake it can also be mixed with a spoonful or a small amount of cold or lukewarm food immediately prior to use. The patient should be sure to take the entire dose.

In children, THORENS can be mixed with a small amount of children's foods, yogurt, milk, cheese or other dairy products. The parents should be warned not to mix THORENS into a bottle of milk or container of soft foods in case the child does not consume the whole portion, and does not receive the full dose. The parents should ensure that their child takes the entire dose. In children who are not breast-feeding, the prescribed dose should be administered with a meal.

See also section 6.6, Special precautions for handling and disposal.

4.3 Contraindications

Hypersensitivity to the active substance, colecalciferol (vitamin D_3), or to any of the excipients listed in section 6.1.
Hypercalcaemia, hypercalciuria
Hypervitaminosis D
Kidney stones (nephrolithiasis, nephrocalcinosis) in patients with current chronic hypercalcaemia
Severe renal impairment

4.4 Special warnings and precautions for use

Vitamin D_3 should be used with caution in patients with impairment of renal function 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 insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D have to be used.

Caution is required in patients receiving treatment for cardiovascular disease (see section 4.5 Interaction with other medicinal products and other forms of interaction - cardiac glycosides including digitalis).

THORENS should be prescribed with caution in patients with sarcoidosis, due to a possible increase in the metabolism of vitamin D_3 in its active form. In these patients the serum and urinary calcium levels should be monitored.

Allowances should be made for the total dose of vitamin D_3 in cases associated with treatments already containing vitamin D_3, foods enriched with vitamin D_3, cases using milk enriched with vitamin D_3, and the patient's level of sun exposure.

There is no clear evidence for causation between vitamin D_3 supplementation and renal stones, but the risk is plausible, especially in the context of concomitant calcium supplementation. The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

During long-term treatment with a daily dose exceeding 1 000 I.U. vitamin D_3 the serum calcium values must be monitored.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use of anticonvulsants (such as phenytoin) or barbiturates (and possibly other drugs that induce hepatic enzymes) may reduce the effect of vitamin D_3 by metabolic inactivation.

In cases of treatment with thiazide diuretics, which decrease urinary elimination of calcium, monitoring of serum calcium concentration is recommended.

Concomitant use of glucocorticoids can decrease the effect of vitamin D_3.

In cases of treatment with drugs containing digitalis and other cardiac glycosides, the administration of vitamin D_3 may increase the risk of digitalis toxicity (arrhythmia). Strict medical supervision is needed, together with serum calcium concentration and electrocardiographic monitoring if necessary.

Simultaneous treatment with ion exchange resin such as cholestyramine, colestipol hydrochloride, orlistat or laxative such as paraffin oil, may reduce the gastrointestinal absorption of vitamin D_3.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D_3 activity by inhibiting the conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of colecalciferol (vitamin D_3) in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). The recommended daily intake for pregnant women is 400 I.U. (2 drops), however, in women who are considered to be vitamin D_3 deficient a higher dose may be required (up to 2 000 I.U. /day - 10 drops). 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.
Overdoses of vitamin D must be avoided during pregnancy, as prolonged hypercalcaemia may lead to retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child.

Breast-feeding
Vitamin D3 and its metabolites are excreted in breast milk. Vitamin D_3 can be prescribed while the patient is breast-feeding if necessary. This supplementation does not replace the administration of vitamin D_3 in the neonate.
Overdose in infants induced by nursing mothers has not been observed, however, when prescribing additional vitamin D_3 to a breast-fed child the practitioner should consider the dose of any additional vitamin D_3 given to the mother.

Fertility
There are no data on the effect of THORENS 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

There are no data on the effects of THORENS on the ability to drive. However, an effect on this ability is unlikely.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: uncommon (>1/1,000, <1/100) or rare (>1/10,000, <1/1,000).
Metabolism and nutrition disorders
Uncommon: Hypercalcaemia and hypercalciuria
Skin and subcutaneous disorders:
Rare: pruritus, rash, and 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Discontinue THORENS when calcaemia exceeds 10.6 mg/dl (2.65 mmol/l) or if the calciuria exceeds 300 mg/24 hours in adults or 4-6 mg/kg/day in children. An overdose manifests as hypercalcaemia and hypercalciuria, the symptoms of which include the following: nausea, vomiting, thirst, constipation, polyuria, polydipsia and dehydration.
Chronic overdosage may lead to vascular and organ calcification, as a result of hypercalcaemia.

Treatment in cases of overdose
Discontinue administration of THORENS and initiate rehydration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vitamin D_3 and analogues, colecalciferol
ATC Code: A11CC05

In its biologically active form, vitamin D_3 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_3. 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

The pharmacokinetics of vitamin D_3 is well known.

Absorption
Vitamin D_3 is well absorbed from the gastro-intestinal tract in the presence of bile, so the administration with the major meal of the day might therefore facilitate the absorption of vitamin D_3.

Distribution and biotransformation
It is hydroxylated in the liver to form 25-hydroxy-colecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1,25-dihydroxy-colecalciferol (calcitriol).

Elimination
The metabolites circulate in the blood bound to a specific α – globin, vitamin D_3 and its metabolites are excreted mainly in the bile and faeces.

Characteristics in Specific Groups of Subjects or Patients
A 57% lower metabolic clearance rate is reported in subjects with renal impairment as compared with that of healthy volunteers.
Decreased absorption and increased elimination of vitamin D_3 occurs in subjects with malabsorption.
Obese subjects are less able to maintain vitamin D_3 levels with sun exposure, and are likely to require larger oral doses of vitamin D_3 to replace deficits.

5.3 Preclinical safety data

Pre-clinical studies conducted in various animal species have demonstrated that toxic effects occur in animals at doses much higher than those required for therapeutic use in humans.
In toxicity studies at repeated doses, the effects most commonly reported were increased calciuria and decreased phosphaturia and proteinuria.
Hypercalcaemia has been reported in high doses. In a state of prolonged hypercalcaemia, histological alterations (calcification) were more frequently borne by the kidneys, heart, aorta, testes, thymus and intestinal mucosa.
Colecalciferol (vitamin D_3) has been shown to be teratogenic at high doses in animals.
At doses equivalent to those used therapeutically, colecalciferol (vitamin D_3) has no teratogenic activity.
Colecalciferol (vitamin D_3) has no potential mutagenic or carcinogenic activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refined olive oil.

6.2 Incompatibilities

In absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
After first opening the container: the product may be stored for a maximum of 6 months.

6.4 Special precautions for storage

Do not store above 30° C.
Do not freeze or refrigerate
Keep the container in the outer carton in order to protect from light.
For storage condition after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bottle with dropper applicator
Amber glass Type III bottle of 20 ml containing 10 ml of oral drops solution (corresponding to 500 drops), sealed by a childproof polypropylene cap.

1 dropper applicator cap (CE mark 0068) with a colourless type III glass stem and polypropylene cap is provided. Each pack contains 1 bottle and 1 dropper applicator cap.

Dropper container
Amber glass Type III dropper container of 20 ml, containing 10 ml of oral drops solution (corresponding to 500 drops), sealed with a polyethylene child-proof cap.

Not all pack presentations may be marketed.

6.6 Special precautions for disposal and other handling

You should preferably take THORENS together with meal (see section 5.2 Pharmacokinetic properties **-** "Absorption").
Do not store any product or food mixture that contains THORENS for use at a later time or a next meal (see section 4.2 Posology and method of administration).
Any unused medicinal product or waste material should be disposed of in accordance with the local requirements.

INSTRUCTION FOR USE OF DEVICE
Instructions for use of bottle with dropper applicator

- To Open the bottle, press down and twist the plastic cap at the same time;
- Unscrew the plastic casing which wraps the dropper glass stem;
- Insert the dropper glass stem into the bottle to take up the contents. Collect the prescribed number of drops onto a spoon;
- To close the bottle, extract the dropper glass stem to re-screw the plastic cap;
- Carefully screw the plastic casing on the dropper to wrap the glass stem
- Place both medicine items (bottle and wrapped dropper) into the original package carton box. **Instructions for use of dropper container**
- To open the dropper container, press down and twist the plastic cap at the same time;
- Put the container upside-down in a vertical position and collect the prescribed number of drops;
- After the administration of drops, bring the dropper container upwards;
- To close the dropper container, re-screw the plastic cap;
- Place the dropper container into the original package carton box.

7 MARKETING AUTHORISATION HOLDER

Galen Pharma Ireland Limited
Finnabair Industrial Estate

Dundalk
Louth
A91P9KD
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22680/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th February 2014
Date of last renewal: 18th July 2018

10 DATE OF REVISION OF THE TEXT

January 2022