SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Colecalciferol 800 IU Film-coated Tablets
Colecalciferol 1000 IU Film-coated Tablets
Colecalciferol 7000 IU Film-coated Tablets
Colecalciferol 30000 IU Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Colecalciferol 800 IU Film-coated Tablets:

Each film-coated tablet contains 8 mg colecalciferol concentrate (powder form) (equivalent to 20 µg colecalciferol = 800 IU vitamin D_3).

Excipients with known effect:
Each film-coated tablet contains 59.52 mg lactose monohydrate and 1.4 mg sucrose.

Colecalciferol 1000 IU Film-coated Tablets:
Each film-coated tablet contains 10 mg colecalciferol concentrate (powder form) (equivalent to 25 µg colecalciferol = 1000 IU vitamin D_3).

Excipients with known effect:
Each film-coated tablet contains 74.4 mg lactose monohydrate and 1.75 mg sucrose.

Colecalciferol 7000 IU Film-coated Tablets:
Each film-coated tablet contains 70 mg colecalciferol concentrate (powder form) (equivalent to 175 µg colecalciferol = 7000 IU vitamin D_3).

Excipients with known effect:
Each film-coated tablet contains 39.9 mg lactose monohydrate and 12.25 mg sucrose.

Colecalciferol 30000 IU Film-coated Tablets:
Each film-coated tablet contains 300 mg colecalciferol concentrate (powder form) (equivalent to 750 µg colecalciferol = 30000 IU vitamin D_3).

Excipients with known effect:
Each film-coated tablet contains 171 mg lactose monohydrate and 52.5 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Colecalciferol 800 IU Film-coated Tablets: Yellow coloured, round, 6.1 mm diameter film-coated tablet with smooth convex surface on both sides.

Colecalciferol 1000 IU Film-coated Tablets : Yellow coloured, round, 7.2 mm diameter film-coated tablet with smooth convex surface on both sides, and 'D' embossed on one side.

Colecalciferol 7000 IU Film-coated Tablets: Yellow coloured, round, 7.2 mm diameter film-coated tablet with smooth convex surface on both sides, and 'W' embossed on one side.

Colecalciferol 30000 IU Film-coated Tablets: Yellow coloured, round, 13.2 mm diameter film-coated tablet with smooth convex surface on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of Vitamin D deficiency (serum 25(OH)D < 25 nmol/l)
- Prevention of vitamin D deficiency in high-risk patients
- 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

Dose should be established on an individual basis depending on the extent of the necessary vitamin D supplementation. Colecalciferol 800 IU and 1000 IU Film-coated Tablets are suitable for daily vitamin D supplementation, while the 7000 IU and 30000 IU doses contain amounts equal to the weekly and monthly vitamin D doses respectively, which should be taken into consideration and dosage should be established by a physician.

Please refer to the respective national guidelines.

<u>Posology</u>

Adults and elderly:

- Prevention of vitamin D deficiency (maintenance):
    - for adults and elderly: 800-1600 IU/day or equivalent weekly or monthly dose.
    - for adults and elderly with osteoporosis: maximum 2000 IU/day or equivalent weekly or monthly dose.

- Treatment of vitamin D deficiency (loading dose):
    - 800-4000 IU/day or equivalent weekly or monthly dose.

Patients should receive supplemental calcium if intake from diet is inadequate.

Hepatic impairment: no dose adjustment is necessary for patients with hepatic impairment.

During vitamin D therapy, calcium and phosphor intake has fundamental significance with respect to the success of the treatment.

Before starting the vitamin D therapy, the patient's dietary habits should be carefully evaluated by the doctor and artificially added vitamin D content of certain food types should be taken into consideration.

Paediatric population
Colecalciferol Film-coated Tablets should not be used in children under 12 years.

Paediatric posology (12-18 years):
- 800 IU daily depending on the severity of the disease and the patient`s response to treatment. Should only be given under medical supervision.

Method of administration

Colecalciferol Film-coated Tablets may be taken independently from meals.

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.
- Severe renal impairment

4.4 Special warnings and precautions for use

In the case of therapeutic treatment the dose should be established on an individual basis for the patients by regular checking (initially weekly, then once in every 2-4 weeks) of plasma calcium levels. During long-term treatment, serum calcium level, urinary calcium excretion and renal function should be monitored by measuring the serum creatinin 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 hypercalciuria (exceeding 300 mg (7.5 mmol)/24 hours) or signs of impaired renal function the dose should be reduced or the treatment discontinued.

Vitamin D may be given to patients with impaired renal function with caution. In this case monitoring of calcium and phosphate levels is necessary, and the risk of soft tissue calcification should be taken into consideration.
In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D should be used.
Similar monitoring is necessary for children whose mother receive treatment with vitamin D in pharmacological amounts. Some children may react with increased sensitivity to the effect of vitamin D.

Colecalciferol Film-coated Tablets should not be taken 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.

Colecalciferol Film-coated Tablets may be carefully administered to patients with sarcoidosis because of the risk of vitamin D's increased transformation to its active form. Blood and urine calcium levels should be regularly monitored in these patients.

In the case of concomitant use with other medicinal product containing vitamin D, its vitamin D content should be taken into consideration. The concomitant use of multivitamin products and dietary supplements containing vitamin D should be avoided.

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.

Lactose: Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption should not take this medicinal product.

Paediatric population
Colecalciferol Film-coated Tablets should not be used in children under 12 years.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with calcium containing products administered in large doses may increase the risk of hypercalcaemia. Thiazid diuretics reduce the excretion of calcium with urine. Regular monitoring of the serum calcium level is necessary in the case of concomitant use with thiazid diuretics or with calcium containing products taken in large doses because of the increased risk of hypercalcaemia.

The effects of digitalis and other cardiac glycosides may be accentuated with the oral administration of calcium combined with Vitamin D. Strict medical supervision is needed and, if necessary monitoring of ECG and calcium.

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

Simultaneous treatment with ion exchange resins (e.g. colestyramin), or laxatives (like paraffin oil) may impair the absorption of vitamin D.

Products containing magnesium (like antacids) may not be taken during vitamin D treatment because of the risk of hypermagnesaemia.

Anticonvulsants, hydantoin, barbiturates or primidone may reduce the effect of vitamin D due to the activation of the microsomal enzyme system.

Concomitant use of calcitonin, etidronate, gallium nitrate, pamidronate or plicamycin with vitamin D may antagonise the effect of these products in hypercalcaemia treatment.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
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. 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.
Daily vitamin D intake during pregnancy may not exceed 600 IU. Overdoses of vitamin D have been shown to have teratogenic effects in animal experiments.
In pregnant women, overdosage of vitamin D_3 should be avoided, since prolonged hypercalcaemia has been sometimes associated with retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child.

Breast-feeding:
Vitamin D3 can be used during breastfeeding. Vitamin D and its metabolites pass into breast-milk. This should be considered when giving additional vitamin D to the child.

4.7 Effects on ability to drive and use machines

There is no available data concerning the negative effect of the product on on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are ranked by frequency and system organ classes. Frequency categories are defined 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: may not be established on the basis of available data

Immune system disorders:
Not known (cannot be estimated from the available data): Hypersensitivity reactions such as angio-oedema or laryngeal oedema

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

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, colecalciferol, ATC code: A11CC05

Mechanism of action
Vitamin D increases the intestinal absorption of calcium, increases the calcium reabsorption in the kidneys and bone formation, and decreases the level of parathyroid hormone (PTH). Vitamin D receptors are present in several other tissues besides the skeletal system, therefore vitamin D has diverse effect in several physiological processes. As for its cellular biological effects, study data are available for the autocrine/paracrine realization of growth and differentiation control on hematopoietic and immune cells, skin-, skeletal- and smooth muscle cells, as well as on the cells of the brain, liver and certain endocrine organs.

Doses lower than the 800 IU dose of previous recommendations are sufficient for the maintenance of the ideal vitamin D supplementation but not sufficient for the treatment of vitamin D deficiency. The vitamin D supplementation required in the treatment of osteoporosis should be differentiated from the treatment of vitamin D deficiency and from therapeutic doses of vitamin D monotherapy.

The once-a-week/once-a-month administration of the weekly/monthly total dose results in the same effect daily administration because of the pharmacokinetic parameters of vitamin D (see section 5.2). However, most experience from randomised controlled trials comes from daily dosages.

Daily 200 IU and 400 IU vitamin D has increased the mineral content of the femur by 14.3% and 17.2% respectively in a 1-year randomised, double-blind study performed with 228 adolescent girls. The daily 400 IU dose has also significantly increased the mineral content of the spine. At the same time, the serum 25(OH)D level has increased by 5.7±15.7 nM and 12.4±13.7 nM in the groups taking 200 IU and 400 IU doses while it decreased by 6.7±11.3 nM in the placebo group.

Vitamin D, through its effect of increasing calcium absorption very effectively increases the bone resorption decreasing effect of calcium. In a study with 148 elderly, postmenopausal women, concomitant administration of 800 IU vitamin D (colecalciferol) and 1200 mg calcium resulted in 72% increase in 25(OH)D level and 17% decrease in PTH level as compared to supplementation with calcium alone.

A clinical study performed with vitamin D deficient patients treated in hospital showed that daily supplementation with 100 mg calcium and 800 IU vitamin D over 6 months has normalised plasma levels of the 25-hydroxylised metabolite of vitamin D, mitigated secondary hyperparathyreosis and decreased alkaline phosphatase levels.

In the case of muscle weakness or decreased muscle mass (for example in the elderly or patients with stroke) supplementation of vitamin D with the 800 IU dose (or higher) has a clearly demonstrated effect on muscle strength: it reduced the number of falls and had a beneficial effect on muscle mass.

In another clinical trial the results demonstrated that a concomitant administration of vitamin D and calcium-citrate decreases the risk of falling due to muscle weakness in the elderly. In a 3-year placebo-controlled, double-blind study performed with the participation of 445 patients over 65 years of age, the participants received calcium citrate malate corresponding to 700 IU vitamin D /day and 500 mg elemental calcium /day resulting in significant decrease (46%) of the risk of falling (OR 0,54; 95% CI, 0,30-0,97) among treated women.

5.2 Pharmacokinetic properties

Absorption
Fat-soluble vitamin D_3 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 D_3 enters the blood as part of chylomicrons. Vitamin D_3 is rapidly distributed mostly to the liver where it undergoes metabolism to 25-hydroxyvitamin D_3, the major storage form. Lesser amounts are distributed to adipose and muscle tissue and stored as vitamin D_3 at these sites for later release into the circulation. Circulating vitamin D_3 is bound to vitamin D-binding protein.

Biotransformation
Vitamin D_3 is rapidly metabolized by hydroxylation in the liver to 25-hydroxyvitamin D_3, and subsequently metabolized in the kidney to 1,25-dihydroxyvitamin D_3, which represents the biologically active form. Further hydroxylation occurs prior to elimination. A small percentage of vitamin D_3 undergoes glucuronidation prior to elimination.

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

5.3 Preclinical safety data

There is no further information available concerning the product's safety besides the information given in other parts of the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
cellactose 80 (lactose monohydrate and powdered cellulose (E460 (ii)),

modified food starch,
maize starch,
croscarmellose sodium (E468),
sucrose,
colloidal anhydrous silica (E551),
colloidal hydrous silica (E551),
magnesium stearate (E572),
sodium ascorbate (E301),
medium chain triglycerides,
DL-alpha-tocopherol (E307).

Coating:
Opadry II Yellow 85F 32659, consisting of:
polyvinyl alcohol (E1203),
titanium dioxide (E171),
macrogol,
talc (E553b),
quinoline yellow aluminum lake (E104),
yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

800 IU, 1000 IU, 7000 IU (in blisters): 2 years
30000 IU (in blisters): 3 years
800 IU (in tablet container): 9 months

6.4 Special precautions for storage

Blisters: Store below 25°C.
Store in the original package in order to protect from light.
Tablet container: Store in the original tablet container in order to protect from light.

6.5 Nature and contents of container

Colecalciferol 800 IU Film-coated Tablets: 30, 60 or 90 film-coated tablets in opaque PVC/PVdC-Alu blisters and box. 250 film-coated tablets in plastic HDPE container with LDPE cap, in a box.

Colecalciferol 1000 IU Film-coated Tablets: 30, 60 or 90 film-coated tablets in opaque PVC/PVdC-Alu blisters and box.

Colecalciferol 7000 IU Film-coated Tablets: 4, 8, 12 or 32 film-coated tablets in opaque PVC/PVdC-Alu blisters and box.

Colecalciferol 30000 IU Film-coated Tablets: 1, 2, 3,4, 6, 8, or 12 film-coated tablets in opaque PVC/PVdC-Alu blisters and box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Consilient Health Limited
Floor 3, Block 3, Miesian Plaza,
Dublin 2, D02 Y754, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

800 IU Film-coated Tablets : PL 24837/0084
1000 IU Film-coated Tablets: PL 24837/0085
7000 IU Film-coated Tablets: PL 24837/0086
30000 IU Film-coated Tablets: PL 24837/0087

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th January 2015
Date of last renewal: 14th November 2019

10. DATE OF REVISION OF THE TEXT

23.05.2024