SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Domnisol 266 micrograms soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 266 micrograms of calcifediol monohydrate.

Excipients with known effect:
Each capsule contains 4.98 mg of ethanol and 22 mg of sorbitol (E-420).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft
Yellow coloured oval soft gelatin capsule containing a clear, low viscous liquid free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of vitamin D deficiency in adults.
Prevention of vitamin D deficiency in adults with identified risks.
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
Dietary intake of vitamin D and sun exposure vary among patients and should be taken into account when calculating the appropriate dose of vitamin D analogue drugs such as Domnisol.

The dose, frequency and duration of the treatment will be determined by the prescriber taking into account the plasma levels of 25(OH)D, type and condition of the patient and other comorbidities such as obesity, malabsorption syndrome, treatment with corticosteroids.

The general posology for the treatment and maintenance of vitamin D deficiency is one capsule per month, (refer to section 5.1 for clinical data) although higher doses may be required in certain cases.

Treatment of vitamin D deficiency:
Adults: one capsule (266 micrograms of calcifediol) once a month.

Higher doses may be necessary in some patients after analytical verification of the extent of the deficiency. In those cases, the maximum dose administered should not exceed one capsule per week. Once the plasma levels of 25(OH)D are stabilised within the desired range the treatment frequency of administration should be lowered.

Maintenance therapy following treatment of deficiency:

Adults: one capsule (266 micrograms of calcifediol) once a month.

Blood levels of 25(OH)D should be measured approximately 3 to 4 months after beginning maintenance therapy to confirm that target level has been reached. Thereafter, the levels should be measured at 6 monthly intervals to ensure that effective therapeutic levels are maintained.

Prevention of deficiency:

Adults: one capsule (266 micrograms of calcifediol) once a month.

Adjunct to specific therapy for osteoporosis:

Adults: one capsule (266 micrograms of calcifediol) once a month.

Certain populations are at higher risk of vitamin D deficiency and may require higher doses, e.g.:

- People who are institutionalised or hospitalised long term
- Darker skinned people, especially at higher latitudes
- Obese people
- People using certain concomitant medications (e.g., anticonvulsants, glucocorticoids)
- People with conditions causing malabsorption, including inflammatory bowel disease and coeliac disease.

Paediatric population

Not recommended for children

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.

Vitamin D must not be used in patients with severe renal impairment.

Pregnancy and breastfeeding

Not recommended during pregnancy unless the clinical condition of the woman requires treatment.

Vitamin D and its metabolites are excreted in breast milk. Overdose in infants induced by nursing mothers has not been observed but allowance for any maternal dose should be made when prescribing vitamin D products to a breast-fed child.

Other conditions (see above):

Such as obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, higher doses might require for the treatment and prevention of vitamin D deficiency.

Method of administration

This medicine is taken orally.
Domnisol should not be administered with a daily frequency.

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
- Hypercalcemia (serum calcium > 10.5 mg/dl) or hypercalciuria
- Calcium lithiasis
- Hypervitaminosis D

4.4 Special warnings and precautions for use

- To obtain an adequate clinical response to oral administration of Domnisol, an appropriate dietary calcium intake is also required. Therefore, to control the therapeutic effects, the following parameters should be monitored, in addition to 25(OH)D: serum calcium, phosphorus and alkaline phosphatase as well as urinary calcium and phosphorus in 24 hours. A decrease in serum levels of alkaline phosphatase normally precedes the onset of hypercalcemia. Once parameters are stabilized and the patient is under maintenance treatment, the above-mentioned determinations should be performed regularly, especially for serum levels of 25(OH)D and calcium.
- Renal impairment: To be administered with caution. Use of this drug in patients with chronic kidney disease should be accompanied by periodic monitoring of serum calcium and phosphorus, and hypercalcemia prevention. Transformation to calcitriol takes place in the kidney; thus, in case of severe renal impairment (creatinine clearance of less than 30 ml/min) a very significant reduction in the pharmacological effects may occur.

- Heart failure: Special caution is required. The patient's serum calcium should be monitored constantly, especially in patients on digitalis, because hypercalcemia may occur, and arrhythmias appear. Twice-a- week determinations are recommended at the beginning of treatment.
- Hypoparathyroidism: 1-alpha-hydroxylase is activated by parathyroid hormone. As a result, in case of parathyroid insufficiency the activity of calcifediol monohydrate may decrease.
- Kidney stones: Calcemia should be monitored, since vitamin D increases absorption of calcium and may aggravate the situation. In these patients supplements of vitamin D should be administered only if the benefits outweigh the risks.
- In patients with prolonged immobilization, it may be necessary to reduce the dose to avoid hypercalcemia.
- Patients with sarcoidosis, tuberculosis, or other granulomatous diseases: to be administered with caution since these conditions lead to a greater sensitivity to the effect of vitamin D as well as to an increase of the risk of adverse effects at doses lower than the recommended dose. It is necessary to monitor serum and urinary calcium concentrations in these patients.
- Patients and their families and/or caregivers should be informed of the importance of complying with the prescribed dosage and with recommendations about diet and concomitant intake of calcium supplements in order to prevent overdosing.
- Interference with laboratory tests: Patients should be warned that this drug contains a component that can alter the results of laboratory tests: Determination of cholesterol: calcifediol monohydrate may interfere with Zlatkis-Zak method, leading to false increases in serum cholesterol levels.

Warnings on excipients
This medicine contains 1% ethanol (alcohol), which corresponds to 4.98 mg/capsule.
This medicine contains 22 mg sorbitol in each capsule. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

- **Phenytoin, phenobarbital, primidone** and other enzyme inducers: enzyme inducers may reduce plasma concentrations of calcifediol monohydrate and inhibit its effects by inducing its hepatic metabolism. For this reason, it is generally recommended to monitor plasma 25-OH-D levels when calcifediol

monohydrate is administered with antiepileptics that are CYP3A4 inducers in order to consider supplementation.

- **Cardiac glycosides:** Calcifediol monohydrate can cause hypercalcemia, which can, in turn, enhance the inotropic effects of digoxin and its toxicity, producing cardiac arrhythmias.
- **Paraffin and mineral oil**: Due to liposolubility of calcifediol monohydrate, the product can dissolve in paraffin and intestinal absorption may decrease. Using other types of laxatives or at least spacing doses is recommended.
- **Thiazide diuretics**: Co-administration of a thiazide diuretic (hydrochlorothiazide) with vitamin D supplements in patients with hypoparathyroidism may lead to hypercalcemia, which may be temporary or require the interruption of the treatment with the vitamin D analogue.
- Some antibiotics, such as **penicillin, neomycin** and **chloramphenicol** can increase calcium absorption, meanwhile others commonly used to treat tuberculosis (rifampicin, isoniazid) have the potential to reduce Vit D levels as well as antifungal agents (clotrimazole, ketoconazole)
- Cholesterol-lowering statin drugs (atorvastatin) increase vitamin D levels
- **Phosphate-binding agents such as magnesium salts**: Since vitamin D has an effect on phosphate transport in the intestine, kidney and bone, hypermagnesemia may occur. The dosage of agents that bind to phosphate shall be adjusted according to phosphate concentrations in serum.
- **Antacids containing aluminium**: Vitamin D can increase absorption of aluminium. This interaction might be a problem for people with kidney disease. It is recommended to take vitamin D two hours before, or four hours after antacids.
- **Verapamil, diltiazem:** Some studies show potential inhibition of antianginal action, due to antagonism of their actions.
- **Vitamin D:** Co-administration of any vitamin D analogue should be avoided as additive effects and hypercalcemia can occur.
- **Calcium supplements:** Uncontrolled intake of additional preparations containing calcium should be avoided.
- **Corticosteroids:** They counteract the effects of vitamin D analogue drugs such as calcifediol monohydrate.
- **Weight loss drug** orlistat may reduce absorption of vitamin D. So does the cholesterol-lowering drug cholestyramine. People taking these drugs should discuss vitamin intake with their physician.
- **Stimulant laxatives.** Long-term use of high doses of stimulant laxatives can reduce vitamin D and calcium absorption.

<u>Interaction with food and drinks</u>

Food supplemented with vitamin D should be considered, since additive effects may occur.

4.6 Fertility, Pregnancy and lactation

Pregnancy

High doses of vitamin D should not be administrated during pregnancy. Animal reproduction studies have shown toxicity for reproduction when it is administered at higher doses than the therapeutic usual doses (see section 5.3). There is no or limited data from the use of calcifediol monohydrate in pregnant women.

Domnisol is not recommended during pregnancy; during first and second trimesters when it should not be used. If the mother baseline condition requires treatment with Vitamin D, it should be evaluated if the potential benefit outweighs the possible risk to the foetus. In this scenario, a strict control of the calcium and calcifediol monohydrate levels during the treatment should be performed. Vitamin D overdose should be avoided during pregnancy, as potential hypercalcaemia may lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

Breast-feeding

Calcifediol monohydrate is poorly excreted into breast milk.

In case of administration of Domnisol 266 micrograms soft capsules to a breast-feeding woman, the dose administered to the mother should be considered when prescribing a vitamin D supplement to the new-born/infant.

Fertility

There are no data on the effect of calcifediol monohydrate on fertility. However, normal endogenous levels of 25(OH)D are not expected to have any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

Domnisol capsules have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions to Domnisol are generally uncommon (≥ 1/1 000 to <1/100) but sometimes they are moderately significant.

The most significant adverse effects are related to excessive intake of vitamin D, i.e., they are often associated with overdose or prolonged treatment, especially when associated with high doses of calcium. The doses of vitamin D analogues required for hypervitaminosis vary considerably from one subject to another. The most common adverse reactions are due to the hypercalcemia which can occur initially or at a later stage:

Endocrine disorders:

Pancreatitis, among the late symptoms of hypercalcemia

Metabolism and nutrition disorders:
Elevation of blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, hypercalcemia

Nervous system disorders:
In case of moderate hypercalcemia, the following symptoms may appear weakness, fatigue, drowsiness, headache, irritability.

Eye disorders:
Rarely (≥1/10 000 to <1/1 000), at very high doses photophobia and conjunctivitis with corneal calcifications may occur.

Cardiac disorders:
In case of hypercalcemia cardiac arrhythmias may occur.

Gastrointestinal disorders:
Nausea, vomiting, dry mouth, constipation, taste disturbances, with a metallic taste, abdominal cramps. If hypercalcemia progresses anorexia may occur.

Hepatobiliary disorders:
High calcemia levels can lead to increased transaminase (SGOT and SGPT).

Musculoskeletal and connective tissue disorders:
Bone and muscle pain may occur in initial stages of hypercalcemia, calcification in soft tissues.

Renal and urinary disorders:
Manifestations of hypercalcemia are: nephrocalcinosis and deterioration of kidney function (with polyuria, polydipsia, nocturia and proteinuria).

General disorders and alterations in the place of administration:
Later symptoms of hypercalcemia include: rhinorrhoea, pruritus, hyperthermia, decreased libido.

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.

4.9 Overdose

Symptoms:
Administration of vitamin D in high doses or for prolonged periods of time may cause hypercalcemia, hypercalciuria, hyperphosphatemia and renal failure. As early symptoms of overdose, weakness, fatigue, drowsiness, headache, anorexia, dry mouth, metallic taste, nausea, vomiting, abdominal

cramps, polyuria, polydipsia, nocturia, constipation or diarrhoea, dizziness, tinnitus, ataxia, rash, hypotonia (especially in children), muscle or bone pain and irritability may appear.
Among later symptoms of hypercalcemia the following are included: runny nose, itching, decreased libido, nephrocalcinosis, renal failure, osteoporosis in adults, growth retardation in children, weight loss, anaemia, conjunctivitis with calcification, photophobia, pancreatitis, elevated blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, increased transaminases (SGOT and SGPT), hyperthermia, generalized vascular calcification, convulsions, soft tissue calcification. Rarely, patients may develop hypertension or psychotic symptoms; serum alkaline phosphatase may decrease; electrolyte imbalances together with moderate acidosis can lead to cardiac arrhythmias.
In the most serious cases, where serum calcium exceeds 12 mg/dl, syncope, metabolic acidosis, and coma may happen. Although symptoms of overdose are usually reversible an overdose might lead to kidney or heart failure.
It is accepted that serum levels of 25-OH-cholecalciferol above 150 ng/ml may be associated with an increased incidence of adverse effects.
Increased calcium, phosphate, albumin, and urea nitrogen in blood as well as cholesterol and blood transaminases are typical of this kind of overdose.

Treatment:
Treatment of Domnisol overdose consists of:

1. Withdrawal of treatment (with calcifediol monohydrate) and with any calcium supplement being administered.
2. Follow a diet low in calcium. Administration of large volumes of liquids, both orally and parenterally, is advisable to increase calcium excretion. If necessary, administer steroids and induced forced diuresis with loop diuretics such as furosemide.
3. If intake has occurred in the previous 2 hours, gastric emptying and forced emesis are advisable. If vitamin D has already passed through the stomach, a laxative (paraffin or mineral oil) can be administered. If vitamin D has already been absorbed, haemodialysis or peritoneal dialysis with a dialysis solution free of calcium can be performed.

Hypercalcemia derived from prolonged administration of Domnisolpersists for approximately 4 weeks after discontinuation of treatment. Signs and symptoms of hypercalcemia are usually reversible. However, metastatic calcification can cause serious kidney or heart failure and death.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues, ATC code: A11CC06

Mechanism of action

Vitamin D has two main forms: D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is mainly synthesized in the skin by exposure to sunlight (ultraviolet radiation) and is also obtained from the diet. Vitamin D must undergo a two-step metabolic process to be active; the first step occurs in the microsomal fraction of the liver where Vitamin D is hydroxylated at position 25 leading to 25-hydroxycholecalciferol (calcifediol monohydrate or calcidiol); the second step takes place mainly in the kidney where 1,25-dihydroxycholecalciferol or calcitriol is formed due to the activity of enzyme 1-alpha-hydroxylase; conversion to 1,25-dihydroxycholecalciferol is regulated mainly by its own concentration, by parathyroid hormone (PTH) and by the fibroblastic growth factor 23 (FGF23). Calcitriol is transported from the kidney to target tissues (intestine, bone and possibly kidney and parathyroid gland) where it binds to the calcitriol receptors and activates the responsive pathways that result in increased intestinal absorption of calcium and phosphorus and reduced parathyroid hormone synthesis.

Pharmacodynamic effects

Vitamin D increases absorption of calcium and phosphorus in the intestine and improves normal bone formation and mineralization and acts on three levels:
Intestine: Vitamin D enhances absorption of calcium and phosphorus in the small intestine.
Bone: calcitriol enhances bone formation by increasing levels of calcium and phosphate and stimulates action of osteoblasts.
Kidney: calcitriol enhances tubular reabsorption of calcium.
Parathyroid glands: vitamin D inhibits the secretion of parathyroid hormone.
Immune system: modulates innate and adaptative immune response.

Clinical efficacy and safety

The efficacy and safety of Domnisol 266 micrograms soft capsules were evaluated in a randomized, double-blind study in post-menopausal women with vitamin D deficiency. 303 subjects were randomized and 298 conformed the intention to treat population. Patients were treated with calcifediol monohydrate 266 micrograms/month or cholecalciferol at recommended therapeutic guidelines dose (25000 IU/month). After 1 month, 13.5 % of patients treated with calcifediol achieved 25(OH)D levels greater than 30 ng/mL (75 nmol/l) and 59.1% achieved levels greater than 20 ng/mL (50 nmol/l). After 4 months 35% of patients treated with calcifediol monohydrate achieved 25(OH)D levels greater than 30 ng/mL (75 nmol/l) and 81% achieved levels greater than 20 ng/mL (50 nmol/l). The mean (SD) increase in 25(OH)D concentrations with respect to baseline levels was 9.7 (6.7) ng/mL (24.3 (16.8) nmol/l) after 1 month and 14.9 (8.1) ng/mL (37.3 (20.3) nmol/l) after 4 months of treatment. Highest 25(OH)D levels with calcifediol were achieved after 4 months of treatment and remained stable for 12 months in the long term, indicating a non-accumulative effect. Calcifediol monohydrate was safe and well tolerated.

5.2 Pharmacokinetic properties

Absorption

The intestinal absorption of radiolabelled calcifediol monohydrate is 93% in normal subjects and (nearly) equally efficient in patients with severe fat malabsorption due to celiac disease or pancreatectomy, and only slightly decreased in patients with short bowel disease. Absorption of calcifediol monohydrate from the gut is largely achieved by the vena porta. The intestinal absorption of calcifediol monohydrate is not dependent on the presence of bile acids and micelle formation unlike cholecalciferol.

Distribution
Serum concentrations of 25-OH-cholecalciferol reflect the vitamin D stored in the body, usually from 30 to 60 ng/ml (75 to 150 nmol/l) in healthy subjects. Following oral administration of calcifediol monohydrate, the maximum serum concentration is reached after 4 hours approximately. Its half-life is around 18 to 21 days and storage in adipose tissue is less significant than cholecalciferol, due to its lower lipid solubility.

Biotransformation
The conversion of calcifediol monohydrate to calcitriol is catalysed by the 1-alpha-hydroxylase enzyme, CYP27B1 which is located in the kidney and other tissues. The enzyme responsible for the catabolization of both calcifediol monohydrate and calcitriol to inactive metabolites is CYP24A1, located in all vitamin D-responsive tissues.

Elimination
Calcifediol monohydrate is primarily excreted in the bile.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
High doses of vitamin D (4 to 15 times the recommended dose in humans) have proved to be teratogenic in animals, but there are few studies in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous
Medium chain triglycerides
Gelatin
Glycerol
Sorbitol (70%) (E420)
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not refrigerate. Store in the original package to protect from moisture

6.5 Nature and contents of container

This medicinal product is packed in PVC/PVDC-Al blisters containing 1, 3, 5 or 10 capsules.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

19/06/2023