Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dnord 255 microgram soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 255 micrograms of calcifediol as calcifediol monohydrate.

Excipients with known effect:
Each soft capsule contains 5 mg of ethanol, 22 mg of sorbitol (E420) and 1 mg of sunset yellow (E110).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule
Orange, oval soft gelatin capsule, 15 mm by 9 mm containing a clear, low viscous and free from particles liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of vitamin D deficiency (i.e., 25(OH)D levels < 25 nmol/L) in adults.

Prevention of vitamin D deficiency in adults with identified risks such as in patients with malabsorption syndrome, chronic kidney disease mineral and bone disorder (CKD-MBD) or other identified risks.

As adjuvant for the specific treatment of osteoporosis in patients with vitamin D deficiency or at risk of vitamin D deficiency.

4.2 Posology and method of administration

Posology
Treatment of vitamin D deficiency and prevention of vitamin D deficiency in patients with identified risks: one capsule once a month.

As adjuvant for the specific treatment of osteoporosis: one capsule 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 plasma levels of 25(OH)D are stabilised within the desired range, treatment should be discontinued, or the frequency of administration lowered.

Dnord should not be administered with a daily frequency.

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. Dnord is recommended when administration spaced in time is preferred.

Serum concentrations of 25(OH)D should be monitored after initiation of the treatment, usually after 3-4 months.

The potency of this medicinal product is sometimes expressed in international units. These units are not interchangeable with the units used to express the potency of cholecalciferol (Vitamin D) preparations (see section 4.4)

Patients with Renal Impairment
Use of Dnord in patients with chronic kidney disease should be accompanied by periodic monitoring of serum calcium and phosphorus, and hypercalcemia prevention (see section 4.4).

Elderly population
No overall differences in safety or efficacy were observed between geriatric patients and younger adults.

Paediatric population
The safety and efficacy of Dnord in children and adolescents below the age of 18 years have not yet been established. No data are available.

Method of administration
Oral administration

4.3 Contraindications

- Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1.
- Hypercalcemia (serum calcium > 2.6 mmol/L) or hypercalciuria
- Calcium lithiasis
- Hypervitaminosis D

4.4 Special warnings and precautions for use

Hypercalcemia and hyperphosphatemia
To obtain an adequate clinical response to oral administration of calcifediol, 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 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.

Prolonged immobilization
In patients with prolonged immobilization, it may be necessary to reduce the dose in order to avoid hypercalcemia.

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.

Laboratory Tests:
Interference with laboratory tests: calcifediol may interfere with determination of cholesterol (Zlatkis-Zak method), leading to false increases in serum cholesterol levels.

Warnings on excipients
This medicine contains 5 mg of alcohol (ethanol) in each soft capsule. The amount in one capsule of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains 22 mg sorbitol in each soft capsule.

This medicine contains sunset yellow (E-110) which may cause allergic reactions.

International Units (IU) should not be used for determination of the dose of calcifediol as this could lead to overdosing. Instead, the dosing recommendation in section 4.2 should be followed.

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 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 is administered with antiepileptics that are CYP3A4 inducers in order to consider supplementation.
- **Cardiac glycosides:** Calcifediol can cause hypercalcemia, which can, in turn, enhance the inotropic effects of digoxin and its toxicity, producing cardiac arrhythmias.
- Drugs that decrease the absorption of calcifediol such as **cholestyramine, colestipol or orlistat**, which can result in decreased effects. It is recommended to space doses of these medicines and vitamin D supplements at least 2 hours.
- **Paraffin and mineral oil**: Due to liposolubility of calcifediol, 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
- **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.
- **Verapamil:** 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.

Interaction with food and drinks
Food supplemented with vitamin D should be taken into account, since additive effects may occur.

4.6 Fertility, pregnancy and lactation

Pregnancy
No controlled studies with calcifediol in pregnant women have been performed.
Studies performed in animals have shown toxicity for reproduction (see section 5.3).

Do not use this medicine during pregnancy.

Breast-feeding
Calcifediol is excreted into breast milk.
The risk in newborns/infants cannot be excluded. Maternal ingestion of high doses of calcifediol can produce high levels of calcitriol in milk and cause hypercalcemia in infants.

This medicine should not be used during breast-feeding.

Fertility
There are no data on the effect of calcifediol on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Frequencies are assigned as follows: 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) and not known (cannot be estimated from the available data).

The adverse effects related to vitamin D are associated to increased levels of calcium when an excessive intake of Vit D may occur i.e. associated with overdose or prolonged treatment. The doses of vitamin D analogues required for hypervitaminosis vary considerably from one subject to another. The adverse reactions due to increased levels of calcium can occur initially or at a later stage (see section 4.9 Overdose).

The immune system
Unknown frequency (cannot be calculated from the available data): Hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, rash, localised oedema / local swelling, and erythema).

Metabolism and nutrition disorders:
Unknown frequency (cannot be calculated from the available data): Hypercalcaemia and hypercalciuria.

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 HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms:
Administration of vitamin D in high doses or for long 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 3 mmol/L, 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 375 nmol/L 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 calcifediol overdose consists of:

1. Withdrawal of treatment (with calcifediol) 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, hemodialysis or peritoneal dialysis with a dialysis solution free of calcium can be performed.

Hypercalcemia derived from prolonged administration of calcifediol persists for approximately 4 weeks after discontinuation of treatment. Signs and symptoms of hypercalcemia are usually reversible. However, calcification due to long-term hypercalcemia 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 synthesized in the skin by exposure to sunlight (ultraviolet radiation) and is obtained from the diet. Vitamin D3 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 (25-hydroxycholecalciferol or calcifediol); the second step takes place in the kidney where 1,25-dihydroxycholecalciferol or calcitriol is formed due to the activity of enzyme 25-hydroxycholecalciferol 1-hydroxylase; conversion to 1,25-dihydroxycholecalciferol is regulated by its own concentration, by parathyroid hormone (PTH) and by serum calcium and phosphate concentration. Other metabolites with unknown function exist. 1,25-dihydroxycholecalciferol is transported from the kidney to target tissues (intestine, bone and possibly kidney and parathyroid gland) by binding to specific plasma proteins.

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.

Clinical efficacy and safety
The efficacy and safety of calcifediol 255 micrograms soft capsules were evaluated in a randomized, double-blind study in post-menopausal women with serum 25(OH)D levels <50 nmol/L. 303 subjects were randomized and 298 conformed the intention to treat population. Patients were treated with calcifediol 255 micrograms/month (N=200) or cholecalciferol (N=98) at dose of 625 micrograms/month (25000 IU). In the calcifediol group 98 patients received treatment for 4 months, the remaining patients (N=102) and the cholecalciferol group received treatment for 12 months.

After 1 month, 13.5 % of patients treated with calcifediol achieved 25(OH)D levels greater than 30 ng/mL (75 nmol/L) and after 4 months, this percentage increased to 35%. Highest 25(OH)D levels with calcifediol were achieved after 4 months of treatment, indicating a non-accumulative effect.

The table below shows 25(OH)D concentration increases from baseline in ng/mL, as mean values (SD).

	Calcifediol 255 microgram	**Cholecalciferol 625 microgram**
Baseline	12.8 (3.9)	13.2 (3.7)
Increases from baseline:		
Month 1	9.7 (6.7)	5.1 (3.5)
Month 4	14. 9 (8.1)	9.9 (5.7)
Month 12	11.4 (7.4)	9.2 (6.1)

*Results are shown as mean (SD)

5.2 Pharmacokinetic properties

Absorption
Calcifediol is well absorbed in the intestine, approximately 75-80% is absorbed through this process. Following oral administration of calcifediol, the maximum serum concentration of 25-OH-cholecalciferol is reached after 4 hours approximately.

Biotransformation
Production of calcitriol from calcifediol is catalysed by the 1-alpha-hydroxylase enzyme, CYP27B1, located in the kidney and all vitamin D-responsive tissues. CYP24A1, located in these tissues, catabolises both calcifediol and calcitriol to inactive metabolites.

Distribution
Calcifediol circulates in the blood bound to a specific α-globulin (DBP). Is stored in adipose tissue and muscle for prolonged periods. Storage in adipose tissue is less significant than vitamin D, due to its lower lipid solubility.

Elimination
Calcifediol half-life is around 18 to 21 days and it 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. Vitamin D can cause hypercalcemia in pregnant women, which could lead to a syndrome of supravalvar aortic stenosis, retinopathy and intellectual disability in infants and newborn.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous
Medium chain triglycerides
Gelatin
Glycerol
Sorbitol (70%) (E-420)
Titanium dioxide (E171)
Sunset yellow (E-110)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

This medicine is packed in PVC/PVDC-Alu blisters containing 1, 2, 3, 5 or 10 capsules. Blisters are packed in a cardboard box.

6.6 Special precautions for disposal and other handling

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

Nordic Pharma Limited
4045 Kingswood Road

Citywest Business Campus
Dublin 24
Dublin
D24 V06K
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23343/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th August 2022

10 DATE OF REVISION OF THE TEXT

September 2022