PRESCRIBING INFORMATION

Pr EURO-D 5 000 IU
Vitamin D Gelcaps (D_3, Cholecalciferol)

Pr EURO-D 10 000 IU
Vitamin D Gelcaps (D_3, Cholecalciferol)

Pr EURO-D 50 000 IU
Vitamin D Gelcaps (D_3, Cholecalciferol)

Vitamin

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PRESCRIBING INFORMATION

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Pr EURO-D 10 000 IU
Pr EURO-D 50 000 IU

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THERAPEUTIC CLASSIFICATION

Vitamin

PHARMACOLOGY

Vitamin D is a fat-soluble vitamin that helps regulate serum calcium and phosphorous concentrations by enhancing the efficiency of the small intestine to absorb these minerals from the diet. The term Vitamin D collectively refers to a group of structurally similar chemicals and their metabolites, which includes alfacalcidol (1α-hydroxycholecalciferol), calcitriol (1,25-dihydroxycholecalciferol), cholecalciferol· (Vitamin D_3), dihydrotachysterol (DHT) and ergocalciferol (Vitamin D_2). These agents have antirachitic properties.

In human beings there is no practical difference between the biologic activity of cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). One microgram (μg) of either compound is equivalent to 40 IU of vitamin D activity. Vitamin D is essential for the absorption and utilization of (calcium and phosphate and aids in the mobilization of bone calcium and maintenance of serum calcium concentrations.

In humans, cholecalciferol (vitamin D_3) is synthesized in the skin, from7-dehydrocholesterol, on exposure to ultraviolet radiation. Cholecalciferol is also present in fish, liver oils, Ergocalciferol (vitamin D_2) is produced by ultraviolet irradiation of provitamin D sterol (ergosterol). Ergosterol is not synthesized in humans but is consumed in the diet from yeasts and plants. Cholecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D-25-hydroxylase to form 25-hydroxycholecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D-hydroxylase to form the active metabolites 1,25-dihydroxycholecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol respectively. These are the primary active metabolites of cholecalciferol and ergocalciferol, respectively (Source: Gilman). Dihydrotachysterol is produced by synthetic reduction of ergocalciferol. Patients with chronic renal disease cannot convert calcifediol to calcitriol. Alfacalcidol (1α-hydroxyvitamin D_3), a synthetic analogue of calcitriol, is rapidly converted in the liver to calcitriol, bypassing the renal conversion step. Because alfacalcidiol, calcitriol and dihydrotachysterol do not require renal hydroxylation, they are useful in patients with renal failure.

PHARMACOKINETICS

Table 1: Pharmacokinetics

	T½ (hours)	Onset of action (hours)	Duration of action
Alfacalcidol	3	6	Up to 48 hours
Calcitriol	3-6	2-6	3-5 days
Dihydrotachysterol	N/A	Several	Up to 9 weeks
Ergocalciferol	19-48[a]	12-24[b]	Up to 6 months[c]

[a] Increase in serum calcium level
[b] Therapeutic effect may require 10-14 days
[c] Cumulative effect occurs with repeated dosing

Vitamin D analogues are readily absorbed from the small intestine if fat absorption is normal. Bile is required for absorption. As described previously, cholecalciferol and ergocalciferol are converted. To active metabolites through a two-step hydroxylation process, the first occurs in the liver and the second occurs in the kidney.

Dihydrotachysterol and alfacalcidol are converted to their active metabolites in the liver. The liver activates Dihydrotachysterol and alfacalcidol. Vitamin D is eliminated renally and by biliary excretion.

INDICATIONS

EURO-D 5 000 IU, EURO-D 10 000 IU and EURO-D 50 000 IU are indicated for:

- the treatment of refractory rickets (vitamin D resistant rickets)
- the treatment of hypoparathyrodism

CONTRAINDICATIONS

EURO-D 5 000 IU, EURO-D 10 000 IU and EURO-D 50 000 IU should not be used in patients with:

- known hypersensitivity to Vitamin D or any of its analogues and derivatives
- hypercalcemia
- malabsorption syndrome
- abnormal sensitivity to the toxic effects of Vitamin D
- hypervitaminosis D

PRECAUTIONS

Chronic or acute administration of excessive doses may lead to hypervitaminosis D, manifested by hypercalcemia and its sequelae.

The therapeutic index of Vitamin D analogues is narrow and there is great interindividual variation in the dose that will lead to chronic toxicity. Daily doses of cholecalciferol ranging from 50 000 to 100 000 IU (1.25 to 2.5 mg) in adults and 1000 IU (25 µg) in children may result in hypervitaminosis. Other Vitamin D analogues with shorter duration of action may have a lower propensity to accumulate and to cause hypercalcemia.

Early symptoms of hypercalcemia may include weakness, fatigue, somnolence, headache, anorexia, dry mouth, metallic taste, nausea, vomiting, vertigo, tinnitus, ataxia and hypotonia. Later and possibly more serious manifestation include nephrocalcinosis, renal dysfunction, osteoporosis in adults, impaired growth in children, anemia, metastatic calcification, pancreatitis, generalized vascular calcification and seizures.

Periodic monitoring of serum calcium, phosphate, magnesium, and alkaline phosphatase is recommended for patients taking Vitamin D_3. Serum calcium should be maintained in the range of 2.25-2.5 mmol/L and not allowed to exceed 2.75 mmol/L.

Drug Interactions

Antacids (Magnesium-containing):
Hypomagnesemia may develop when these agents are used concurrently with Vitamin D, particularly in patients with chronic renal failure

Anticonvulsants (Phenytoin, Phenobarbital):
Decreased Vitamin D effects may occur when certain anticonvulsants are administered, as they may induce hepatic microsomial enzymes and accelerate the conversion of Vitamin D to inactive metabolites.

Cholestyramine, Colestipol, Mineral Oil:
Intestinal absorption of Vitamin D may be impaired. Patients on cholestyramine or colestipol should be advised to allow as much time as possible between the ingestion of these drugs and Vitamin D.

Digoxin:
Vitamin D should be used with caution in patients on digoxin as hypercalcemia (which may result with Vitamin D use) may precipitate cardiac arrhythmias.

Thiazide diuretics:
There is-an increased risk of hypercalcaemia if vitamin D is co-administered with thiazide diuretics and calcium: Plasma-calcium concentrations should be monitored in patients receiving the drugs concurrently. (Source: Martindale,

Different Vitamin D analogues should not be administered concurrently.

Special Population

Pregnancy:
Safety of doses in excess of 400 IU (10 µg) of Vitamin D_3 daily during pregnancy has not been established. Maternal hypercalcemia, possibly caused by excessive Vitamin D intake during pregnancy, has been associated with hypercalcemia in neonates, which may lead to supravalvular aortic stenosis syndrome, the features of which may include retinopathy, mental or growth retardation, strabismus and other effects.

Hypercalcemia during pregnancy may also lead to suppression of parathyroid hormone release in the neonate, resulting in hypocalcemia, tetany and seizures.

Lactation:
Vitamin D is deficient in-maternal milk; therefore, breastfed infants may require supplementation. Use of-excessive amounts of Vitamin D in nursing mothers may result in hypercalcemia in infants. Doses of Vitamin D_3 in excess of 10 µg daily should not be administered daily to nursing women.

ADVERSE EFFECTS

Vitamin D_3 (cholecalciferol) is generally well tolerated in doses that do not exceed the recommended daily intake. Chronic excessive dosing can lead to toxicity (see precautions).

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

OVERDOSE

Symptoms:
Acute intoxication with Vitamin D_3 (cholecalciferol) may cause hypervitaminosis D (See Precautions).

Treatment:
Treatment of acute or chronic intoxication includes withdrawal of the Vitamin D_3 and any calcium supplements, maintenance of low-calcium diet, administration of oral IV fluids and, if needed, corticosteroids or calciuric diuretics, such as furosemide and ethacrymic acid, to decrease serum calcium concentrations. Peritoneal or hemodialysis with calcium free dialysate will help remove calcium.

If acute ingestion is recent, gastric lavage or emesis may minimize further absorption. If the drug has already passed through the stomach, administration of mineral oil may promote faecal elimination.

Hypercalcemia is usually reversible, however, if metastatic calcification has occurred, severe renal or cardiac failure or even death may result.

For management of a suspected drug overdosage, contact your regional Poison Control Centre Immediately

DOSAGE

At the higher doses of Vitamin D used for active treatment, the range between therapeutic and toxic doses is narrow. The dosage of vitamin D_3 must be individualized with careful monitoring of serum-calcium levels. Readjust therapeutic dosage as soon as there is clinical improvement. Careful titration is necessary to avoid overdose. Dietary and other sources of vitamin D must be considered. Calcium intake should be adequate.

For treatment of Vitamin D resistant rickets: 12 000 to 500 000 IU (0.3 to 12.5 mg) daily.

For treatment of hypoparathyroidism: 50 000 to 200 000 IU (1.25 to 5 mg) daily.
Calcium supplementation is also required.

A specialist must be consulted in the treatment of Hypophosphatemia, Hypocalcemia, Renal Osteodystrophy, and Corticosteroid induced Osteoporosis.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EURO-D 5 000 IU: Each oval shaped red soft gelcap, with a slightly yellow oleaginous solution inside, contains Vitamin D_3 5 000 IU. Non-medicinal ingredients: FD&C red # 40, D&C Yellow # 10, FD&C Yellow # 6, Gelatin, Glycerin, Purified Water, Hydrogenated Soybean Oil.
Available in bottles of 100 gelcaps.

EURO-D 10 000 IU: Each oblong shaped red soft gelcap, with a slightly yellow oleaginous solution inside, contains Vitamin D_3 10 000 IU. Non- medicinal ingredients: FD&C Yellow No. 6, FD&C Red No. 40, Gelatin, Glycerin, Purified Water, Soybean Oil.
Available in bottles of 30, 60 and 100, and sample blister packs of 10 gelcaps.

EURO-D 50 000 IU: Each oval shaped light green soft gelcap, with a slightly yellow oleaginous solution inside, contains Vitamin D_3 50 000 IU. Non-medicinal ingredients: FD&C Blue # 1, Gelatin, Glycerin, Purified Water, Corn Oil.
Available in bottles of 10, 15, 30 and 100, and in sample bottles of 3 gelcaps.

STORAGE CONDITIONS

Store between 15°C and 30°C. Protect from light.

FOR MORE INFORMATION

This document, prepared for health professionals, can be obtained by contacting the sponsor, Euro-Pharm International Canada Inc. at:
Toll Free: 1-888-929-0835

This leaflet was prepared by
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REFERENCES

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4. Martindale, The Extra Pharmacopoeia, 29th Edition, pp. 1280-84.

5. AHFS Drug information 2003 p. 3519-3524.

6. Euro-D 10 000 Prescribing Information (Euro-Pharm International Canada Inc.), April 2004.