1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

A-LENNON CALCIFEROL (tablet)

COMPOSITION

Each A-LENNON CALCIFEROL tablet contains 1,25 mg of ergocalciferol (equivalent to 50 000 IU of vitamin D_2)

Excipients:

Acacia powder, benzoic acid, calcium carbonate light, cetyl palmitate, cocoa, gelatin, kaolin heavy, lactose monohydrate, Lennon red (C.I. 45430), Lennon violet, magnesium stearate, maize starch, propyl hydroxybenzoate sodium, purified talc, sodium benzoate, sodium ethyl parabenzoate, sodium methyl parahydroxybenzoate, sucrose, titanium dioxide (dye Lennon white)

Contains sugar: Sucrose 140,13 mg and lactose monohydrate 136,1 mg

CATEGORY AND CLASS

A 22.2 Vitamins - Other

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Vitamin D is best characterised as a positive regulator of calcium homeostasis. Phosphate metabolism is affected by the vitamin in a manner parallel to that of calcium. The mechanism by which Vitamin D acts to maintain normal concentrations of calcium and phosphate in plasma are to facilitate their absorption by the small intestine, to interact with parathyroid hormone to enhance their mobilisation from bone, and to decrease their excretion by the kidney. Vitamin D is essential for normal calcification of bone. Normal bone formation occurs when calcium and phosphate concentrations in the plasma are adequate.

Pharmacokinetic properties

Absorption

Vitamin D is well absorbed from the gastrointestinal tract. Most of the vitamin appears first within chylomicrons in lymph.

The presence of bile is essential for adequate intestinal absorption.

Distribution

Absorbed Vitamin D circulates in the blood in association with Vitamin D-binding protein. The vitamin disappears from the plasma with a half-life of 19 to 25 hours but is stored in fat depots for prolonged periods.

Metabolism

Vitamin D and its metabolites undergo extensive enterohepatic recirculation.

Whether derived from diet or endogenously synthesised, Vitamin D requires modification to become biologically active. The primary active metabolite of the vitamin is calcitriol [1α, 25-dihydroxyvitamin D, 1,25$(OH)_2$D], the product of two successive hydroxylations of vitamin D.

The initial step in vitamin D activation occurs in the liver where ergocalciferol is hydroxylated in the 25 position to generate 25-OH-ergocalciferol.

Reduced extracellular Ca^{2+} levels stimulate 1α-hydroxylation of 25-OHD, increasing the formation of biologically active 25-OH-ergocalciferol.

Elimination

The primary route of excretion of Vitamin D is the bile, with a small percentage found in the urine. There is also enterohepatic re-cycling.

INDICATIONS

A-LENNON CALCIFEROL is indicated for:

- Rickets;
- osteomalacia;
- hypoparathyroidism.

CONTRAINDICATIONS

A-LENNON CALCIFEROL is contraindicated in:

- Patients with hypersensitivity to calciferol or to any of the excipients in A-LENNON CALCIFEROL (see COMPOSITION).
- Patients with hypercalcaemia and/or hypercalciuria.
- Patients with nephrolithiasis (renal calculi).
- Patients with severe renal impairment.
- Patients with hypervitaminosis.
- Pregnancy and lactation (see HUMAN REPRODUCTION).

WARNINGS AND SPECIAL PRECAUTIONS

Adequate dietary calcium is necessary for clinical response to A-LENNON CALCIFEROL therapy.

The effects of A-LENNON CALCIFEROL may be reduced in patients taking barbiturates or anticonvulsants.

Patients who have intestinal bypass surgery or have severe shortening or inflammation of the small intestine may fail to absorb vitamin D sufficiently; hepatic or biliary dysfunction also may seriously impair vitamin D absorption.

Dietary supplementation with A-LENNON CALCIFEROL may be detrimental in persons already receiving an adequate intake through their diet and exposure to sunlight since the difference between therapeutic and toxic concentrations is relatively small.

A-LENNON CALCIFEROL should be administered with caution in patients with mild to moderate renal impairment or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred.

Because of the effect on serum calcium, A-LENNON CALCIFEROL should be avoided.

Plasma phosphate concentrations should be controlled during A-LENNON CALCIFEROL therapy to reduce the risk of ectopic calcification.

Adverse events are generally associated with excessive intake of A-LENNON CALCIFEROL

leading to the development of hypercalcaemia. The symptoms of hypercalcaemia can include:

Early: weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, diarrhoea, abdominal pain, fatigue, muscle weakness or pain, bone pain, metallic taste.

Late: polyuria, polydipsia, anorexia, irritability, weight loss, nocturia, mild acidosis, reversible uraemia, generalised vascular calcification, nephrocalcinosis, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhoea, pruritus, hyperthermia, decreased libido, elevated blood urea nitrogen, albuminuria, hypercholesterolaemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac dysrhythmias, overt psychosis (rare) (see SIDE EFFECTS and KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENTS).

Should hyperglycaemia develop, A-LENNON CALCIFEROL should be discontinued immediately.

A-LENNON CALCIFEROL should be prescribed with caution to patients suffering from sarcoidosis because of the risk of increased metabolism of vitamin D to its active form. These patients should be monitored with regard to the calcium content in serum and urine.

The need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

All patients receiving doses of A-LENNON CALCIFEROL should have their plasma calcium and 25-hydroxycalciferol concentrations checked at initiation of treatment and whenever nausea and vomiting are present.

Effects on ability to drive and use machines

Since adverse reactions such as dizziness and drowsiness have been reported in patients receiving A-LENNON CALCIFEROL, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that A-LENNON CALCIFEROL, does not adversely affect their ability to do so.

Excipients

Lactose and sucrose warning:

A-LENNON CALCIFEROL contains lactose monohydrate and sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption, fructose intolerance or sucrase-isomaltase insufficiency should not take A-LENNON CALCIFEROL.

INTERACTIONS

Magnesium-containing antacids: hypermagnesaemia may develop in patients on chronic renal dialysis.

Digoxin: hypercalcaemia in patients on digoxin may precipitate cardiac dysrhythmias.

Verapamil: atrial fibrillation has recurred when supplemental calcium and A-LENNON CALCIFEROL have induced hypercalcaemia.

Anti-convulsants: A-LENNON CALCIFEROL requirements may be increased in patients taking anti-convulsants (e.g. carbamazepine, phenobarbitone, phenytoin and primidone)

(see WARNINGS AND SPECIAL PRECAUTIONS).

Thiazide diuretics: hypoparathyroid patients on A-LENNON CALCIFEROL may develop hypercalcaemia due to increased calciferol levels.

Rifampicin: may reduce the effectiveness of A-LENNON CALCIFEROL due to hepatic enzyme induction.

Isoniazid: may reduce the effectiveness of A-LENNON CALCIFEROL due to inhibition of the metabolic activation of calciferol.

Glucocorticosteroids: can reduce the serum 25-hydroxycalciferol levels, requiring additional dose supplementation of A-LENNON CALCIFEROL.

Medicines leading to fat malabsorption e.g. *orlistat, liquid paraffin, cholestyramine,* may impair the absorption of A-LENNON CALCIFEROL.

Additional monitoring of serum calcium is recommended when therapy is combined with vitamin D analogues or metabolites.

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

Phosphate infusions should not be administered to lower hypercalcaemia of hypervitaminosis D because of the dangers of metastatic calcification.

HUMAN REPRODUCTION

Pregnancy

Hypercalcaemia during pregnancy may produce congenital disorders in the off-spring and neonatal hypoparathyroidism. A-LENNON CALCIFEROL must therefore not be used during pregnancy (see CONTRAINDICATIONS).

Lactation

Women receiving therapeutic doses of A-LENNON CALCIFEROL must not breastfeed their infants as this may lead to the development of hypercalcaemia in the infant (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

In the treatment of rickets and osteomalacia:

One tablet daily (50 000 units).

In the treatment of hypoparathyroidism:

One to four tablets daily (50 000 to 200 000 units).

SIDE EFFECTS

Metabolism and nutritional disorders

Frequent: Elevated serum creatinine levels

Less frequent: Hypercalcaemia, hypercalciuria

Frequency unknown: Anorexia, weight loss, mild acidosis, polydipsia

Psychiatric disorders

Frequency unknown: Mental disturbances, irritability, decrease libido, overt psychosis

Nervous system disorders

Frequency unknown: Headache, somnolence

Eye disorders

Frequency unknown: Conjunctivitis (calcific), photophobia

Ear and labyrinth disorders

Frequency unknown: Vertigo

Cardiac disorders

Frequency unknown: Changes in ECG measurements, cardiac dysrhythmias, hypertension

Vascular disorders

Frequency unknown: Generalised vascular calcification, hypertension

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Rhinorrhoea

Gastrointestinal disorders

Frequency unknown: Nausea, vomiting, diarrhoea, constipation, abdominal pain, metallic taste, dry mouth, pancreatitis

Skin and subcutaneous disorders

Less frequent: Pruritus, rash, urticaria

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: Muscle weakness or pain, joint pain, bone pain, ectopic calcification

Renal and urinary disorders

Frequency unknown: Kidney failure, nephrocalcinosis, renal calculi, polyuria, nocturia, albuminuria, reversible uraemia

General disorders and administration site conditions

Frequency unknown: Fatigue, weakness, hyperthermia

Investigations

Frequency unknown: Elevated blood urea nitrogen, elevated AST and ALT

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

A-LENNON CALCIFEROL is the most likely of all vitamins to cause overt toxicity. Infants and children are generally more susceptible to its toxic effects.

Administration to patients in excess of their daily requirements can cause hypercalcaemia, hypercalciuria and hyperphosphataemia. Concomitant high intake of calcium and phosphate may lead to similar abnormalities.

A-LENNON CALCIFEROL should be withdrawn if toxicity occurs.

Adverse events are generally associated with excessive intake of A-LENNON CALCIFEROL leading to the development of hypercalcaemia (see WARNINGS AND SPECIAL

PRECAUTIONS and SIDE EFFECTS).

Treatment

Treatment of hypervitaminosis D consists of immediate withdrawal of A-LENNON CALCIFEROL, a low calcium diet, avoidance of sunlight administration of glucocorticoids, and vigorous fluid support.

Severe cases may require hydration with intravenous saline together with symptomatic and supportive treatment as indicated by the patient's clinical condition. Plasma calcium U & E's (urea and electrolytes) should be monitored.

Phosphate infusion should not be administered to lower hypercalcaemia of hypervitaminosis D because dangers of metastatic calcification.

IDENTIFICATION

Mauve sugar coated normal biconvex tablet.

PRESENTATION

100 tablets packed in a white, polypropylene securitainer with a white low density polyethylene closure together with a leaflet.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protected from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

H2053 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE APPLICANT

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

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