X-BONE

COMPOSITION:

X-bone 0.25mcg tablets
Each tablet contains:
Alfacalcidol (B.P.) 0.25mcg
X-bone 0.5mcg tablets
Each tablet contains:
Alfacalcidol (B.P.) 0.5mcg
X-bone 1mcg tablets
Each tablet contains:
Alfacalcidol (B.P.) 1mcg
Product conforms to the Manufacturer's Specifications.

DESCRIPTION:

Alfacalcidol (1a-hydroxycholecalciferol) chemically is (5Z, 7E)-9, 10-secocholesta-5, 7, 10(19)-triene-1a, 3ß-diol.Its empirical formula is C27H44O2 and molecular weight is 400.65. Alfacalcidol is a colorless crystalline compound. It is sensitive to light and very soluble in methanol,ethanol and chloroform, soluble in ether, sparingly soluble in methylformate and acetonitrile.

MECHANISM OF ACTION:

1 α -hydroxyvitamin D3 (1 α -OHD3) stimulates intestinal calcium and phosphorus absorption and possibly the renal reabsorption of calcium. To be effective in disorders resulting from vitamin D deficiency, vitamin D must undergo two metabolic conversions, first in the liver to 25-hydroxyvitamin D and then in the kidney to the physiologically active metabolite, 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3). In patients with chronic renal failure, progressive nephron destruction blocks the production of 1,25-(OH)2D3 by the kidneys resulting in diminished serum levels of this metabolite.

PHARMACOKINETICS:

When Alfacalcidol (X-bone) is administered in this clinical situation, it is rapidly converted to 1,25-(OH)2D3 in the liver effectively bypassing the critical renal metabolic conversion. This hepatic conversion of Alfacalcidol (X-bone) is accomplished very rapidly, before any stimulation of the intestine or bone occurs.
The biological half life of Alfacalcidol has been shown to be approximately 3 hours in the presence of renal insufficiency. However, serum levels of 1,25-(OH)2D3 peak approximately 12 hours after a single dose of Alfacalcidol (X-bone) and remain measurable for at least 48 hours. The effect of 1 µg of Alfacalcidol on intestinal calcium absorption has been observed within 6 hours of ingestion and was maximal at 24 hours.
One of the first abnormalities to be observed in patients with chronic renal failure is the disturbance of calcium metabolism due to increased phosphate retention and impaired production of 1,25-(OH)2D3. Because calcium metabolism and production of 1,25-(OH)2D3 is at least partially mediated by the parathyroid glands, hypocalcemia leads to increased parathyroid hormone (PTH) secretion and high plasma PTH levels. Therefore, the patients with renal bone disease most likely to benefit from Alfacalcidol (X-bone) therapy are those characterized by abnormally low plasma calcium levels, elevated alkaline phosphatase and PTH levels and histological evidence of osteitis fibrosa and osteomalacia.
In the majority of patients treated with Alfacalcidol (X-Bone), clinical symptoms of bone pain and

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muscle weakness begin to remit promptly, within 2 weeks to 3 months of the start of therapy. Malabsorption of calcium is rapidly corrected. Plasma alkaline phosphatase and PTH levels generally begin to fall within 3 months, but plasma calcium levels may not normalize for several months. This delay should not necessarily be construed as a poor response. Inorganic phosphorus absorption is less marked, although it is important to recognize that the drug may increase plasma phosphorus concentrations, which may increase the requirements for phosphate binding agents.

INDICATIONS:

Alfacalcidol (X-bone) is used for treating conditions in which calcium metabolism is disturbed due to impaired 1α hydroxylation, (i.e. reduced renal function), in other disorders associated with Vitamin D resistance and in calcium malabsorption of osteoporosis.
The main indications are renal bone disease (renal osteodystrophy), hypoparathyroidism (with bone disease), nutritional and malabsorptive rickets and osteomalacia, hypophosphatemic Vitamin D resistant rickets and osteomalacia, pseudo-deficiency (D dependent Type I) rickets with osteomalacia and osteoporosis.

DOSAGE & ADMINISTRATION:

The daily dose must be carefully individualized and titrated according to such factors as the state of renal function, degree of bone mineralization and initial plasma calcium and alkaline phosphatase concentrations. Other factors which may be taken into account are urinary calcium excretion, plasma PTH and phosphorus.
The success of Alfacalcidol (X-bone) is also based on the assumption that the patient is receiving an adequate daily intake of calcium during treatment. The recommended daily allowance of calcium in adults is about 800 to 1000 mg (from all sources such as dialysate, diet and calcium supplements). The physician should ensure that each patient receives an adequate daily intake of calcium by prescribing a calcium supplement or instructing the patients in appropriate dietary measures.
Dose Titration: Predialysis Patients: A dose of Alfacalcidol (X-bone) that maintains serum calcium (adjusted for albumin concentration) within the normal range should be selected. An initial dose of 0.25 µg/day is recommended, followed by dose adjustment until an appropriate dose is achieved. Alfacalcidol (X-bone)has been shown to be safe and effective in the prevention of renal bone disease when doses were maintained at or below 1 µg/day. Alfacalcidol (X-bone) is usually administered as a single dose each day taken with food.
Protocol for Dosage Adjustment: An initial dose of 0.25µg/day should be administered for 2 months, unless hypercalcemia develops. If hypercalcemia occurs then the dose should be reduced to 0.25µg on alternate days. If serum calcium is below the desired range, the dose may be adjusted in increments of 0.25 µg/day every 2 months. Most patients will be maintained on a dose of 0.5 µg/day. However, doses up to 1 µg/day may be necessary to maintain serum calcium within the desired range. If hypercalcemia develops at any time during treatment then the dose of Alfacalcidol (X-bone) should be reduced by 50% and all calcium supplements stopped until calcium levels return to normal.
Serum calcium and phosphate levels should be monitored at monthly intervals or as is considered necessary if hypercalcemia develops. Calcium supplements should not exceed 500mg of elemental calcium per day.
Dose Titration for Hemodialysis Patients: The recommended initial dose is 1µg daily. If a satisfactory response in the biochemical parameters and Antacids containing magnesium should be avoided as they may contribute towards hypermagnesemia clinical manifestation is not observed within 4

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Patients and their immediate relatives should be informed about the need for compliance with the dosage instructions, strict adherence to prescribed calcium intake, dietary and supplementary and avoidance of unapproved nonprescription drugs or medications.
Patients should be made aware of symptoms of hypercalcemia and should be instructed to seek medical attention if such symptoms appear.

ADVERSE DRUG REACTIONS:

In general, the adverse effects of Alfacalcidol (X-bone) are similar to those encountered with excessive vitamin D intake.
Early symptoms: Pruritus, weakness, headache, red-eyes, somnolence, nausea, cardiac arrhythmia, vomiting, excessive thirst, dry mouth, constipation, muscle pain, bone pain and metallic taste.
Late symptoms: Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis, corneal calcification, photophobia, rhinorrhea, pancreatitis, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias and, rarely, overt psychosis.
Hypercalcemia and possibly an exacerbation of hyperphosphatemia are the most frequent adverse reactions that have been reported with Alfacalcidol (X-bone) in patients with renal osteodystrophy. Elevated levels of calcium and phosphorus increase the risk of metastatic calcification and may accelerate the decline in renal function in some patients with chronic renal failure.

OVER DOSAGE:

Symptoms: Hypercalcemia, hypercalciuria and hyperphosphatemia. A high intake of calcium and phosphate concomitantly with therapeutic doses of Alfacalcidol (X-bone) may cause similar abnormalities.
Treatment of Hypercalcemia Due to Overdose: General treatment of hypercalcemia (more than 1mg/dL or 0.25 mmol/L above the upper limit of the normal range (usually 8.0-10.4 mg/dL or 2.2-2.6 mmol/L)) consists of immediate discontinuation of Alfacalcidol (X-bone), institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium levels should be determined daily until the patient achieves normocalcemia. Hypercalcemia frequently resolves in 2 to 7 days. When serum calcium levels have returned to within normal limits, Alfacalcidol therapy can be reinstituted at half the previous dose. Serum calcium levels should be carefully monitored (at least twice weekly) during this period of dosage adjustment and subsequent dosage titration. Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium free dialysate.
Treatment of Accidental Overdosage: General supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium ion), rate of urinary calcium excretion and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and low calcium diet are also indicated in accidental overdosage. Due to the relatively short pharmacological action of Alfacalcidol, further measures are probably unnecessary. However, if persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered depending on the underlying condition of the patient. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce an appropriate forced diuresis. The use of dialysis against a calcium free dialysate has also been reported.

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weeks, the daily dose may be increased by 0.5 µg every 2 to 4 weeks. Most patients respond eventually to a dose of between 1 and 2 µg/day. Exceptionally, a dose of 3 µg is required. Maintenance Therapy: Once serum calcium levels are normalized or only slightly reduced, the dose requirement of Alfacalcidol (X-bone) generally decreases. Maintenance doses usually range from 0.25 to 1.0 µg/day. If this small maintenance dose still proves too high, adequate control can usually be achieved by giving the dose on alternate days or even less frequently.

CONTRAINDICATIONS:

As with all vitamin D preparations and metabolites, Alfacalcidol (X-bone) is contraindicated with hypercalcemia.

PRECAUTIONS:

Alfacalcidol (X-bone) should not be used concomitantly with other vitamin D products or derivatives. As with all vitamin D preparations and metabolites, hypercalcemia must be anticipated when using Alfacalcidol (X-bone). Regular monitoring of plasma calcium is essential. Indeed, Alfacalcidol (X-bone) should only be used when adequate facilities are available for monitoring of blood and urine chemistries on a regular basis. During treatment with Alfacalcidol (X-bone), progressive hypercalcemia either due to hyperresponsiveness or overdose may become severe enough to require emergency treatment.Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis or calcifications of the cornea or other soft tissues. During treatment with Alfacalcidol (X-bone), the total serum calcium (mg/dL) times serum inorganic phosphate (mg/dL) should be maintained at accepted levels. A dialysate calcium level of 7.0mg/dL (1.75 mmol/L) or above, in addition to excess dietary calcium supplements may lead to frequent episodes of hypercalcemia. To control serum inorganic phosphate levels and dietary phosphate absorption, appropriate oral phosphate binding agents in association with a low phosphate diet may be necessary to prevent hyperphosphatemia and extra skeletal calcifications. Serum phosphate levels were maintained below 2 mmol/L in the study that demonstrated the benefits of Alfacalcidol (X-bone) on the development of bone disease in predialysis patients.In patients on digitalis, hypercalcemia may precipitate cardiac arrhythmias. Use Alfacalcidol (X-bone) with extreme caution in these patients.

The therapeutic margin with Alfacalcidol (X-Bone) is narrow, the optimal daily dose must be carefully titrated for each individual patient. The occurrence of hypercalcemia depends on such factors as the degree of bone mineralization, the state of renal function and the dose of Alfacalcidol (X-bone). Excessive doses of the drug induce hypercalcemia and hypercalciuria.

PREGNANCY AND LACTATION:

Safety in pregnancy has not been established. Use of Alfacalcidol (X-bone) in pregnancy may be considered only when the potential benefits have been weighed against possible hazards to mother and fetus. Alfacalcidol (X-bone) may be excreted in human milk, therefore breastfeeding during treatment should be avoided.

DRUG-DRUG INTERACTION:

Alfacalcidol (X-bone) should be used with extreme caution in patients on digitalis, as hypercalcemia may trigger cardiac arrhythmias. Resins such as cholestyramine and mineral oil used as a laxative may interfere with the intestinal absorption of Alfacalcidol. Patients concurrently treated with barbiturates and other anticonvulsant drugs may require higher doses of Alfacalcidol (X-bone), as these drugs may interfere with the action of vitamin D.

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STORAGE:

Store in a cool & dry place below 25OC.
Protect from light, heat and moisture.
Keep out of reach of children

PRESENTATION:

X-bone 0.25 mcg tablets are available in a blister pack of 30's.
X-bone 0.5 mcg tablets are available in a blister pack of 30's.
X-bone 1.0 mcg tablets are available in a blister pack of 30's.