Bonefos adalah obat baru yang terdaftar tahun 2007.
Informasi di bawah ini merupakan informasi update tahun 2008.

BONEFOS 800 mg

Important information, please read carefully!

Composition
1 tablet contains 800 mg disodium clodronate.

Properties
Clodronate is chemically defined as a bisphosphonate and is an analogue of the natural pyrophosphate. Bisphosphonates have a strong affinity for mineralized tissue such as bone. In vitro, they inhibit the precipitation of calcium phosphate, block its transformation into hydroxyapatite, delay the aggregation of apatite crystals into larger crystals and slow down the dissolution of these crystals.

However, the most important mechanism of action of clodronate is its inhibitory effect on osteoclastic bone resorption. Clodronate inhibits bone resorption induced in several ways. In growing rats, this inhibition of bone resorption at high doses of clodronate causes broadening of long bone metaphyses.

In ovariectomized rats, bone resorption is inhibited at doses as low as 3 mg/kg administered subcutaneously once a week. At pharmacological doses clodronate prevents reduction of bone strength. The pharmacological efficacy of clodronate has been demonstrated in different types of preclinical experimental models of osteoporosis, including estrogen deficiency. Clodronate has been shown to inhibit dose-dependently bone resorption, without deleterious effects on mineralization or on other bone quality aspects. Bone resorption in experimental renal osteodystrophy is also inhibited by clodronate.

The ability of clodronate to inhibit bone resorption in humans has been established in histological, kinetic and biochemical studies. However, the exact mechanisms of bone resorption inhibition are partly unknown. Clodronate suppresses the activity of osteoclasts, reducing the serum calcium concentation and urinary excretion of calcium and hydroxyproline. Clodronate prevents bone loss associated with breast cancer in the hip and lumbar spine in pre- and postmenopausal women. When clodronate is used alone at doses inhibiting bone resorption, no effects on normal bone mineralization in humans have been observed. A decrease in fracture risk has been observed in patients with breast cancer and multiple myeloma. In primary breast cancer clodronate has been shown to reduce the occurrence of bone metastases.

Pharmacokinetic Properties

As with other bisphosphonates, the gastrointestinal absorption of clodronate is low, about 2%. The absorption of clodronate is rapid: the peak serum concentration after a single oral dose is reached within 30 minutes. Due to the strong affinity of clodronate for calcium and other divalent cations, absorption is negligible when clodronate is taken with meals or drugs containing divalent cations. In a study where clodronate was administered 2 hours before breakfast as the reference treatment, a dose breakfast interval of 1 h or 0.5 h decreased the bioavailability of clodronate, but the difference was not statistically significant (relative bioavailability 91% and

69%, respectively). In addition, there is large inter-and intra-individual variation in the gastrointestinal absorption of clodronate. Despite the large intraindividual variation in the absorption of clodronate, the exposure to clodronate remains constant when repeated doses are used.

Only a small part of clodronate is bound to plasma proteins. The distribution volume of clodronate is 20-50 liters. The elimination of clodronate from serum is characterized by two clearly distinct phases: the distribution half life is about two hours, and the elimination is very slow due to the high affinity of clodronate for bone. Clodronate is eliminated mainly via the kidneys. About 80% of the absorbed clodronate appears in urine within a few days, and the renal clearance is about 75% of the plasma clearance. The substance bound to bone (about 20% of the absorbed amount) is excreted more slowly.

Because clodronate affects bone, there is no clear relationship between plasma or blood concentrations of clodronate and the therapeutic activity, or the adverse drug reactions. Apart from renal insufficiency, which decreases the renal clearance of clodronate, the pharmacokinetic profile is not affected by any known factor related to age, drug metabolism, or other phatological conditions.

Preclinical safety data

Single dose studies in mice and rates gave the following LD_{50} values:

Oral administration >3600 mg/kg (mouse)
2200 mg/kg (rat)

Intravenous administration 160 mg/kg (mouse)
120 mg/kg (rat)

In mice and rats, clinical signs of acute toxicity comprised decreased motor activity, convulsions, unconsciousness, and dyspnea. In the mini-pig, an intravenous dose of 240 mg/kg was toxic after two or three infusions, probably due to hypocalcemia.

Studies or repeated dose toxicity lasting from 2 weeks to 12 months have been performed in rats and minipigs. A few deaths were reported in all of these studies. Intravenous administration was lethal to rats at daily dose of 140 and 160 mg/kg after 1-7 days. In the mini-pig, an intravenous daily dose 80 mg/kg caused after 7-13 days vomiting and general weakness before death. No clodronate related mortality was noted in rats on oral daily doses of 100-480 mg/kg or in mini-pigs on oral daily doses of 800 mg/kg.

In toxicity studies, clodronate was observed to affect the following organs (the observed changes with brackets) : bone (sclerosis related to the pharmacological effects of clodronate), gastrointestinal tract (irritation), blood (lympopenia, effects on hemostasis), kidneys (dilated tubules, proteinurea), and liver (elevation of serum transaminase levels).

In animal studies, clodronate therapy during pregnancy did not cause fetal damage but large doses decreased male fertility. After one month of subcutaneous administration of clodronate to newborn offspring, skeletal changes resembling osteopetrosis were found; the changes are related to the pharmacological effects of clodronate.

Clodronate has not proved to have genotoxic effects. No carcinogenic effects have been observed in studies in rats and mice.

Indications
Treatment of hypercalcemia due to malignancy. Treatment of osteolysis due to malignancy. Reduction of occurrence of bone metastases in primary breast cancer.

Dosage and Method of Administration
Clodronate is mainly eliminated via the kidneys. Therefore, adequate fluid intake must be maintained during clodronate treatment.

- Children
  Safety and efficacy in pediatric patients have not been established.

- Elderly
  There are no special dosage recommendations for the elderly. Clinical trials have included patients over 65 years and no adverse effect specific to this age group have been reported.

A Bonefos 800 mg tablet may be divided into two to ease swallowing, but the halves have to be taken at the same time of administration. Bonefos tablets should not be crushed or dissolved before intake.

A daily dose of 1600 mg is recommended to be taken as a single doses. When higher daily doses are used, the part of the doses exceeding 1600 mg is recommended to be taken separately (as a second dose) as recommended below.

The single daily dose and the first dose of two should preferably be taken in the morning on an empty stomach together with a glass of water. The patient should then refrain from eating, drinking (other than plain water), and taking any other oral drugs for one hour.

When twice daily dosing is used, the first doses should be taken as recommended above. The second dose should be taken between meals, more than two hours after and one hour before eating, drinking (other than plain water), or taking any other oral drugs.

Clodronate should in no case be taken with milk, food or drugs containing calcium or other divalent cations because they impair the absorption of clodronate.

- Adult patients with normal renal function

Treatment of hypercalcemia due to malignancy

Intravenous clodronate is recommended for the treatment of hypercalcemia due to malignancy. However, if oral therapy is used, a high starting dose of 2400 or 3200 mg daily should be used and, depending on the individual response, this can be reduced gradually to 1600 mg daily in order to maintain normocalcemia.

Treatment of osteolysis due to malignancy

When oral therapy is used to treat increased bone resorption without hypercalcemia the dosage is individual. The recommended starting dose is 1600 mg daily. If clinically necessary, the dose may be increased, but is not recommended to exceed 3200 mg daily.

Reduction of occurrence of bone metastases in primary breast cancer

The recommended dose is 1600 mg daily.

- Patients with renal failure
  Clodronate is eliminated mainly via the kidneys. Therefore, it should be used with caution in patients with renal failure; daily doses exceeding 1600 mg should not be used continuously.

Special warnings and special precautions for use
Adequate fluid intake must be maintained during clodronate treatment. This is particularly important when administering clodronate as intravenous infusion and in patients with hypercalcemia or renal failure.

Clodronate should be used with caution in patients with renal failure (see dose adjustment under Dosage).

Intravenous administration of doses notably higher than those recommended may cause severe renal damage, especially if the infusion rate is too high.

Pregnancy and lactation
Although in animals clodronate passes through the placental barrier, it is not known if it is secreted in breast milk or passes into the fetus in humans. Furthermore, it is not known if clodronate can cause fetal damage or affect reproduction in humans. Therefore, clodronate should not be used for pregnant or lactating women, unless the therapeutic advantages clearly outweigh any risks.

Overdose

- Symptoms
  Increases in serum creatinine and renal dysfunction have been reported with high intravenous doses of clodronate.
- Treatment
  Treatment of overdose should be symptomatic. Adequate hydration should be ensured, and renal function and serum calcium should be monitored.

Effect on ability to drive and use machines
There is no reason to expect clodronate to have any effect on ability to drive vehicles or use machines.

Undesirable Effects

The most common reported adverse drug reactions are nausea, vomiting and diarrhea occurring in approximately 10% of patients: these reactions are usually mild and occur more commonly with higher doses.

These adverse reactions may occur in connection with both oral and intravenous treatment, although the frequency of reactions may differ.

- Metabolism and nutritional disorders
  Common : Asymptomatic hypocalcemia
  Rare : Symptomatic hypocalcemia

  Elevated serum parathyroid hormone levels have observed usually associated with the reduction of serum calcium levels.

Changes in serum concentrations of alkaline phosphatase have been observed. In patients with metastatis disease alkaline phosphatase may also be elevated due to liver and bone metastases.

- Respiratory, thoracic and mediastinal disorders
  Very rare : Impairment of respiratory function in patients with aspirin-sensitive asthma. Hypersensitivity reactions manifesting as respiratory disorder.

- Gastrointestinal disorders
  Common : Nausea, vomiting, and diarrhea, which are usually mild.

- Hepato-biliary disorders
  Common : Elevations of aminotransferases usually within normal range.
  Rare : Elevations of aminotransferases exceeding twice the normal range without associated impairment of liver function.

- Skin and subcutaneous tissue disorders
  Rare: Skin reactions fitting the picture of hypersensitivity-type skin reaction.

- Renal and urinary disorders
  Rare : Impairment of renal function (elevation of serum creatinine and proteinuria), severe renal damage especially after rapid intravenous infusion of high doses of clodronate (for dosing instructions see the table under Dosage).

Contraindications
Known hypersensitivity to bisphosphonates. Concomitant treatment with other bisphosphonates

Interaction with other medicaments and other forms of interaction
Concomitant use with other bisphosphonates is contraindicated.

Clodronate has been reported to be associated with renal dysfunction when used simultaneously with non-steroidal anti-inflammatory analgesics (NSAIDs), most often diclofenac.

Due to increased risk of hypocalcemia, caution should be taken when using clodronate together with aminoglycosides.

Concomitant use of estramustine phosphate with clodronate has been reported to increase the serum concentration of estramustine phosphate by 80% at the maximum.

Clodronate forms poorly soluble complexes with divalent cations. Therefore, simultaneous administration with food or drugs containing divalent cations, e.g. antacids or iron preparations, leads to significantly reduced bioavailability of clodronate.

Storage

Store all drugs properly and keep them out of reach of children
Do not store above 25ºC.

Shelf-life : 5 years.

Pack Size:
Box, 3 blister @ 10 tablets
Reg.No.:DKI0775601217A1

Harus dengan resep dokter

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