BONEFOS® 60 mg/ml

Concentrate for parenteral infusion

Important information, please read carefully!

Composition

1 ml concentrate for solution for infusion contains 60 mg disodium clodronate. One 5 ml ampoule contains 300 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 concentration and urinary excretion of calcium and hydroxyproline. Clodronate prevents bone loss associated with breast cancer in the hips 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 or multiple myeloma.
Preclinical safety data

- Acute toxicity
  Studies with single doses in mice and rats gave the following LD_{50} values:

<table>
<thead>
<tr>
<th>Oral administration</th>
<th>Intravenous administration</th>
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</thead>
<tbody>
<tr>
<td>&gt;3600 mg/kg (mouse)</td>
<td>160 mg/kg (mouse)</td>
</tr>
<tr>
<td>2200 mg/kg (rat)</td>
<td>120 mg/kg (rat)</td>
</tr>
</tbody>
</table>

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.

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

In toxicity studies, the effect of clodronate was observed in the following organs (the observed changes within brackets): bone (sclerosis related to the pharmacological effects of clodronate), gastrointestinal tract (irritation), blood (lymphopenia, effects on hemostasis), kidneys (dilated tubules, proteinuria), and liver (elevation of serum transaminases).

- Reproduction toxicity
  In animal studies, clodronate did not cause fetal damage, but large doses decreased male fertility. After one month of subcutaneous administration of clodronate to newborn rats, skeletal changes resembling osteopetrosis were found, which are related to the pharmacological effects of clodronate.

- Genotoxic potential, tumorigenicity
  Clodronate has not shown genotoxic potential. No carcinogenic effects have been observed in studies with rats and mice.

Indications

Treatment of hypercalcemia due to malignancy.
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.

Adequate hydration should be ensured, and renal function and serum calcium levels should be monitored before and during treatment.

The length of time that a clinically acceptable serum calcium level is maintained after infusion of clodronate varies considerably from patient to patient. The infusion may be repeated if necessary to control the serum calcium level or, alternatively, treatment with oral clodronate may be appropriate.

- **Adult patients with normal renal function**
  Clodronate is given as an intravenous infusion of 300 mg (one 5 ml ampoule)/day diluted into 500 ml of either saline (sodium chloride 9 mg/ml) or 5% glucose (50 mg/ml) solution. The prepared solution shall be infused over a period of a minimum of two hours on successive days until normocalcemia is achieved, which usually happens within five days. Such therapy should normally not be continued for more than seven days. Alternatively, the dose of 1500 mg clodronate can be given as a single dose, diluted in a volume of 500 ml as recommended above, with an infusion time of four hours.

- **Patients with renal failure**
  It is recommended that the clodronate dosage to be infused should be reduced as follows:

<table>
<thead>
<tr>
<th>Degree of renal failure</th>
<th>Creatinine clearance (ml/min)</th>
<th>Reduction in dosage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>50-80</td>
<td>25</td>
</tr>
<tr>
<td>Moderate</td>
<td>12-50</td>
<td>25 - 50</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 12</td>
<td>50</td>
</tr>
</tbody>
</table>

It is recommended that 300 mg clodronate be infused prior to hemodialysis and that the dose be reduced by 50 % on non-dialysis days, and limit the treatment schedule to 5 days. It should be noted that peritoneal dialysis removes clodronate poorly from the circulation.
**Contraindications**

Known hypersensitivity to the active substance or to any of the excipients. Concomitant treatment with other bisphosphonates.

**Special warnings and 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 and Method Administration).

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

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including both intravenous and oral bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids.

Preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor dental hygiene) and invasive dental procedures should be avoided while patients are being treated with bisphosphonates.

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. So far, these fractures have not been reported with Bonefos. These transverse or short oblique, fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported.

Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.
Interaction with other medicinal products 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 antiinflammatory 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, clodronate should not be administered intravenously with solution containing divalent cations (e.g. Ringer's solution). In addition clodronate tablets/capsules should not be taken with food or drugs containing divalent cations (e.g. antacids or iron preparations).

Pregnancy and lactation

Pregnancy
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, unless the therapeutic advantages clearly outweigh any risks.

Lactation
It is not known whether clodronate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from clodronate, breast feeding under the treatment with clodronate is not recommended

Effects on ability to drive or use machines
Not known

Undesirable effects
The most common reported drug reaction is diarrhea which is usually mild and occurs more commonly with higher doses. In a randomized, placebo-controlled clinical trial investigating the prevention of skeletal metastases in primary operable breast cancer, 1079 patients were evaluated for safety, and non-severe diarrhea was the only adverse event being significantly more common in the clodronate group as compared with the placebo group.
These adverse reactions may occur in connection with both oral and intravenous treatment, although the frequency of reactions may differ.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 1/100</td>
<td>≥ 1/10,000</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypocalcemia, Asymptomatic</td>
<td>Hypocalcemia, Symptomatic, increased serum parathyroid hormone associated with Serum calcium decreased. Serum alkaline phosphatase increased*</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea**, Nausea**, Vomiting**</td>
<td>Transaminases increased usually within normal range Transaminases increased exceeding twice the normal range without associated Hepatic function abnormal</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Hypersensitivity reaction manifesting as Skin reaction</td>
</tr>
</tbody>
</table>

* in patients with metastatic disease, may also be due to hepatic and bone disease.
** usually mild

**Post-marketing experience**

- **Eye disorders**

Uveitis has been reported with Bonefos during post-marketing experience. The following reactions have been reported with other bisphosphonates: Conjunctivitis, episcleritis and scleritis.

Conjunctivitis was only reported with Bonefos in one patient concomitantly treated with another bisphosphonate. So far, episcleritis and scleritis have not been reported with Bonefos (bisphosphonate class adverse reaction)

- **Respiratory, thoracic and mediastinal disorders**

Impairment of respiratory function in patients with aspirin-sensitive asthma. Hypersensitivity reactions manifesting as respiratory disorder.

- **Renal and urinary disorders**

Impairment of renal function (elevation of serum creatinine and proteinuria), severe renal damage especially after rapid intravenous infusion of high doses of clodronate (for dosage instructions see section “Dosage and method of administration” under “Intravenous infusion" chapter "Patients with renal failure”

Single cases of renal failure, in rare cases with fatal outcome have been reported especially with concomitant use of NSAIDs, most often diclofenac

- **Musculoskeletal and connective tissue disorders:**

Isolated cases of osteonecrosis of the jaw have been reported, primarily in patients who were previously treated with amino- bisphosphonates like zoledronate and pamidronate (see also section “Special warnings and special precautions for use”)

Severe bone, joint, and/or muscle pain has been reported in patients taking Bonefos. However, such reports have been infrequent and in randomised placebo controlled studies no differences are apparent between placebo and Bonefos treated patients. The onset of symptoms varied from days to several months after starting Bonefos.

During post-marketing experience the following reactions have been reported with other bisphosphonates: Atypical subtrochanteric and diaphyseal femoral fractures. So far, these reactions have not been reported with Bonefos (bisphosphonate class adverse reaction) (see also section 'Special warnings and precautions for use').

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.
ADR term representation in section “UNDESIREABLE EFFECTS” is based on MedDRA version 8.1

**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.

**Incompatibilities**
Concentrate for solution for infusion: The compatibility of Bonefos 60 mg/ml concentrate for solution for infusion with other admixed drugs or injection solutions has not been studied. Therefore, the concentrate should only be diluted and administered as advised in section "Instructions for use / handling".

**Instructions for use / handling**
For intravenous administration the content of one 5 ml ampul is diluted into 500 ml of either saline (sodium chloride 9 mg/ml) or 5% glucose (50 mg/ml) solution. Alternatively, for the 1500 mg regimen, the contents of five 5 ml ampuls (altogether 25 ml) are diluted into 500 ml of either sodium chloride 9 mg/ml or glucose 50 mg/ml solution.

Store all drugs properly and keep them out of reach of children.
**Presentation**
Dus, 5 ampoules @ 5 ml

**Shelf life**
3 years.
Diluted infusion solution shall be used within 12 hours.

**Storage**
Do not store above 30°C and do not freeze.

**Harus dengan resep dokter**

Manufactured by:
JenaHexal Pharma GmbH,
Jena - Germany
For Bayer Oy, Turku-Finland

Imported by:
PT. Bayer Indonesia,
Jakarta-Indonesia