Bonefos® 60 mg/ml

Concentrate for solution for infusion

1. NAME OF THE MEDICINAL PRODUCT

Bonefos 60 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of the concentrate for solution for infusion contains 60 mg disodium clodronate.

One 5-ml ampule contains 300 mg disodium clodronate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear and colorless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypercalcemia due to malignancy and treatment of osteolytic bone metastases in connection with conventional cancer therapy.

4.2 Posology and method of administration

Clodronate is eliminated mainly via the kidneys. Therefore, adequate fluid intake must be maintained during clodronate treatment.

Pediatric patients: Safety and efficacy in children have not been established.

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

Adequate hydration must 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

The normal dose is 300 mg (one 5-ml ampule) clodronate daily, diluted into 500 ml of either glucose (50 mg/ml) or sodium chloride (9 mg/ml) solution.

The prepared solution will 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 4 hours.

Patients with renal failure

It is recommended that the clodronate dose to be infused be reduced as follows:

Renal failure	Creatinine clearance, ml/min	Reduction in dose (%)
Mild	50–80	25
Moderate	12–50	25–50
Severe	< 12	50

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Concomitant treatment with other bisphosphonates.

4.4 Special warnings and precautions for use

Adequate fluid intake must be maintained during clodronate treatment. This is particularly important in patients with hypercalcemia or renal failure.

Renal function with serum creatinine, calcium and phosphate levels should be monitored before and during treatment.

In clinical trials, asymptomatic, reversible elevations of transaminases have occurred, without changes in other liver function tests. Monitoring of serum transaminases is advised (see also section 4.8).

Clodronate should be used with caution in patients with renal failure (see dose recommendations under section 4.2 Posology and method of administration).

Infusion of doses 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 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 other 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.

Dental surgery may exacerbate the condition in patients who develop osteonecrosis of the jaw while on bisphosphonate therapy. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement by the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Bonefos 60 mg/ml concentrate for solution for infusion contains 53 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondular flare. These fractures usually 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. The fractures may be 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.

4.5 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 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 orally administered estramustine phosphate by up to 80%.

Clodronate forms poorly soluble complexes with divalent cations. Therefore, clodronate should not be administered intravenously with solutions containing divalent cations (e.g. Ringer's solution).

4.6 Fertility, pregnancy and lactation

Fertility

In animal studies, clodronate did not cause fetal damage, but large doses decreased male fertility.

No clinical data on the effect of clodronate on fertility in humans is available.

Pregnancy

It is not known if clodronate passes into the fetus in humans. In animal studies, clodronate did pass through the placental barrier into the fetus. Furthermore, it is not known if clodronate can affect reproduction or cause fetal damage in humans. There are only limited amount of data from the use of clodronate in pregnant women. Bonefos is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Lactation

It is unknown whether clodronate is excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Bonefos.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

The most common reported drug reaction is diarrhea which is usually mild and occurs 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.

System organ class	Common ≥ 1/100, < 1/10	Rare ≥ 1/10,000, < 1/1,000
Metabolism and nutrition disorders	Asymptomatic hypocalcemia	Symptomatic hypocalcemia, increased serum parathyroid hormone associated with a reduction in serum calcium, increased serum alkaline phosphatase*
Gastrointestinal disorders	Diarrhea**, nausea**, vomiting**	
Hepatobiliary disorders	Increased aminotransferases, usually within normal range	Increased aminotransferases, exceeding twice the normal range without associated hepatic failure
Skin and subcutaneous tissue disorders		Hypersensitivity-type skin reactions

* in patients with metastatic disease, may also be due to hepatic or bone metastases

** 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.

▶ 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 "Posology and method of administration – Patients with renal failure").

Single cases of renal failure have been reported, especially when clodronate has been used simultaneously with non-steroidal anti-inflammatory analgesics (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 aminobisphosphonates such as zoledronate and pamidronate (see also section "Special warnings and 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 randomized 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.

The following reactions have been reported during post-marketing experience (with rare incidence):

Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction) (see also section 4.4).

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

4.9 Overdose

Symptoms

Increases in serum creatinine and kidney dysfunction have been reported after 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonates, clodronate
ATC code: M05BA02

Clodronate is chemically defined as a bisphosphonate, and it is an analogue of the natural pyrophosphate. Bisphosphonates have a strong affinity for mineralized tissues such as bone. *In vitro,* they inhibit the precipitation of calcium phosphate, block its transformation into hydroxyapatite, delay the aggregation of hydroxyapatite 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 bone resorption dose-dependently, 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 not known. 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 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.

5.2 Pharmacokinetic properties

Absorption

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 administration 2 h before breakfast was used 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 intraindividual 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.

Distribution and elimination

The plasma protein binding of clodronate is low, and the distribution volume is 20–50 L. The elimination of clodronate from serum is characterized by two clearly distinct phases: the distribution phase with a half-life of about 2 hours, and an elimination phase which is very slow since clodronate is strongly bound to 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.

Specific patient groups

Because clodronate affects bone, there is no clear relationship between plasma or blood concentrations of clodronate and the therapeutic activity or with 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 pathological conditions.

5.3 Preclinical safety data

Acute toxicity

Studies with single doses in mice and rats 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.

Systemic tolerability

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 clodronate related mortality was noted.

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

Reproduction toxicology

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

Genotoxicity, tumorigenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

Water for injection

6.2 Incompatibilities

The compatibility of Bonefos concentrate for solution for infusion with other admixed drugs or injection solutions has not been studied. Therefore, the concentrate should only be used as advised in section 6.6.

6.3 Shelf-life

3 years.

Once diluted, immediate use of the solution is recommended. The chemical and physical stability of the ready-to-use solution for infusion has been demonstrated for 12 hours at 15–25°C. However, from a microbiological point of view, the ready-to-use solution should be used immediately after preparation. If not used immediately, the user is responsible for storage times and conditions; 12-hour storage at 2 to 8°C should not be exceeded.

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

6.5 Nature and contents of container

Clear, colorless glass ampule: 5 x 5 ml

6.6 Instructions for use and handling

Preparation of infusion solution:

Add 5 ml of the infusion concentrate (60 mg/ml; 1 ampule = 300 mg clodronate) in 500 ml of glucose (50 mg/ml) or sodium chloride solution (9 mg/ml).

For further instructions, see section 4.2 Posology and method of administration.

7. Manufacturer

Bayer Oy, Turku, Finland

8. Registration Holder

Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in January 2013.