"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו ביוני 2013"

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

1. NAME OF THE MEDICINAL PRODUCT

Bonefos 800 mg

2. Qualitative and quantitative composition

1 tablet contains 800 mg disodium clodronate.
In the preparation, the active ingredient is in the form of disodium clodronate tetrahydrate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet
White, oval, scored, film-coated tablet, marked L 134 on one side. Size of tablet 9 mm x 20 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypercalcemia due to malignancy. Palliative treatment of osteolysis due to malignancy.

4.2 Posology and method of administration

Clodronate is mainly eliminated 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.

Bonefos tablets should be swallowed whole. 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 must not be crushed or dissolved before intake.

A daily dose of 1600 mg should be taken as a single dose. When higher daily doses are used, the part of the dose exceeding 1600 mg should 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 dose 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 drugs.

Clodronate should in no case be taken with drinks, 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 treatment is recommended for the start of treatment in hypercalcemia. Subsequently, an oral dosage of 1600–3200 mg clodronate daily may be used. However, if oral therapy is used, a high starting dose of 2400 -3200 mg should be used and, depending on the individual response, this can be reduced gradually to 1600 mg daily..

Treatment of osteolysis due to malignancy:

When oral therapy is used to treat increased bone resorption without hypercalcemia 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.

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.

It is recommended that the clodronate dosage be reduced as follows:

Renal insufficiency	Creatinine Clearance, ml/min	Dose
Mild	50-80 ml/min	1600 mg/daily (no need to reduce the dose)
Moderate	30-50 ml/min	1200 mg/daily
Severe*	≤10-30 ml/min	800 mg/daily

*) No pharmacokinetic data are available in patients with renal failure with creatinine clearance below 10 ml/min for oral clodronate.
Bonefos tablets are contraindicated in patients with severe renal failure (creatinine clearance below 10ml/min),

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Concomitant treatment with other bisphosphonates.
Bonefos tablets are contraindicated in patients with severe renal failure (creatinine clearance below 10ml/min).

4.4 Special warnings and special 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).

Osteonecrosis of the jaw, generally 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 bisphosphonates treatment reduces the risk of osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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, simultaneous administration with food or drugs containing divalent cations, e.g. antacids or iron preparations, leads to significantly reduced bioavailability of clodronate.

4.6 Fertililty ,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.

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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 not known 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 to < 1/1,000
Metabolism and nutrition disorders	Asymptomatic hypocalcemia	Symptomatic Hypocalcemia. elevated serum parathyroid hormone levels associated with a reduction in serum calcium levels . increased serum alkaline phosphatase levels.*
Gastrointestinal disorders	Diarrhea** Nausea** Vomiting**	
Hepatobiliary system	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 reaction

* 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 ans scleritis. Conjunctivitis was only reported with Bonefos in one patient concomitantly treated with another bisphosphonate.

- Respiratory, thoratic 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- Intravenous infusion- 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.

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- Musculoskeletal and connective tissue disorders

Isolated cases of osteonecrosis of the jaw have been reported, primarily in patients who were previously treated with amino-bisphsophonates such as 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 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 symptom and its synonyms and related conditions.

4.9 Overdose

Symptoms

Increases in serum creatinine and renal 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

Clodronate is chemically defined as a bisphosphonate and 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 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 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, the

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 of 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 distinguished phases: the distribution phase with a half-life of about 2 hours, and an elimination phase which is very slow because clodronate is strongly bound to bone. Clodronate is eliminated mainly via the kidneys. About 80% of the absorbed clodronate appears in urine whithin a few days, and the renal clearance is about 75% of the plasma clearance. The substance which is 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 factors 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 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 on 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 therapy during pregnancy did not cause fetal damage but large doses decreased male fertility. After one month of subcutaneous administration of clodronate to newborn, skeletal changes resembling osteopetrosis were found the changes are related to the pharmacological effects of clodronate.

- Genotoxic potential, tumorigenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Silicified microcrystalline cellulose (consisting of microcrystalline cellulose and colloidal anhydrous silica), croscarmellose sodium, stearic acid, magnesium stearate,
Coat:
Opadry II white (consisting of: polyvinyl alcohol, macrogol 3350, titanium dioxide, talc).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Three years.

6.4 Special precautions for storage

Do not store above +25˚C.

6.5 Nature Contents of container

PVC/Aluminium foil blister pack, 10, 30,60,100 tablets.
Not all package sizes may be marketed.

6.6 Instructions for use/handling

Bonefos tablets should be swallowed whole. 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.

Keep all medicines out of reach of children.

7. Manufacturer: Bayer Oy, Turku, Finland

8. Registration Holder: Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240