Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bonefos 800 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sodium clodronate 800 mg (as tetrahydrate).

Each tablet contains sodium 128 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, oval, scored, tablets marked ‘L134’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of hypercalcaemia due to malignancy.
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.

- Children

Safety and efficacy in paediatric 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 effects 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 may 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 (in the case of twice daily dosing) 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), or 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), and 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 hypercalcaemia due to malignancy
Intravenous clodronate is recommended for the treatment of hypercalcaemia 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 normocalcaemia.

Treatment of osteolysis due to malignancy
When oral therapy is used to treat increased bone resorption without hypercalcaemia 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.

- 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 clodronate dosage be reduced as follows:

Degree of renal Failure	**Creatinine Clearance ml/min**	**Dose**
Mild	50-80 ml/min	1600mg daily (no dose reduction recommended)
Moderate	30-50 ml/min	1200mg daily
*Severe**	<30 ml/min	800 mg daily

* No pharmacokinetic data are available in patients with renal failure with creatinine clearance below 10ml/min for oral clodronate. Use in such instances should be avoided except for short term use in the presence of purely functional renal insufficiency caused by elevated serum calcium levels.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. 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 when using clodronate in patients with hypercalcaemia or renal failure.

Renal function with serum creatinine, serum 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 adjustment in section 4.2, “Posology and method of administration”).

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

For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. 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 of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

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 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. So far, these fractures have not been reported with Bonefos. 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 estramustine phosphate by 80% at the maximum.

Clodronate forms poorly soluble complexes with divalent cations. Therefore, clodronate should not be taken with food or drugs containing divalent cations (e.g. antacids or iron preparations).

4.6 Fertility, pregnancy and lactation

4.6.1 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 are available. For use of clodronate in pregnancy and during lactation, see sections 4.6.2 and 4.6.3.

4.6.2 Pregnancy
Although in animals clodronate passes through the placental barrier, it is not known if it passes into the fetus in humans. Furthermore, it is not known if clodronate can cause fetal damage or affect reproduction 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.

4.6.3 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

No known effects on the ability to drive or use machines.

4.8 Undesirable effects

The most common reported adverse drug reaction is diarrhoea which is usually mild and occurs more commonly with higher doses.

In a randomised, placebo controlled clinical trial investigating the prevention of skeletal metastases in primary operable breast cancer, 1079 patients were evaluated for safety, and non-severe diarrhoea was the only adverse event being significantly more common in the clodronate group (1600 mg per day for 2 years) compared with the placebo group.

In a randomised, placebo-controlled study of 5592 patients all aged 75 years or more receiving clodronate 800 mg per day for 3 years for the prevention of osteoporotic fractures only diarrhoea, nausea and vomiting were increased compared with placebo.

System Organ Class	**Common (≥ 1/100, < 1/10)**	**Rare (≥ 1/10,000, < 1/1,000)**
Metabolism and nutrition disorders	Hypocalcaemia, asymptomatic	Hypocalcaemia, symptomatic Increased serum parathyroid hormone associated with decreased serum calcium Increased serum alkaline phosphatase*
Gastrointestinal disorders	Diarrhoea** Nausea** Vomiting**	
Hepatobiliary disorders	Transaminases increased, usually within normal range	Transaminases increased, exceeding twice the normal range without associated abnormal hepatic function
Skin and subcutaneous disorders		Hypersensitivity reaction manifesting as skin reaction

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

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

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.

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 such as zoledronate and pamidronate (see also section 4.4, “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 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 (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures. So far, these reactions have not been reported with Bonefos (bisphosphonate class adverse reaction) (see also section 4.4, “Special warnings and precautions for use”).

Very rare: Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

- Symptoms

Increases in serum creatinine and renal dysfunction have been reported with high intravenous doses of clodronate. One case of acute renal failure and liver injury has been reported after accidental ingestion of 20,000 mg (50x400 mg) clodronate.

- Treatment

Treatment of overdose should be symptomatic. Adequate hydration should be ensured, and renal and hepatic function and serum calcium should be monitored.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 3mg/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 clondronate 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 hours before breakfast was used as the reference treatment, a dose-breakfast interval of 1 hour or 0.5 hour 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 during long-term treatment.

- 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 mainly eliminated via the kidneys. About 80% of the absorbed clodronate appears in urine during a follow-up of a few days. The substance which is bound to bone (about 20% of the absorbed amount) is excreted more slowly, and the renal clearance is about 75% of the plasma clearance.

- Characteristics in patients
  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 LD50 values:

Oral administration	Intravenous administration
>3600 mg/kg (mouse) 2200 mg/kg (rat)	160 mg/kg (mouse) 120mg/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 240mg/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 80mg/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 foetal 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Silicified microcrystalline cellulose
Stearic acid
Magnesium stearate

Coating:
Opadry Y-1-7000
- Hypromellose 5 cP
- Titanium dioxide (E171)
- Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bonefos tablets are supplied in clear, colourless PVC/aluminium blister packs of 60 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA 1410/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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