PRODUCT MONOGRAPH

Pr BONEFOS®

Clodronate disodium for injection
60 mg/mL
for slow intravenous infusion only

and

Clodronate disodium capsules
400 mg/capsule

Bone metabolism regulator
(Antihypercalcemic agent)

Bayer Inc.
2920 Matheson Boulevard East,
Mississauga, Ontario
L4W 5R6
www.bayer.ca

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[Pr] BONEFOS®

clodronate disodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous (IV) For slow infusion	Solution / 60 mg/mL	No clinically relevant nonmedicinal ingredients *For a complete listing see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*
Oral	Capsule / 400 mg	Lactose *For a complete listing see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

BONEFOS (clodronate disodium) is indicated:

- for the management of hypercalcemia of malignancy;
- as an adjunct in the management of osteolysis resulting from bone metastases of malignant tumors.

Prior to treatment with BONEFOS, renal excretion of excess calcium should be promoted by restoration and maintenance of adequate fluid balance and urine output.

In responsive patients, intravenous infusion of BONEFOS decreases the flux of calcium from the bones by inhibiting the osteoclastic activity and bone resorption, thus reducing the calcium level in the blood.

Treatment with oral clodronate following intravenous infusion has been found to prolong the duration of action (see **DOSAGE AND ADMINISTRATION**).

Geriatrics: No data is available. As older patients may have decreased renal function, please refer to the **WARNINGS AND PRECAUTIONS – Renal** section.

Pediatrics: The safety and efficacy of BONEFOS in children have not been established.

CONTRAINDICATIONS

- Renal functional impairment when serum creatinine exceeds 440 µmol/L (5.0 mg/dL) (see **WARNINGS AND PRECAUTIONS**).
- Severe inflammation of the gastrointestinal tract.
- Pregnancy and lactation.

- Concomitant treatment with other bisphosphonates.
- Hypersensitivity to bisphosphonates, clodronate disodium or to any ingredient in the formulation or component of the container. For a complete listing, see the **SUMMARY PRODUCT INFORMATION** and the **DOSAGE FORMS, COMPOSITION AND PACKAGING** sections of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

The recommended daily dose of **IV BONEFOS must be diluted in 500 mL of 0.9% sodium chloride injection USP or 5% dextrose injection USP and administered as a slow intravenous infusion lasting at least two hours. BONEFOS should not be mixed with other intravenous infusions.** No other drugs or nutrients should be added to the diluted infusion solution (see **DOSAGE AND ADMINISTRATION**). BONEFOS (clodronate disodium) should NOT be given as a bolus injection **since rapid bolus injection may precipitate acute renal failure, severe local reactions, and thrombophlebitis.** Extravasation should be avoided. Local reactions may occur (see **ADVERSE REACTIONS**).

Patients must be adequately hydrated before and during the treatment period. This is particularly important when administering clodronate as an intravenous infusion and in patients with hypercalcemia and/or impaired renal function (see **ADVERSE REACTIONS**). Excess calcium impairs the renal concentrating mechanisms resulting in polyuria and excessive fluid loss. Nausea and lethargy caused by hypercalcemia can also reduce oral fluid intake leading to a profound negative fluid balance. Isotonic saline should be administered at a rate determined by the severity of hypercalcemia, the degree of dehydration and the cardiovascular status of the patient (see **WARNINGS AND PRECAUTIONS – Renal**).

Administration of oral dosage form: The drug should be taken on an empty stomach, with a glass of plain water, at least two hours before or after food or any other oral drugs, because food or other drugs may decrease the amount of clodronate disodium absorbed by the body.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection, including osteomyelitis.

A dental examination with appropriate preventative dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (eg, cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ 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 ONJ. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

For injectables, the start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth.

For both the oral and injectable formulations, the following should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds),
- Route of administration (higher risk for parenteral administration)
- Cumulative dose of bone resorption therapy.
- Co-morbid conditions (eg, anemia, coagulopathies) and smoking
- Periodontal disease, poorly fitting dentures, history of dental disease.

Temporary interruption of BONEFOS treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Endocrine and Metabolism

Hypocalcemia: Intravenous or oral administration of clodronate may present a risk of hypocalcemia. When given intravenously, the drug tends to chelate blood calcium during therapy which may contribute to hypocalcemia. Asymptomatic hypocalcemia is a common adverse reaction which occurs in approximately 3% of treated patients. Symptomatic hypocalcemia is rare. Symptomatic hypocalcemia can be reversed by the administration of calcium gluconate.

Serum phosphate: Hyperphosphatemia has not been reported during clodronate therapy. However, transient hypophosphatemia can occur following therapy with clodronate.

Hyperparathyroidism: Increased serum parathyroid hormone levels have been observed in patients receiving clodronate and are attributed to a homeostatic response to the fall in serum calcium. The clinical importance has not been established.

Neurologic

The effect of BONEFOS on the ability to drive and use machinery is not known.

Ophthalmologic

Ocular disturbances including conjunctivitis, uveitis, episcleritis and scleritis have been reported with bisphosphonate therapy. Patients with ocular events other than uncomplicated

conjunctivitis should be referred to an ophthalmologist for evaluation. Treatment may need to be discontinued.

Renal

Administration of clodronate may aggravate renal function in some patients. Intravenous administration of doses notably higher than those recommended may cause severe renal damage, especially if the infusion rate is too high. Appropriate monitoring of the renal function during and after intravenous infusion is required. Since the drug is excreted by the kidneys, it is essential to establish that the excretion of the fluid load and of the drug would not present an excessive medical risk. Adequate fluid intake must be maintained during clodronate treatment. If during therapy there is deterioration of renal function, the intravenous infusion must be stopped.

Clodronate should be used with caution in patients with renal impairment. When the benefits of the use of clodronate in renal impairment outweigh the risks, dose adjustment should be considered, otherwise, the drug should be withheld. Data for dose adjustment in relation to renal function have been derived from a study involving 24 subjects with chronic renal impairment of varying severity and 24 healthy volunteers with normal renal function. Based on the results of this study, dose reductions are recommended depending on the degree of renal insufficiency (see **DOSAGE AND ADMINISTRATION**). Serum creatinine and blood urea nitrogen should be monitored when the drug is administered intravenously in patients with impaired renal function.

Note: Caution should be exercised in determining dosage adjustment for patients with malignancy and severe skeletal disease, given the potential for wide variation in nonrenal clearance in such patients.

Skeletal

Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse of short oblique in orientation without evidence of comminution. Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching pain, weeks to months before a complete fracture occurs. Poor healing of these fractures was also reported. Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered pending a risk/benefit assessment.

Special Populations

Pregnant women: The safety and efficacy of BONEFOS in pregnant women has not been established (see **CONTRAINDICATIONS**).

Nursing women: There is no clinical experience with BONEFOS in lactating women and it is not known whether BONEFOS passes into breast milk (see **CONTRAINDICATIONS**).

Pediatrics: The safety and efficacy of BONEFOS in children have not been established.

Geriatrics: No data is available. As older patients may have decreased renal function, please refer to the **WARNINGS AND PRECAUTIONS – Renal** section.

Impaired renal function: Clodronate is eliminated mainly via the kidneys. A study examining the pharmacokinetics of clodronate in renally impaired subjects that enrolled a total of 60 subjects in 4 groups (18 subjects with mild, 12 with moderate, and 16 with severe renal insufficiency, and 14 healthy volunteers) demonstrates a clear increase in the mean clodronate serum $AUC_{(0\text{-}24h)}$ with decreasing renal function after daily oral clodronate administration. There was no increase in adverse events with worsening renal function. No dose adjustment is considered necessary for subjects with mild renal impairment. Dosage adjustment in patients with moderate and severe renal impairment is recommended (see **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests

As many patients with hypercalcemia have other electrolyte abnormalities at presentation, appropriate attention must be given to maintaining electrolyte balance. Serum electrolytes should be monitored at least daily and supplementation provided as needed during treatment of hypercalcemia (see **ADVERSE REACTIONS**).

Calcium levels should be monitored throughout the treatment. Corrected (adjusted) serum calcium values may be calculated using established algorithms, such as:

$Ca_{adj} = Ca_r - 0.71\ (A - A_m)$

Ca_{adj} = adjusted calcium concentration (mg/100 mL)
Ca_r = total calcium concentration (mg/100 mL)
A = albumin concentration (g/100 mL)
A_m = mean normal albumin concentration of the given laboratory (g/100 mL)

Serum creatinine and blood urea nitrogen should be monitored when the drug is administered intravenously in patients with impaired renal function.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Bisphosphonates are generally well tolerated, especially when taken properly by appropriately selected patients (see **DOSAGE AND ADMINISTRATION** and **CONTRAINDICATIONS**).

Adverse Drug Reactions

The following adverse reactions have been observed with both oral and intravenous treatment with clodronate, although the frequency of reactions may differ.

Gastrointestinal: Gastrointestinal disturbances including nausea, vomiting, gastric pain and diarrhea were the most frequently reported adverse events with oral clodronate and occurred in approximately 10% of patients. These reactions were usually mild. In rare cases, treatment had to

be discontinued. Difficulty in swallowing the capsule, irritation of the mouth and ulcerative pharyngitis were rarely reported.

Renal: Severe renal damage has occurred, especially after bolus injection or rapid intravenous infusion of high doses of clodronate. Fatal renal failure, which may have been related to the underlying hypercalcemia and dehydration, has occurred in patients receiving intravenous clodronate.

Respiratory: Very rare instances of bronchoconstriction have been observed in patients with acetylsalicylic acid-sensitive asthma.

Skin and subcutaneous tissue disorders: Some cases of skin disorders, usually manifesting as erythematous or maculopapular lesions, have been reported. Immediate hypersensitivity reactions seem to be rare. Local reaction may occur following extravasation.

Abnormal Hematologic and Clinical Chemistry Findings

Renal: Occasional mild to moderate abnormalities in renal function (increase in mean serum creatinine concentrations, transient proteinuria) occurred after IV clodronate therapy.

Biochemical changes: Asymptomatic hypocalcemia is a common adverse reaction which occurs in approximately 3% of treated patients. Symptomatic hypocalcemia is rare. Although not yet reported during BONEFOS (clodronate disodium) therapy, hyperphosphatemia has been known to occur with other bisphosphonates.

Endocrine: Secondary hyperparathyroidism may develop as a result of BONEFOS therapy. This is a homeostatic response to the fall in serum calcium and will reverse upon discontinuation of therapy.

Hepato-biliary: During a 12-month study of 610 postmenopausal osteopenic women randomized to receive placebo or clodronate, elevations of aminotransferases were common, exceeding the normal range in up to 18% of clodronate-treated subjects versus up to 7% of placebo-treated subjects. Aminotransferases were elevated to more than twice the normal range in 1.8% (9/491) of clodronate-treated subjects. No serious adverse events due to liver disease were reported during the 12 months of follow-up. Changes in serum concentrations of alkaline phosphatase have been observed. In patients with metastatic diseases, alkaline phosphatase may also be elevated due to liver and bone metastases.

Postmarket Adverse Drug Reactions

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. Osteonecrosis of the jaw has other well-documented multiple risk factors. It is not possible to determine if these events are related to bisphosphonates, to concomitant drugs or other therapies (eg, chemotherapy, radiotherapy, corticosteroids), to the patient's underlying disease or to other co-morbid risk factors (eg, anemia, infection, pre-existing oral disease).

Severe bone, joint, and/or muscle pain has been reported in patients taking BONEFOS; however, such reports have been infrequent. The onset of symptoms varied from days to several months after starting BONEFOS.

During post-marketing experience the following reactions have been reported with bisphosphonates: Atypical subtrochanteric and diaphyseal femoral fractures.

Eye Disorders : Uveitis has been reported.

During post-marketing experience the following reactions have been reported with bisphosphonate therapy: conjunctivitis, episcleritis and scleritis. (see **WARNINGS AND PRECAUTIONS**, **Ophthalmologic**).

Renal and urinary disorders: Impairment of renal function (elevation of serum creatinine and proteinuria) and severe renal damage have been reported, especially after rapid intravenous infusion of high doses of clodronate (see **DOSAGE AND ADMINISTRATION**, **Dosing Considerations – Renal impairment**).

Single cases of renal failure, in rare cases with fatal outcome, have been reported, especially with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), most often diclofenac.

Respiratory, thoracic and mediastinal disorders: Impairment of respiratory function in patients with acetylsalicylic acid-sensitive asthma and hypersensitivity reactions manifesting as respiratory disorder have been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 1 : Drug-Drug Interactions with Clodronate

Drug	Effect	Management
NSAIDs, especially diclofenac	Increased potential of renal dysfunction	Caution. Closely monitor serum creatinine levels.
Aminoglycosides, corticosteroids, phosphate, calcitonin, mithramycin, loop diuretics	Increased incidence of hypocalcemia	Caution or avoid. Closely monitor serum calcium levels.
Estramustine phosphate	Increased toxicity due to increased serum levels of estramustine. Estramustine levels can increase by up to 80%.	Caution. Therapeutic monitoring of serum estramustine levels recommended.
Calcium-containing IV solutions, eg, Ringer's solution	Chelates to clodronate	Avoid mixing with clodronate IV infusion.
Antacid or drug containing calcium, iron, magnesium or aluminum	Chelates to clodronate, significantly reducing bioavailability	Avoid. Take oral clodronate two hours before or after meals and other drugs.

- Clodronate has been reported to be associated with renal dysfunction when used simultaneously with NSAIDs, most often diclofenac.

- The use of clodronate with other agents indicated for the reduction of calcium, such as corticosteroids, phosphate, calcitonin, mithramycin or loop diuretics, may result in increased hypocalcemic effect depending on tumor type and pathophysiological situation.
- Due to increased risk of hypocalcemia, caution should be exercised when using clodronate together with aminoglycosides.
- Bisphosphonates are not known to affect the antineoplastic activity of most anticancer agents, including carmustine, cyclophosphamide, doxorubicin and fluorouracil. However, concomitant use of estramustine phosphate with clodronate has been reported to increase the serum concentration of estramustine by up to 80%.
- Clodronate IV solutions must not be mixed with calcium-containing solutions, such as Ringer's solution, since clodronate forms poorly soluble complexes with divalent cations.
- For oral administration, simultaneous administration with food, liquids or drugs containing divalent cations (ie, calcium, magnesium, aluminum or iron), such as antacids or iron preparations, leads to significantly reduced bioavailability of clodronate.
- Clodronate is compatible with 0.9% saline and 5% dextrose injections.

Drug-Food Interactions

The drug should be taken on an empty stomach, with a glass of plain water, at least two hours before or after food or any other oral drugs, because food or other drugs may decrease the amount of clodronate disodium absorbed by the body.

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

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Renal impairment

Since clodronate is eliminated mainly via the kidneys, it should be used with caution in patients with renal impairment. Dosage should be reduced in patients with renal impairment, and daily doses exceeding 1600 mg should not be used continuously (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Limited data suggest that clodronate can be effectively removed from plasma by standard hemodialysis immediately following clodronate infusion but is poorly removed by peritoneal dialysis. No formal study has been conducted for a regimen recommendation of clodronate use in subjects undergoing hemodialysis or peritoneal dialysis.

Intravenous infusion: The following dose reductions are recommended depending on the degree of renal insufficiency:

Table 2: Intravenous Dose Reductions for Renal Impairment

Degree of Renal Failure: Creatinine Clearance (mL/min)	Percent of Normal Dose
50 – 80	75 – 100%
12 – 50	50 – 75%
< 12	50%

Oral administration: The following dose reductions are recommended depending on the degree of renal impairment.

Table 3 : Oral Dose Reductions for Renal Impairment

Degree of Renal Insufficiency	Creatinine Clearance (mL/min)	Dose
Mild	50 – 80	No dose reduction recommended
Moderate	30 – 50	25% reduction
Severe	< 30	50% reduction

Caution should be exercised in determining dosage adjustment for patients with malignancy and severe skeletal disease, given the potential for wide variation in nonrenal clearance in such patients.

Recommended Dose and Dosage Adjustment

Intravenous Infusion

The recommended adult dose is 300 mg per day (one 5 mL ampoule).

Oral Administration

Hypercalcemia due to malignancy: The oral recommended daily maintenance dose following intravenous therapy is in the range of 1600 mg (four capsules) to 2400 mg (six capsules) given preferably as a single dose or in two divided doses. The maximal recommended daily dose is 3200 mg (eight capsules).

Osteolytic bone metastases due to malignancy: In patients with increased bone resorption, but no hypercalcemia, the recommended starting dose is 1600 mg/day. The dose may be increased if this is deemed clinically appropriate. However, the daily dose should not exceed 3200 mg.

Retreatment: Controlled studies have not been undertaken for retreatment with clodronate. Limited clinical experience has suggested that patients developing hypercalcemia following termination of therapy with clodronate or during oral administration may be retreated either with a higher oral dosage (up to 3200 mg/day) or with the IV infusion preparation (300 mg/day).

Administration

Intravenous Infusion: The contents of the ampoule must be diluted in 500 mL of 0.9% sodium chloride injection or 5% dextrose injection and administered by infusion lasting at least two hours. The compatibility of BONEFOS with other admixed drugs or injection solutions has not been studied. Treatment should be continued until plasma calcium levels return to normal, which is generally achieved after two to five days of treatment. Treatment should not be prolonged beyond seven days. 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.

Oral Administration: BONEFOS capsules should be swallowed whole, and should not be taken with food (see **WARNINGS AND PRECAUTIONS**). The drug should be taken on an empty stomach, with a glass of plain water, at least two hours before or after food or any other oral drugs.

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 oral drugs.

Reconstitution

Parenteral Products

Ampoule Size	Volume of Diluent to Be Used	Approximate Available Volume	Nominal Concentration per mL
300 mg / 5 mL	500 mL of 0.9% saline injection or 500 mL of 5% dextrose injection	505 mL	0.6 mg/mL

One 5 mL ampoule should be diluted in 500 mL of 0.9% (9 mg/mL) saline injection or 5% (50 mg/mL) dextrose injection and administered as an infusion over at least two hours.

The diluted product may be stored for up to 24 hours at room temperature.

OVERDOSAGE

For management of suspected overdose, consult your regional poison control centre.

There is a lack of documented experience on acute overdosing with clodronate. An overdose of the intravenous preparation can result in renal damage. Renal function should be monitored. Overdosage may result in hypocalcemia. Careful monitoring for several days for signs and symptoms of hypocalcemia, in addition to monitoring of serum calcium levels, is recommended in cases where the dose given was too high in relation to initial serum calcium levels (see **WARNINGS AND PRECAUTIONS**).

Treatment of overdose should be symptomatic. Adequate hydration should be ensured, and oral or parenteral calcium supplementation may be required to restore plasma calcium levels. Milk or antacids may be given to bind the unabsorbed clodronate following acute oral overdosage.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Clodronate belongs to the class of bisphosphonates which bind to hydroxyapatite and inhibit formation and dissolution of calcium crystals in vitro.

Bisphosphonates, including clodronate, act on the bony skeleton causing reduction of normal and abnormal bone resorption. The most likely mechanism of action of clodronate appears to be suppression of osteoclast activity, resulting in reduction of bone resorption. However, clodronate may also have indirect inhibitory effects through osteoblastic cells, which control the recruitment and activity of osteoclasts.

Pharmacodynamics

In responsive patients, inhibition of increased bone resorption by clodronate leads to reduction of hypercalcemia of malignancy presenting with or without demonstrable skeletal metastases.

During and also after intravenous administration of clodronate the elevated serum calcium decreases, in some instances to hypocalcemic levels. The decrease in serum calcium concentration is rapid with significant reductions usually attained within two days after starting intravenous therapy and continuing for five to six days after discontinuing therapy.

Clodronate is not metabolized, and absorbed drug is excreted unchanged by the kidneys. The kidneys have a prominent role in calcium homeostasis. In addition to skeletal osteolysis, renal dysfunction becomes a contributor to the pathogenesis of hypercalcemia. At the time of diagnosis most hypercalcemic patients are significantly dehydrated. The antagonistic effects of calcium on the action of antidiuretic hormone impair the renal concentration mechanisms resulting in polyuria and excessive fluid loss. Hydration status is further compromised by reduction of oral fluid intake due to nausea, vomiting and mental status. Prior to initiation of therapy with BONEFOS (clodronate disodium) for treatment of hypercalcemia, the state of the negative fluid balance requires vigorous and adequate hydration with isotonic saline (0.9%). Normalization of blood calcium levels by clodronate in adequately hydrated patients may also normalize plasma parathyroid hormone (PTH) levels without resulting impairment of desired clodronate effects (decrease in urinary calcium, hydroxyproline and phosphate excretion).

Pharmacokinetics

Intravenous Administration

After an IV dose, clodronate exhibits a plasma concentration profile which fits a two-compartment model with $t_{½\alpha}$ approximately 0.3 h and $t_{½\beta}$ approximately 2 h. The $t_{½}$ of the

terminal elimination phase is approximately 13 h, and accounts for 10 to 15% of renal excretion. Total clearance is about 110 mL/min and renal clearance is approximately 90 mL/min.

Distribution

Volume of distribution is approximately 20 L. The substance which is bound to bone is about 20% of the absorbed amount. The binding of clodronate to serum proteins is variable, between 2% to 36%.

Metabolism

Clodronate is not metabolized.

Excretion

Clodronate is eliminated mainly via the kidneys and 60 to 80% of the absorbed dose will be found in urine within 48 hours. The substance which is bound to bone (about 20% of the absorbed amount) will be excreted more slowly, at a rate depending on the turnover of the bone.

Oral Administration

Absorption

Following a single oral dose, the absorption of clodronate is rapid and the peak serum concentration is reached within 30 minutes. Absorption is estimated at 1 to 3% of the ingested dose.

Metabolism

Clodronate is not metabolized.

Excretion

Unabsorbed drug is excreted unchanged in the feces.

STORAGE AND STABILITY

BONEFOS (clodronate disodium) capsules and intravenous infusion should be stored between 15°C and 30°C.

The diluted intravenous solution may be stored for up to 24 hours at room temperature.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Capsules

Each yellow hard gelatin capsule contains 400 mg of anhydrous clodronate (as the tetrahydrate).

Nonmedicinal ingredients: calcium stearate, colloidal anhydrous silica, gelatin, iron oxide (red and yellow), lactose, talc, titanium dioxide.

BONEFOS 400 mg capsules are available in high density polyethylene bottles of 120 capsules.

Intravenous Infusion

Each 1 mL of the intravenous solution for infusion contains clodronate tetrahydrate, corresponding to 60 mg of anhydrous clodronate, sodium hydroxide (to adjust the pH) and water for injection.

BONEFOS 60 mg/mL intravenous infusion is available in 5 mL ampoules in packages of 5 x 5 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

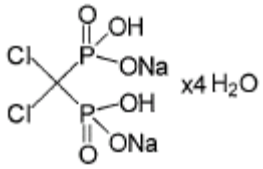
Common name: Clodronate disodium

Chemical name: Disodium (dichloromethylene) bisphosphonate tetrahydrate

Molecular formula: $CH_2Cl_2Na_2O_6P_2 \bullet 4H_20$

Molecular mass: 360.92

Structural formula:



Physicochemical properties: White to off-white, odourless crystalline powder. Freely soluble in water (approx. 2.5 g/10 mL), slightly soluble in methanol, very slightly soluble in dehydrated alcohol, insoluble in toluene, acetone and diethylether. Various pKa values of pKa_1 = approx. 1, pKa_2 = 1.8, pKa_3 = 5.96, pKa_4 = 9.49.

CLINICAL TRIALS

Study Demographics and Trial Design

Randomized controlled and open clinical studies using both intravenous and/or oral formulations of clodronate have been carried out. These studies have shown that clodronate has clinical efficacy in the treatment of malignant hypercalcemia and tumor-induced osteolysis.

Study Results

Hypercalcemia: In a double-blind, cross-over comparison with placebo, oral clodronate (3200 mg/day x 4 weeks) was given to five patients with hypercalcemia due to bone metastases of breast or renal cancer. Four of the five patients showed a rapid decrease in serum calcium concentration with the lowest value being reached within 7 to 10 days. Urinary calcium excretion decreased and an increase in serum alkaline phosphatase was observed. The remaining patient developed a sudden paraplegia at the onset of clodronate therapy followed by a marked increase in serum calcium levels and urinary calcium excretion; clodronate was able to reduce serum and urinary calcium to normal values.

In a second double-blind, cross-over comparison trial of 8 patients with malignant hypercalcemia, clodronate 3200 mg daily orally for 4 weeks was associated with a rapid decrease in mean serum calcium value as early as the third day (122 mg/L vs. 105 mg/L of calcium). At the end of the clodronate treatment, 6 out of the 8 patients had normal calcium levels. There was a decrease in calciuria from 397 mg/g creatinine/24 hours to 241 mg/g creatinine/24 hours, but there was no decrease in hydroxyproline, and serum phosphorus and PTH levels remained normal.

The effect of intravenous clodronate (300 mg IV up to 7 days) has been studied in a double-blind, parallel, placebo-controlled trial in 36 patients with malignant diseases. A significantly shorter time to reach normal serum calcium levels was observed with clodronate; 15 of 18 clodronate patients achieved normal levels versus 3 of 14 placebo patients.

In a similar randomized, placebo-controlled trial of 27 hypercalcemic patients (12 on placebo; 10 on clodronate 12 mg/kg IV for 1 day; and 5 on 4 mg/kg IV for 3 days), there was a significant reduction in serum calcium levels of 0.70 mM/L after 4 mg/kg on day 3 when compared to baseline measurements. No statistically significant overall changes from pretreatment were observed on day 3 in the placebo group and in the group receiving 12 mg/kg for one day.

Tumor-induced osteolysis: A randomized, double-blind, placebo-controlled study was conducted in patients with osteolytic bone metastases from breast cancer. The patients were randomized to receive either oral clodronate 1600 mg daily or an identical placebo in addition to chemotherapy or hormonotherapy for one year at most. One hundred forty-four (n=144) were enrolled, of which 137 were evaluable (69 on clodronate, 68 on placebo). Patient groups were well matched for age, performance status, bone condition (except more prior fractures in the clodronate group) and bone pain. Compared to placebo, clodronate significantly delayed the onset of new bone events ($p=0.05$). Median time to onset of a new bone event was 244 days in the clodronate group vs. 180 days in the placebo group. Also compared to the patients on placebo, patients on clodronate had a significant reduction in the level of visual pain scale ($p<0.01$) and in the use of analgesic treatments ($p=0.02$).

In a double-blind, placebo-controlled study in 173 patients with advanced breast cancer, oral administration of clodronate 1600 mg/day for 3 years produced significant reductions in: a) the incidence of hypercalcemia (28 vs. 52 events/100 patient-years, $p<0.01$); b) the incidence of vertebral fractures (84 vs. 124 events/100 patient-years, $p<0.025$); and c) the overall rate of morbid events including hypercalcemia, fractures, and the need for radiotherapy to treat bone-related pain (219 vs. 305 events/100 patient-years, $p<0.001$). Trends were seen in favour of clodronate for nonvertebral fracture rates and radiotherapy requirements for pain (particularly bone pain). No significant survival differences were observed between the two groups.

Clodronate has also been shown to reduce the skeletal morbidity (incidence of hypercalcemia, bone pain and pathological fracture) in patients with multiple myeloma.

DETAILED PHARMACOLOGY

Animal

Pharmacodynamics

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. Clodronate inhibits cell-mediated bone resorption associated with cultured mouse calvaria.

In vitro, clodronate inhibits the precipitation of calcium phosphate, blocks its transformation into hydroxyapatite, delays the aggregation of apatite crystals into larger crystals and slows down the dissolution of these crystals.

During modelling in growing rats, clodronate inhibits resorption in the metaphysis which becomes club-shaped and radiographically sclerotic. In the zones of cartilage calcification and vascular permeation, the mineralized longitudinal intercellular septa are retained rather than removed by the action of chondroclasts as in control animals. In a three week study in the rat, clodronate inhibited bone resorption without affecting bone formation.

Administration of clodronate to hypercalcemic tumor-bearing Fischer 344 rats resulted in a rapid fall in serum calcium with maximal response occurring within 24 to 48 hours at a dose of 40 mg/kg.

Pharmacokinetics

Following oral administration, absorption of clodronate is limited. In the rat and mini-pig, total absorption is about 3% with approximately 2% excreted in the urine and the remainder retained in the bone.

The main share of intravenously administered clodronate is deposited in bone tissue. Retention in the rat bone tissue during a 2 minute intravenous infusion was 37% at the dose level of 10 mg/kg and 25% at the dose level of 80 mg/kg on the first day and decreased slightly on the 28th day to 26% and 23%, respectively. In the mini-pig, retention in the skeleton is approximately 40% of the administered intravenous dose.

The main share of a single oral dose is excreted unchanged in feces with only a small part in urine. In the rat, from 2.2 to 5.7% of a 300 mg/kg dose is found in the urine and 73 to 87% in the feces collected during 96 hours after dosing. The elimination half-life ($t_{½ß}$) from serum varied from 7.1 to 8.2 hours in male rats and 4.0 to 4.4 hours in female rats.

Human

Pharmacodynamics

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. When clodronate is used alone at doses inhibiting bone resorption, no effects on normal bone mineralization in humans have been observed.

Pharmacokinetics

Please refer to **ACTION AND CLINICAL PHARMACOLOGY** section in **PART I: HEALTH PROFESSIONAL INFORMATION** for the description of pharmacokinetic parameters.

TOXICOLOGY

Acute

Acute toxicity studies are summarized in Table 4.

Table 4: Acute Toxicity in Various Species

Species	Route	LD_{50} (mg/kg)
Mouse (NMRI)	oral	1818
Rat (Sprague-Dawley)	oral	2349
Mouse (NMRI)	IV	162
Rat (Mol:SRPD)	IV	206
Mini-pig	IV	300

Based upon the presented data, acute oral toxicity is low and intravenous toxicity is moderate.

The clinical signs of decreased motor activity, convulsions and difficulty in breathing induced by clodronate were similar in studies involving mice, rats and mini-pigs. Acute hypocalcemia was likely the immediate cause of death and kidney damage may have contributed to later deaths.

Sub-acute

During 2 to 4 week intravenous toxicity studies in the rat and mini-pig, the most prominent finding caused by clodronate was bone sclerosis. This was characterized by accumulation of abnormal spongious matrix and new bone trabeculae in the metaphysis of femur, iliac bone and sternum of the rat and almost solely in the iliac bone of the pig. The dose-dependent changes were observed at 10 to 80 mg/kg in the rat and 10 to 60 mg/kg in the mini-pig.

Small hyaline foci in the lamina propria of the stomach were detected after intravenous administration of 10 mg/kg for 28 days in mini-pigs. After oral administration to mini-pigs, clinical signs of gastrointestinal disturbances, vomiting and diarrhea were not observed until the third month of a six month study, even at a high dose of 1000 mg/kg. Kidney and liver toxicity, bleeding tendency and reduction of lymphocytes with a concomitant decrease in thymus weight were also detected, but only after higher drug exposure. Doses at which toxicity first appears are summarized in Table 5.

Table 5 : Doses at which Toxicity First Appears in Rats and Mini-pigs

Species	Lymphopenia and Thymus Weight Decrease	Kidney Toxicity	Liver Toxicity	Bleeding Tendency
Rat	60 mg/kg IV	100 mg/kg IV	100 mg/kg IV	60 mg/kg IV
Mini-pig	Not detected	60 mg/kg IV	100 mg/kg IV	None

Long-term

Oral administration of clodronate for 52 weeks to Sprague-Dawley rats at daily doses of 100, 250 and 400 mg/kg caused no overt morbidity or mortality. Reversible changes included hair loss, increased ALAT and ASAT at the lower dose as well as decreased serum total proteins, cholesterol, glucose and plasma fibrinogen. Dose-dependent decreases in liver, kidney, heart and spleen weights occurred at all doses. Drug-induced metaphyseal extension in all bones examined was dose-dependent and irreversible.

Six and 12 month oral administration of clodronate to Gottingen mini-pigs at daily doses of 100 to 1000 mg/kg led to changes in the bone spongious substance with the arrangement of trabecula in close longitudinal rows. The lamina propria of the stomach exhibited homogeneous, fibrous material after 600 mg/kg for 12 months and 100 mg/kg for 6 months. On bone marrow microscopy, no significant changes were seen in the morphology or distribution of nucleated cells in the blood nor were differences seen in bone marrow cellularity in histological slides of bones from controls and treated animals. In bone marrow smears, a rapid and marked reduction in erythropoiesis in treated animals was seen in addition to a reduction in marrow cellularity and myelopoiesis as compared with the controls. Microscopic evidence of nephrotoxicity was found in the kidneys of mini-pigs receiving 1000 mg/kg clodronate for 6 months and was suggested to be secondary to earlier injuries including tubular and glomerular damages and cortical embolization.

Carcinogenicity

No carcinogenic effects have been observed in studies with rats and mice.

Mutagenicity

Clodronate showed no mutagenic potential in the Ames Salmonella assay, mouse micronucleus test and human cytogenetic investigation.

In the Chinese hamster ovary cell, clodronate induced chromosome aberrations, but that effect, although reproducible, was weak and observed only in the presence of metabolic activation. Clodronate was unable to induce mutation at the HGPRT locus in mouse lymphoma cells. No evidence of DNA damaging activity was seen in an in vitro test of DNA repair in rat hepatocytes.

Reproduction and Teratology

No significant differences were observed in the litter size, pre- and post implantation loss or gross and visceral malformations between treated groups and controls in Wistar rats treated with oral clodronate at doses of 200, 600 and 1000 mg/kg from day 6 to 19 of pregnancy. Clodronate

was not teratogenic, but caused signs of fetotoxicity manifested as decreased fetal weights and delayed ossifications at dose levels above 200 mg/kg orally in the rat.

In a reproduction study in Crl:CDBR rats, clodronate was administered at daily doses of 50, 100, 200 and 600 mg/kg from day 15 of gestation through day 21 post partum. The higher dose levels caused significant reductions in maternal weight gain during gestation and pup body weights were significantly reduced at 200 mg/kg/day. There were too few pups for evaluation at 600 mg/kg/day because of the death of 21 of 25 dams.

New Zealand white rabbits received clodronate at daily doses of 70, 300 and 700 mg/kg from day 6 to 18 of gestation. There was no effect on the offspring at any of the doses but maternal effects included soft feces, reduced weight gain and death of 6 of 20 rabbits at the highest dose.

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PART III: CONSUMER INFORMATION

Pr BONEFOS®
clodronate disodium

This leaflet is part III of a three-part "Product Monograph" published when BONEFOS was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about BONEFOS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

BONEFOS is used:

- for the management of hypercalcemia due to malignancy (high blood calcium in adult patients who have cancer), and
- as an adjunct in the management of osteolytic bone metastases (bone destruction when cancer cells have spread to the bone)

What it does:

BONEFOS belongs to a group of medicines called bisphosphonates. BONEFOS binds tightly to bone and blocks the function of cells which re-absorb bone. This strengthens the bones, and thus helps to relieve bone pain and prevent future problems with your bones (such as fractures). It also prevents the release of too much calcium into the blood (hypercalcemia).

When it should not be used:

You should not take BONEFOS if any of the following conditions apply to you.

- You have severe kidney disease.
- You have severe stomach or bowel problems.
- You are pregnant or breastfeeding.
- You are being treated with another bisphosphonate.
- You have an allergy to bisphosphonates, clodronate disodium, or to any ingredient in the formulation or component of the container of BONEFOS.

What the medicinal ingredient is:

Clodronate disodium

What the important nonmedicinal ingredients are:

Capsules: calcium stearate, colloidal anhydrous silica, gelatin, iron oxide (red and yellow), lactose, talc, titanium dioxide.

Solution for injection: sodium hydroxide, water for injection.

What dosage forms it comes in:

Capsules: Each yellow BONEFOS capsule contains 400 mg of clodronate disodium. BONEFOS capsules are provided in plastic bottles containing 120 capsules.

Solution for Injection: BONEFOS solution for injection is available in 5 mL glass ampoules containing anhydrous clodronate disodium 60 mg/mL. The solution must be diluted prior to infusion.

WARNINGS AND PRECAUTIONS

BEFORE starting treatment with BONEFOS talk to your doctor if:

- you suffer from kidney problems, as your dose may need to be reduced.
- you have stomach or bowel problems.
- you are pregnant or planning to become pregnant. BONEFOS should not be given during pregnancy.
- you are breast-feeding. Mothers being treated with BONEFOS should not breast-feed their children.
- you have ever had an allergic reaction to BONEFOS (or similar medicines called bisphosphonates) or any other ingredients of the drug or components of the container.
- you are presently taking another bisphosphonate.
- you have any dental problems or any dental procedures planned in the future.
- you have sores in the mouth.

Osteonecrosis (pronounced OSS-tee-oh-ne-KRO-sis) of the jaw, a rare condition that involves the loss or breakdown of the jaw bone, has been reported in patients with cancer receiving bisphosphonates. The majority of the cases were associated with dental procedures such as tooth extraction.

Your doctor may check if you:

- smoke
- have or have had issues with your teeth and/or gum disease
- have dentures that do not fit well
- have other relevant medical conditions at the same time such as a low red blood cell count (called anemia) or if your blood cannot form clots in the normal way.

Other possible factors that may increase the risk of osteonecrosis of the jaw include:

- chemotherapy;
- radiation therapy;
- steroid therapy (eg, cortisone);
- underlying cancer;
- infection; and
- poor oral hygiene.

If any of these risk factors applies to you, you should have a dental exam prior to starting treatment with BONEFOS. Be sure to tell your dentist about your cancer diagnosis and

treatments. If your medical situation changes to include any of these risk factors, contact your doctor. Your doctor may tell you to stop taking BONEFOS until your medical situation improves (ie, sores in your mouth are healed or risk factors improve).

Unusual fractures of the thigh bone have been reported with the use of bisphosphonates.

Contact your doctor if you feel any pain, weakness or discomfort in your thigh, hip or groin as this may be an early sign of a possible fracture of the thigh bone.

Visual (ocular) disturbances have been reported with bisphosphonate therapy. These include inflammation, infection, and/or irritation of the eye. Patients with visual disturbances other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. Contact your doctor if you experience inflammation, infection and/or irritation of the eye.

The effect of BONEFOS on the ability to drive or use machines is not known.

Since there is no clinical experience in children, BONEFOS is only recommended for use in adult patients.

INTERACTIONS WITH THIS MEDICATION

Before you start treatment with BONEFOS, be sure to tell your doctor about any other prescription or over-the-counter medicines that you are using or intend to use.

Medicines that may interact with BONEFOS include:

- nonsteroidal anti-inflammatory drugs (NSAIDs), especially diclofenac;
- other bisphosphonates;
- other calcium-reducing agents, including corticosteroids, phosphate, calcitonin, mithramycin or loop diuretics (eg, furosemide);
- aminoglycoside antibiotics;
- estramustine phosphate;
- antacids; and
- dietary supplements containing calcium, iron, magnesium or aluminum.

BONEFOS capsules should be taken on an empty stomach, with a glass of plain water, at least 2 hours before or after food, because food may decrease the amount of BONEFOS absorbed by the body.

BONEFOS capsules should never be taken with milk or food containing calcium or other divalent cations because they interfere with the absorption of BONEFOS.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will determine the appropriate dose for you. Follow the dosing instructions exactly and ask your doctor or pharmacist if you are not sure.

BONEFOS for Injection:

- 300 mg/day is given as a slow infusion into a vein.

BONEFOS Capsules:

- Hypercalcemia due to malignancy: 1600 mg to 2400 mg (four to six capsules) daily. Maximum daily dose is 3200 mg (eight capsules). The daily dose can be taken once, or in two divided doses.
- Osteolytic bone metastasis due to malignancy: starting dose of 1600 mg (four capsules) daily. Maximum daily dose is 3200 mg (eight capsules).

BONEFOS capsules are to be taken on an empty stomach, with a glass of plain water, at least two hours before or after food or any other oral drugs.

BONEFOS capsules should be swallowed whole.

You will need to drink enough fluid or be hydrated during treatment with BONEFOS.

Overdose:

If you think you have taken or given more BONEFOS than you should, contact your doctor or a poison control centre immediately.

Missed Dose:

If a dose of this medication has been missed, it should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule.

Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, BONEFOS may have, in addition to its beneficial effects, some unwanted effects.

The following side effect has been reported very commonly:

- increased transaminases (a group of liver enzymes) within normal range

The following side effects have been reported commonly:

- nausea;

- vomiting;
- stomach pain;
- diarrhea; and
- increased liver enzyme levels more than twice the normal range without impaired liver function

The following side effects have been reported rarely:

- low blood calcium levels with symptoms (eg, muscle cramps or spasms);
- increased serum parathyroid hormone (a hormone of the small glands adjacent to the thyroid gland) associated with decreased serum calcium;
- increased blood alkaline phosphatase levels (in patients with metastatic disease, this may also be due to liver and bone disease); and
- skin rash due to drug-related allergy.

The following side effects were reported during postmarket experience:

- severe kidney damage (especially after rapid intravenous infusion of high doses of clodronate);
- airway constriction (due to a hypersensitivity reaction or in patients with acetylsalicylic acid-sensitive asthma);
- allergic skin reactions and overactivity of the parathyroid glands which control the amount of calcium in the blood;
- isolated cases of kidney failure, in rare cases with fatal outcome, have been reported, especially when NSAIDs, most commonly diclofenac, were used at the same time;
- severe bone, joint, and/or muscle pain (the onset of symptoms varied from days to several months after starting BONEFOS).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor	
		Only if severe	In all cases
Unknown	Abnormal thigh bone fractures		✓
	Inflammation, infection and/or irritation of the eye		✓
	Symptoms of osteonecrosis of the jaw which may include: • pain, swelling or infection of the gums; • loosening of teeth; • poor healing of the gums; and • numbness or the feeling of heaviness in the jaw.		✓

This is not a complete list of side effects. For any unexpected effects while taking BONEFOS, contact your doctor or pharmacist.

HOW TO STORE IT

BONEFOS should be stored at room temperature (between 15°C and 30°C). Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Canada Vigilance Program:

You can report any suspected adverse reactions associated with the use of heath products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or Canada.medinfo@bayer.com.

This document plus the full Product Monograph, prepared for health professionals, can be found at http://www.bayer.ca or by contacting the manufacturer at the above mentioned phone number and email address.

This leaflet was prepared by:

Bayer Inc.
2920 Matheson Boulevard East
Mississauga, Ontario L4W 5R6
Canada

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