PRODUCT INFORMATION

BONEFOS® (sodium clodronate)

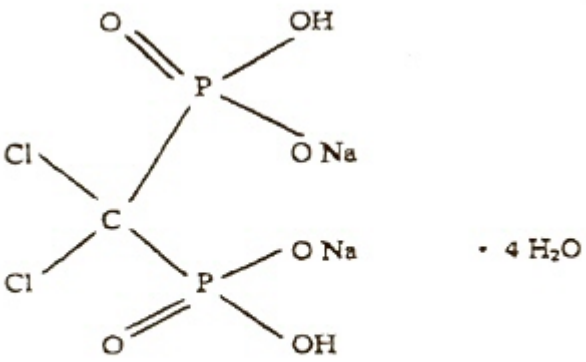
NAME OF THE MEDICINE

BONEFOS contains sodium clodronate which is a bone metabolism regulator.

Chemical Name

The chemical name of sodium clodronate tetrahydrate is disodium (dichloromethylene) bisphosphonate tetrahydrate.

Structural Formula



CAS Number: 22560-50-5

DESCRIPTION

Chemical Properties

Sodium clodronate: A white to off-white, odourless powder which is freely soluble in water, slightly soluble in methanol, very slightly soluble in dehydrated alcohol and insoluble in toluene, acetone and diethylether.

BONEFOS capsules 400 mg: One capsule contains 500 mg sodium clodronate tetrahydrate, equivalent to 400 mg anhydrous sodium clodronate. Each capsule also contains talc, calcium stearate, colloidal anhydrous silica, lactose and a hard gelatin capsule. The hard gelatin capsules contain gelatin, purified water, iron oxide red CI77491, iron oxide yellow CI77492 and titanium dioxide. Each capsule contains the equivalent of 64 mg sodium.

BONEFOS tablets 800 mg: Each 800 mg tablet contains 1000 mg sodium clodronate tetrahydrate, equivalent to 800 mg anhydrous sodium clodronate. Each tablet also contains croscarmellose sodium, microcrystalline cellulose, stearic acid, magnesium stearate, colloidal anhydrous silica and Opadry II complete film coating system 85F18422 white. Each tablet contains the equivalent of 128 mg sodium.

PHARMACOLOGY

Pharmacodynamics

Sodium clodronate belongs chemically to the bisphosphonate group, which act primarily on bone tissue. Its major pharmacological action is inhibition of bone resorption.

The mechanism of sodium clodronate's action lies in its protection against the dissolution of hydroxyapatite crystals and direct reduction of osteoclast activity. There is some evidence that sodium clodronate also has indirect effects on osteoclast activity by inhibition of various mediators. The selectivity of the direct effects most likely arises from the strong affinity of sodium clodronate for calcium phosphate and it will, therefore, be distributed mainly to the skeleton.

In concentrations which induce inhibition of bone resorption, sodium clodronate has no effect on the normal mineralisation process in bone tissue.

The therapeutic effect of sodium clodronate is achieved by inhibition of abnormal bone destruction in diseases with increased osteolysis. In hypercalcaemic states, sodium clodronate reduces elevated serum calcium levels and, in normocalcaemic patients, the inhibitory effect on bone resorption manifests as reduced excretion of calcium and hydroxyproline in urine.

In patients with bone metastases or bone lesions from myeloma, sodium clodronate inhibits the progression of existing skeletal lesions, as well as the formation of new ones. Sodium clodronate also alleviates pain caused by tumour-induced bone destruction and reduces the incidence of fractures in these patients.

Pharmacokinetics

- Absorption

As with other bisphosphonates, the gastrointestinal absorption of oral sodium clodronate is low, at around 2%. Due to strong affinity of sodium clodronate to calcium and other divalent cations of food, the intestinal absorption of sodium clodronate is negligible when given with meals. The inter- and intra-individual variation of gastrointestinal absorption is high. Relative to administration 2 hours before breakfast, the bioavailability of sodium clodronate 2 x 400 mg capsules was reduced by 9%, 31%, 90% and 67% respectively after administration 1 hour before breakfast, 30 minutes before breakfast, with breakfast and 2 hours after breakfast, in healthy volunteers.

- Distribution and Elimination

The total systemic clearance is around 110 mL/min and the renal clearance constitutes about 75% of the plasma clearance. No metabolites of sodium clodronate have been found in the urine, indicating that it is not metabolised, and that the administered drug is the active moiety.

The average volume of distribution is 20 L. This is about 25% of body weight, equivalent to the extracellular water volume. The plasma protein binding of clodronate is low.

The elimination of sodium clodronate from serum is characterised by two clearly distinguished phases: the distribution phase with a half life of about two hours, and a second

elimination phase which is very slow because sodium clodronate is strongly bound to bone. The non-renal clearance of clodronate, in the second phase, is due to skeletal uptake.

Sodium clodronate which is bound to the bone (c. 20% of a single dose) will be excreted very slowly, at a rate corresponding to bone turnover.

There is no specific relationship between the plasma/blood concentrations of sodium clodronate and its therapeutic activity or adverse effects i.e. the relationship is very varied and could be idiosyncratic at times. However, higher doses especially intravenous, appear to be more effective in the treatment of hypercalcaemia of malignancy with the increased likelihood of side effects, e.g. hypocalcaemia, extraosseous calcification/bone formation and renal damage. More studies are needed to elucidate the cause(s) of the variation which may be multifactorial. There is evidence, however, that renal failure decreases the renal clearance of sodium clodronate and this leads to increased AUC_{inf}. The dose of sodium clodronate (± duration of treatment) would therefore need to be reduced in renal failure patients in order to keep the AUC_{inf} in some control and prevent too much accumulation of sodium clodronate in tissues such as bone.

CLINICAL TRIALS

Treatment of Hypercalcaemia of Malignancy

Three randomised, double blind, placebo controlled trials were conducted in eligible patients treated with either sodium clodronate (42 patients) or placebo (32 patients). Patients suffered from various malignancies with or without bone metastases, and hypercalcaemia varied from mild/moderate (corrected total serum calcium 2.8 to 3.1 mmol/L or serum ionised calcium >1.6 mmol/L) to severe (corrected total serum calcium >3.1 mmol/L). Eleven patients received sodium clodronate orally (400 mg x 2 twice daily), 31 patients received intravenous sodium clodronate (300 mg daily), and 32 patients received equivalent placebo treatments. Treatment was continued until normocalcaemia was achieved, or for a maximum of 7 days.

Five of the eleven patients treated with oral sodium clodronate (45%) achieved normocalcaemia (corrected total serum calcium <2.7 mmol/L) compared to none in the placebo exposed patients (p=0.1). Three of these responders achieved normocalcaemia within seven days.

Twenty three of the 31 patients treated with intravenous sodium clodronate (74.2%) achieved normocalcaemia (corrected total serum calcium <2.7 mmol/L or serum ionised calcium <1.4 mmol/L) compare to 4 placebo exposed patients (15.4%), but some of the responders to sodium clodronate took more than seven days to do so.

Treatment of Osteolysis

Multiple myeloma:
Two clinical trials were conducted in patients with recently diagnosed multiple myeloma and osteolytic lesions or a paraprotein in the blood or urine.

In one trial, 536 recently diagnosed patients were randomised to receive either 1600 mg (4 x 400 mg capsules daily) of sodium clodronate (n=264) or placebo (n=272) indefinitely, with a

follow up of 1 to 3 years. There were significant reductions in the incidence of vertebral and non-vertebral fractures in the clodronate group (Table 1).

Table 1

Endpoint	Clodronate n=264 entered	Placebo n=272 entered	P value
Hypercalcaemia >3.0 mmol/L	5.1% n=235	10.1% n=228	0.06
New non-vertebral fractures	6.8% n=221	13.2% n=220	0.04
New vertebral fractures	38% n=108	55% n=109	0.01
Median survival	2.9 years	2.8 years	0.74

A log-rank comparison of the proportion of patients remaining event-free of non-vertebral fracture or hypercalcaemia over 4 years favoured the clodronate group (p=0.021).

In the second trial, 336 recently diagnosed multiple myeloma patients (intent-to-treat) were randomised to receive either 2400 mg (2 x 400 mg capsules tds) of sodium clodronate (n=168) or placebo (n=168) for two years. There was a significant reduction in the incidence of osteolytic lesions in the clodronate group, but no significant reduction in the incidence of vertebral or non-vertebral fractures (Table 2).

Table 2

Endpoint	Clodronate n=168 entered	Placebo n=168 entered	P value
New osteolytic lesions	12.0% n=108	24.0% n=96	0.03
New non-vertebral fractures	24.1% n=108	23.2% n=95	0.88
New vertebral fractures	29.6% n=108	40.0% n=95	0.12
Deaths	32.1%	40.5%	0.19

Breast cancer:

Two clinical trials were conducted in breast cancer patients with bone metastases.

In one trial, 173 women were randomised to receive either 1600 mg (4 x 400 mg capsules daily) of sodium clodronate (n=85) or placebo (n=88) for 18 months to 3 years. Even though this study was designed to evaluate the cumulative number of events and was not powered to evaluate the number of patients having an event (or being event-free) at 1 or 2 years, the proportion of patients remaining event-free of each endpoint at 2 years favoured the sodium clodronate group. However there were no significant differences between treatments on the log-rank comparisons of total experience (Table 3).

Table 3

Endpoint	Proportion event-free at 2 years [95% CI]	
	Clodronate n=85 at start n=27 at 2 years*	Placebo n=88 at start n=22 at 2 years*
Hypercalcaemia	62% [44,76]	45% [28,60]
Radiotherapy for Bone Pain	38% [23,54]	30% [16,45]
Non-vertebral fractures	80% [63,91]	71% [47,86]
Vertebral fractures	36% [18,55]	21% [27,56]
Death	24% [15,35]	14% [7,23]

* Refers to patients alive at two years and not to patients included in the analyses

In the second trial, 144 women received either 1600mg (2 x 400 mg capsules twice daily) of sodium clodronate (n=73) or placebo (n=71). Patients were followed for a period of 1 year. The log-rank comparison of the time patients remained free of a new bone event was marginally significant in favour of the clodronate group. Bone pain was significantly reduced in the clodronate group (Table 4).

Table 4

Endpoint	Clodronate n=73 at start n=23 at 1 year	Placebo n=71 at start n=16 at 1 year	P value
% Free of bone events[1] at 1 year	30%	21%	0.05
Median time free of bone event days	244 [206,307]	180 [133,242]	
Bone pain change[2] mean ± sd mm	-11.8 ± 3.2	+4.5 ± 4.7	0.007

[1] Hypercalcaemia >3.0 mmol/L, bone pain, fracture, bone metastasis, neurological compression, symptoms of bone origin, need for change in therapy because of bone problem, death due to bony progression.
[2] Huskisson visual analogue scale.

In the multiple myeloma and breast cancer trials, there were substantial numbers of patients lost to follow-up, however this did not appear to advantage any particular treatment group.

INDICATIONS

Treatment of hypercalcaemia of malignancy.
Treatment of osteolytic bone metastases due to carcinoma of the breast and treatment of osteolytic lesions of multiple myeloma.

CONTRAINDICATIONS

Hypersensitivity to sodium clodronate or to any of the excipients contained in BONEFOS. Severe inflammation of the gastrointestinal tract. Concomitant use of other bisphosphonates.

PRECAUTIONS

Prior to treatment with sodium clodronate, renal excretion of excess plasma calcium should be promoted by restoration and maintenance of adequate fluid balance and urine output. Adequate fluid intake must be maintained during sodium clodronate treatment. This is particularly important when administering sodium clodronate to patients with hypercalcaemia or renal failure.

In patients with significant renal insufficiency, IV sodium clodronate should be given with extra care and renal function should be closely monitored (see "Patient Monitoring"). Dosage reduction may be warranted since sodium clodronate is mainly excreted by the kidneys (see "Dosage and Administration").

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

The daily dose must be diluted in 500 mL of 0.9% sodium chloride injection or 5% glucose injection only.

No other drugs or nutrients may be added to the diluted injection solution.

BONEFOS tablets, capsules and concentrated injection contain sodium which should be taken into account for patients on a low sodium diet or with renal disease (see "Description" for the sodium content of each presentation).

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

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

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.

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

often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported.

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

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Effects on Fertility

Treatment of male rats with an oral sodium clodronate dose of 600 mg/kg/day (1.5 times the 3200 mg human dose based on surface area mg/m^2) depressed mating behaviour and reduced fertility. No adverse effects on male rat reproductive performance or female fertility were seen with an oral dose of 200 mg/kg/day.

Use in Pregnancy (Category B3)

Sodium clodronate may through its pharmacological effects on calcium homeostasis be hazardous to the foetus and/or newborn child. Reproduction studies in rats using the oral route of administration showed decreased postimplantation survival at 1000 mg/kg/day (2.5 times the 3200 mg human dose based on surface area mg/m^2) and decreased body weight in normal pups at birth (200 mg/kg/day). Sites of incomplete ossification were increased and dry weights of foetal tibiae reduced at 600 mg/kg/day (1.5 times the 3200 mg human dose based on surface area mg/m^2). Protracted parturition due to maternal hypocalcaemia occurred in rats at doses of 600 mg/kg/day. Post implantation survival was reduced also when pregnant rabbits were treated at doses up to 700 mg/kg/day (3.2 times the 3200 mg human dose based on surface area mg/m^2). There are however, no adequate or well controlled trials of sodium clodronate in pregnant women. Sodium clodronate should not be used for pregnant women, unless the therapeutic advantages clearly outweigh the risks.

Use in Lactation

There is no clinical experience with clodronate in lactating women, and it is not known whether it passes into breast milk. There have been no animal studies investigating the passage of sodium clodronate into the milk. Because many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from clodronate, breast feeding under the treatment with clodronate is not recommended.

Paediatric Use

The safety and efficacy of the use of sodium clodronate in children has not been established. Hence, it should not be used in children unless the expected benefits outweigh any potential risks.

Carcinogenicity, Mutagenicity and Impairment of Fertility

Oral sodium clodronate did not show any oncogenic activity in long term animal studies, and was inactive in tests for gene mutations (*Salmonella typhimurium* and mouse lymphoma cells), clastogenicity (Chinese hamster ovary cells *in vitro* and mouse micronucleus assay) and DNA damage (unscheduled DNA synthesis).

Use in Elderly

There are no special dosage recommendations for the elderly.

Interactions with Other Drugs

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

Sodium clodronate infusion should not be mixed with calcium-containing intravenous infusions such as Ringer's solution.

Concomitant use with other bisphosphonates is contraindicated.

Bisphosphonates are known not to affect the antineoplastic activity, in experimental tumours, of various anticancer agents including carmustine, cyclophosphamide, doxorubicin and fluorouracil. Sodium clodronate may enhance serum levels of estamustine phosphate by up to 80%. There are no other known interactions between sodium clodronate and anticancer agents.

The use of sodium clodronate with other agents indicated for reduction of calcium such as corticosteroids, phosphate, calcitonin, mithramycin and loop-diuretics, may potentiate their hypocalcaemic effect depending on tumour type and pathophysiological situation.

Sodium clodronate has been reported to be associated with renal dysfunction when used simultaneously with non steroidal anti inflammatory drugs (NSAIDs), most often diclofenac.

Due to increased risk of hypocalcaemia, caution should be taken when using sodium clodronate together with aminoglycosides. There is no evidence from clinical experience that sodium clodronate interacts with other medication such as steroids, diuretics, analgesics or chemotherapeutic agents as above.

Intravenous Infusion Warning

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

Sodium clodronate should NOT be given as a bolus injection. The recommended daily IV dose should always be diluted and administered as a slow intravenous infusion over a minimum 3 hour period (see "Dosage and Administration").

If during therapy there is a deterioration of renal function, the intravenous infusion must be stopped.

ADVERSE EFFECTS

Clinical Trials Experience

The following 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 to < 1/10	Rare ≥ 1/10,000 to < 1/1,000
Metabolism and nutrition disorders	Hypocalcaemia, asymptomatic Elevated lactic acid dehydrogenase Increased serum parathyroid hormone associated with Serum calcium decreased Serum alkaline phosphatase increased*	Hypocalcaemia, symptomatic
Gastrointestinal disorders	Diarrhea Nausea, Vomiting Epigastric pain	
Hepatobiliary disorders	Transaminases increased	
Skin and subcutaneous tissue disorders		Hypersensitivity reaction manifesting as Skin reaction

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

After intravenous sodium clodronate treatment, reversible proteinuria, elevations of serum creatinine and renal dysfunction have been reported. Severe renal damage may occur after rapid infusion of high doses of sodium clodronate.

Bisphosphonates are rarely reported to cause bronchoconstriction in patients with aspirin-sensitive asthma.

Post Marketing Experience

Body as a whole
Rare: cases of headache, transient fever, generalised erythema, purpura

Haematological
Rare: thrombocytopenia, marrow depression

Respiratory, thoracic and mediastinal disorders
Impairment of respiratory function in patients with aspirin-sensitive asthma. Hypersensitivity reactions manifesting as respiratory disorder.

Renal and urinary disorders
Impairment of renal function (elevation of serum creatinine and proteinuria), severe renal damage especially after rapid intravenous infusion of high doses of clodronate (for dosage instructions see "Dosage and Administration").

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
Cases of osteonecrosis of the jaw have been reported (see "Precautions").
Severe bone, joint and/or muscle pain has been reported in patients taking BONEFOS. However, such reports have been infrequent and in randomised placebo controlled studies no differences are apparent between placebo and BONEFOS treated patients. The onset of symptoms varied from days to several months after starting BONEFOS.

During post-marketing experience the following reactions have been reported with other bisphosphonates: Atypical subtrochanteric and diaphyseal femoral fractures. So far, these reactions have not been reported with BONEFOS (bisphosphonate class adverse reaction) (see also section "Precautions").

Eyes 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).

DOSAGE AND ADMINISTRATION

BONEFOS 400 mg capsules should be swallowed whole. A BONEFOS 800 mg tablet is scored and may be divided into two to ease swallowing, but the halves have to be taken at the same time of administration. The halved BONEFOS 800 mg tablets are not intended to be used in therapy as a substitute for the 400 mg capsule. BONEFOS tablets should not be crushed or dissolved before intake. A daily dose of 1600 mg can be taken either as a single dose or divided into two doses. 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.

When taken as a single dose, BONEFOS should preferably be taken in the morning on an empty stomach together with a glass of plain water. If it is not possible to take the dose in the morning, BONEFOS should be taken more than two hours after eating or drinking (with the exception of plain water). If the daily dose is divided into two intakes, the first dose should be taken as recommended for single dosing and the second dose should be taken more than two hours after eating or drinking or taking any other oral medications.

After BONEFOS intake, it is recommended that the patient refrains from eating and drinking for an hour.

BONEFOS must not be taken with milk, food or drugs containing calcium and other divalent cations because they impair the absorption of sodium clodronate (see "Interactions").

Adult patients with normal renal function

Treatment of hypercalcaemia due to malignancy:
For the treatment of hypercalcaemia of malignancy, a starting dose of 2400 or 3200 mg daily should be used in divided doses and, depending on the individual response, this can be reduced gradually to 1600 mg daily in order to maintain normocalcaemia.

Treatment of osteolytic bone metastases due to carcinoma of the breast and treatment of osteolytic lesions of multiple myeloma.

When oral therapy is used to treat increased bone resorption without hypercalcaemia, the dosage is individual. The recommended starting dose is 1600 mg daily. The majority of patients will be satisfactorily treated at this dosage. If clinically necessary, the dose may be increased, but is not recommended to exceed 3200 mg daily. A daily dose of 1600 mg can be taken either as a single dose or divided into two doses.

Patients with renal failure

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

Degree of renal failure	Creatinine Clearance, mL/min	Dose
Mild	50-80 mL/min	1600 mg daily (no dose reduction recommended)
Moderate	30-50 mL/min	1200 mg/daily
Severe	10-30 mL/min	800 mg/daily

There are no data on use of oral sodium clodronate in patients with creatinine clearance less than 10 mL/min or in patients on dialysis.

Duration of treatment:

The duration of treatment is recommended to be life-long.

OVERDOSAGE

Treatment of overdose should be symptomatic. Adequate hydration should be ensured, and renal function and serum calcium should be monitored. In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

Marketed presentations:

400 mg: 100 capsules in blister packs
800 mg: 60 tablets in blister packs

Non-marketed presentations:

400 mg: 30 capsules in bottles and blister packs, 100 capsules in bottles
800 mg: 10 tablets in bottles and blister packs, 60 tablets in bottles

Shelf life and storage conditions

BONEFOS tablets and capsules should be stored below 25°C.

The shelf life of the capsules is: 5 years
The shelf life of the tablets is: 3 years

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Limited
ABN 22 000 138 714
875 Pacific Highway
Pymble, NSW 2073

POISON SCHEDULE OF THE MEDICINE

(S4) PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

28 November 1996

Date of most recent amendment: 1 March 2012