PRODUCT MONOGRAPH

Pr OSTAC®

clodronate disodium for injection
30 mg/mL

for slow i.v. infusion only

and

clodronate disodium capsules
400 mg/capsule

Professed Standard

Bone Metabolism Regulator

Hoffmann-La Roche Ltd.
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OSTAC
(clodronate disodium)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Clinically Relevant Nonmedicinal Ingredients**
oral	Capsule- 400 mg	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*
Intravenous **For slow i.v. infusion only**	Solution - 30 mg/mL	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

OSTAC is indicated:
- as an adjunct in the management of osteolysis resulting from bone metastases of malignant tumors.
- for the management of hypercalcemia of malignancy.

Prior to treatment with clodronate disodium, 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 clodronate disodium inhibits osteoclastic activity and bone resorption by decreasing the flux of calcium from the bones and thus reducing the calcium level in the blood.

Clodronate disodium may be administered as a higher single infusion dose or a lower dose for multiple infusion use. Both methods have been shown to be effective.

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

CONTRAINDICATIONS

- Patients who are hypersensitive to clodronate disodium, other biphosphonates or any ingredient in the formulation. For a complete listing of ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Renal functional impairment (serum creatinine exceeding 440 μmol/L (5.0 mg/dL).
- Severe inflammation of the gastrointestinal tract.
- Pregnancy and lactation.

WARNINGS AND PRECAUTIONS

OSTAC (clodronate disodium) should NOT be given as a bolus injection since severe local reactions and thrombophlebitis may occur as the result of high local concentrations. The rapid bolus injection may also precipitate acute renal failure.

The recommended daily dose of OSTAC i.v. concentrate for intravenous infusion should always be diluted and administered as a slow intravenous infusion over a minimum 2-hour period (during multiple infusion use) or a minimum 4-hour period (during single infusion use) (see DOSAGE AND ADMINISTRATION).

OSTAC should not be given together with other bisphosphonates since the combined effects of these agents are unknown.

Administration of intravenous infusion
OSTAC i.v. may be administered either as a single infusion or as multiple infusions.

OSTAC for infusion is available as a concentrated preparation which must be diluted before use. The only recommended diluents are 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP.

For single infusion: Five (5) 10 mL ampoules of OSTAC i.v. (concentrate for intravenous infusion 300 mg/10 mL) should be added aseptically to 500 mL 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP. No other drugs or nutrients may be added. The diluted solution should be administered by slow intravenous infusion over a period of not less than 4 hours. As with any other highly concentrated i.v. solution there exists a potential for injection site symptoms if extravenous infiltration occurs. The infusion should be monitored closely to avoid infiltration. Prior to infusion of a single 1500 mg dose, it is important to establish and maintain full hydration with oral or i.v. fluids.

For multiple infusions: A single (1) 10 mL ampoule of OSTAC i.v. (concentrate for intravenous infusion 300 mg/10 mL) should be added aseptically to 500 mL of 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP. No other drugs or nutrients may be added. The diluted injection solution should be administered by slow intravenous infusion over a period of 2 to 6 hours. Slow infusion is important for safety. In patients with hypercalcemia it is recommended that oral or intravenous fluids be administered to establish or maintain full hydration.

Paravenous infiltration should be avoided. Local reactions may occur.

Retreatment
No formalized studies have been carried out with respect to retreatment. Clinical experience shows that patients with re-increased serum calcium after termination of therapy with clodronate disodium or during oral administration may be retreated either with a higher oral dosage (up to 3200 mg/day) or with the i.v. infusion preparation as a single infusion (1500 mg/day) or multiple infusions (300 mg/day). Oral or i.v. treatment should be chosen dependant on the severity of hypercalcemia.

It is recommended that appropriate monitoring of renal function with serum creatinine and/or blood urea nitrogen be carried out during treatment. Serum calcium and phosphate should be monitored periodically. Appropriate monitoring of hepatic function and hematological parameters, including white cell count is advised.

Endocrine and Metabolism
Hypercalcemia
Hypercalcemia causes a reversible tubular defect in the kidney that results in the loss of urinary concentrating ability and polyuria, both of which promote dehydration. Hypovolemia in patients with hypercalcemia can diminish glomerular filtration and lead to progressive renal insufficiency.

Most hypercalcemic patients are significantly dehydrated at initial presentation and restoration of intravascular volume is an important initial measure.

The cornerstone of initial treatment is vigorous hydration with isotonic saline (0.9%). It is essential to institute hydration to replenish extracellular fluid volume and restore normal glomerular filtration, as well as sodium diuresis to promote calcium excretion even after hydration status has been corrected.

The rate of administration of isotonic saline should be determined primarily by the severity of the hypercalcemia, the degree of dehydration, and the cardiovascular status of the patient. In general, at least 3 L/day should be administered initially and hydration continued until normocalcaemia has been achieved. Urine output must be maintained to avoid possible fluid overload. As many patients with hypercalcemia have other electrolyte abnormalities at presentation, appropriate attention must be given to maintaining electrolyte balance. For example, for hypokalemia, which may be further aggravated by aggressive diuresis, supplementation may be required. The development of hypernatremia during rehydration has been reported, especially in obtunded patients, and may complicate management.

Hypocalcemia
Infusion of clodronate disodium may present a risk of hypocalcemia.

The drug may chelate blood calcium during therapy, this may contribute to hypocalcemia.
In most cases, plasma calcium concentrations remain within the normal range during the administration of recommended doses of clodronate disodium. When plasma calcium falls into the hypocalcemic range, the patient may remain asymptomatic.

In these cases intravenous administration should be stopped or the oral dose should be decreased. In severe or symptomatic cases of hypocalcemia, oral or parenteral calcium supplementation may be required.

Serum Phosphate
Hyperphosphatemia has not been reported during clodronate disodium therapy in hypercalcemic patients. However, transient hypophosphatemia can occur following therapy with clodronate disodium.

Hyperparathyroidism
Clodronate disodium has not been shown to affect the renal handling of calcium and/or the action of plasma parathyroid hormone (PTH) on this process. A transitory increase in PTH has been reported in certain subjects.

Renal
Administration of clodronate disodium may aggravate renal function in some patients. Therefore, appropriate monitoring of renal function during and after intravenous infusion is required. The effect of the drug on the renal function of patients with serum creatinine in excess of 220 μmol/L (2.5 mg/dL) has not been studied in controlled trials. In such situations dose reduction should be considered or the drug should be withheld

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

Skeletal
Osteonecrosis of the Jaw (ONJ)
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 preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, head and neck 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. The healthcare professional's clinical judgment should guide the management plan of each patient based on individual benefit/risk assessment.

Special Populations

Pregnant Women: The safety and efficacy of OSTAC in pregnancy has not been established (see CONTRAINDICATIONS).

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

Pediatrics: The safety and efficacy of OSTAC in children has not been established.

Monitoring and Laboratory Tests

Serum calcium levels should be monitored throughout treatment with clodronate disodium.

Corrected (adjusted) serum calcium values should be calculated using established algorithms, such as:

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

Ca_{adj} = adjusted calcium concentration (mg/100 mL)

Ca_t = total calcium concentration (mg/100 mL)

A = albumin concentration (g/100 mL)

A_m = mean normal albumin concentration for the given laboratory (g/100 mL)

Alternative: corrected calcium (mg/dL) = measured calcium + [4.0-albumin (g/dL)] x 0.8

Appropriate monitoring of hepatic function and hematological parameters, including white cell count is advised.

Additionally, serum creatinine and blood urea nitrogen should be monitored in patients with known or suspected renal insufficiency.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Gastrointestinal symptoms such as nausea, vomiting, anorexia and diarrhea are the most frequent adverse events reported during clodronate disodium therapy, particularly with the oral form. A reduction in dosage, a change to i.v. clodronate disodium or a temporary interruption of therapy may assist in the management of patients where these symptoms are relevant.

Adverse events affecting the calcium homeostasis leading to hypocalcemia were all assessed as possible or probable and reflect the calcium lowering properties of clodronate disodium.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Listed in Table 1, are the crude incidence rates for the most common adverse events reported during therapy with OSTAC 400 mg capsules and OSTAC i.v. (concentrate for intravenous infusion).

ADVERSE EVENT	ORAL (N=390) %(N)	I.V. (N=188) %(N)
Digestive System		
Vomiting	---	3.6(14)
Nausea	3.1(12)	1.1(2)
Diarrhea	1.8(7)	0.5(1)
Anorexia	1.0(4)	---
Metabolic and Nutritional		
Hypocalcemia	1.5(6)	---
Creatinine Increased	1.3(5)	---
SGPT Increased	0.3(1)	---
Cardiovascular System		
Heart Failure	1.3(5)	---
Respiratory System		
Pneumonia	1.3(5)	---
Musculoskeletal System		
Spontaneous Fracture	1.0(4)	---

Cardiovascular & Respiratory: Adverse events affecting the cardiovascular and respiratory systems or reported as spontaneous fractures were all assessed as unrelated to clodronate disodium therapy since alternative causalities were evident (e.g. heart failure prior to clodronate disodium therapy; pneumonia; deficient immune state in patients suffering from advanced malignant diseases).

A case of a bronchospastic reaction in a female patient suffering from an acetylsalicylic acid-sensitive asthma bronchiole has been reported after administration of i.v. clodronate disodium.

Hepatic: A causal relationship between clodronate disodium and liver function abnormalities, i.e. increased liver enzymes (SGPT, AP, LDH) is also difficult to assess. Pre-existing liver metastases and abnormal liver function values often exist prior to therapy with clodronate disodium. Causal relationship, however, cannot be excluded with certainty in some patients. Careful monitoring of liver function values is advised.

Hypersensitivity: Hypersensitivity reactions, including angioedema, urticaria, rash and/or pruritus, in association with oral or parenteral clodronate disodium, have been reported in two patients.

Renal: Hypercalcemia of malignancy is frequently associated with abnormal elevation in serum creatinine and BUN. Transient increases in serum creatinine were observed during clodronate disodium therapy. Although in some cases a causal relationship could not be excluded with certainty, the assessment of causality is difficult since in longstanding hypercalcemia, an impairment in renal function, possibly due to the nephrocalcinosis, can reasonably be expected. Careful monitoring of renal function is advised. Transient proteinuria and oliguria have also been reported in few cases immediately following single infusion use of i.v. clodronate disodium.

Abnormal Hematologic and Clinical Chemistry Findings

Patient surveillance encompassing about 2700 patient-years treated with clodronate disodium detected five cases of acute non-lymphocytic leukemia or myelodysplasia in patients without multiple myeloma, and two cases in patients with multiple myeloma (two patients with multiple myeloma also developed non-lymphocytic leukemia while receiving placebo). The causal relationship to clodronate disodium or to the underlying disease has not been established. Appropriate monitoring of hematological parameters, including white cell count is still advised.

Post-Market Adverse Drug Reactions

Although there have been no cases reported for OSTAC, cases of osteonecrosis (primarily of the jaws) have been reported in other biphosphonates. Osteonecrosis of the jaws has other well-documented risk factors. It is not possible to determine if these events are related to biphosphonate use, to concomitant drugs or other therapies (e.g. chemotherapy, head and neck radiotherapy, corticosteroid), to patient's underlying disease or to other co-morbid factors (e.g. anemia, infection, pre-existing oral disease).

DRUG INTERACTIONS

Overview

Drug-Drug Interactions

OSTAC should not be mixed with calcium-containing intravenous infusions.

The use of clodronate disodium with other agents indicated for reduction of calcium such as corticosteroids, phosphate, calcitonin, mithramycin, loop-diuretics may result in increased hypocalcemic effect depending on tumour type and pathophysiological situation.

Concurrent use of antacids or any drug containing calcium, iron, magnesium or aluminum may prevent absorption of oral clodronate disodium.

Concomitant use of clodronate disodium with mithramycin and thiazides is not recommended.

Concomitant use of i.v. clodronate disodium and aminoglycosides can result in an increased incidence of hypocalcemia.

Concomitant use of clodronate disodium and NSAIDs may promote renal dysfunction. However, a synergistic action has not been established.

Drug-Food Interactions

OSTAC capsules should not be taken with food or within one hour before or after food or milk.

Drug-Laboratory Interactions

Since clodronate disodium binds to bone, OSTAC may interfere with bone scintigraphy examinations.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Prior to using clodronate disodium (single or multiple infusions) it is important to establish and maintain full hydration with oral or intravenous fluids.

OSTAC Oral

Recommended Dose and Dosage Adjustment

The oral recommended daily maintenance dose following intravenous therapy is in the range of 1600 mg (4 capsules) to 2400 mg (6 capsules) given in single or two divided doses. Maximal recommended daily dose is 3200 mg (8 capsules).

Oral doses higher than 3200 mg daily have not been evaluated but would be likely to increase the frequency of adverse intestinal effects.

Dosage should be reduced in patients with severe renal impairment (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS).

Administration

OSTAC (clodronate disodium) 400 mg white gelatin capsules should be administered whole with copious fluids, but not with milk. The patient should not eat one hour before or after OSTAC intake.

The total daily amount can be given as one single dose or, if necessary, in two divided doses in order to improve gastrointestinal tolerance. The standard daily dosage generally consists of 4 x 400 mg capsules (1600 mg/day). However, in some individual cases, a higher daily dose of up to 8 x 400 mg capsules (3200 mg/day) may be necessary.

The duration of treatment is normally 6 months. Treatment, however, can be extended beyond 6 months depending on the course of the disease. Similarly it may be necessary to restart treatment after an interruption.

OSTAC i.v. (concentrate for intravenous infusion)

SINGLE INFUSION:

The contents of five (5) 10 mL ampoules is administered by slow intravenous infusion over a period of not less than 4 hours.

MULTIPLE INFUSIONS:

The contents of one (1) 10 mL ampoule is administered as a single daily dose over a period of 2 to 6 hours (see Administration).

Compatibility with i.v. solutions

OSTAC i.v. is a concentrate for intravenous infusion which must be diluted before use. The only recommended diluents are 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP. A single (1) 10 mL ampoule (for multiple infusion use) or five (5) 10 mL ampoules (for single infusion use) of OSTAC i.v. (300 mg/10 mL) should be added aseptically to 500 mL of 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP. No other drugs or nutrients may be added (see DOSAGE AND ADMINISTRATION and PHARMACEUTICAL INFORMATION).

Note: Other diluents should not be used. No other drugs or nutrients may be added.

I.V.-Single Infusion

Five (5) 10 mL ampoules of OSTAC i.v. concentrate for intravenous infusion (300 mg/10 mL) is diluted with 500 mL of 0.9% w/v sodium chloride injections, USP or 5% w/v dextrose, USP and administered by slow intravenous infusion over a period of not less than 4 hours.

I.V.-Multiple Infusion

One (1) 10 mL ampoule of OSTAC i.v. concentrate for intravenous infusion (300 mg/10 mL) is diluted with 500 mL of 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP and administered by slow intravenous infusion over a period of 2 to 6 hours.

Since the duration of treatment is adjusted in accordance with patient response, daily determination of serum calcium levels must be carried out. Duration of treatment by multiple intravenous infusions should not exceed 10 days.

Response: In most cases, elevated serum calcium levels can be reduced to normal within 2 to 5 days, which ever method of infusion is used. Following normalization, treatment should be continued with OSTAC (clodronate disodium) 400 mg capsules in order to maintain normocalcemia. Should the serum calcium level rise again during oral treatment, the intravenous infusion can be reintroduced.

Prior to using clodronate disodium (single or multiple infusions) it is important to establish and maintain full hydration with oral or intravenous fluids.

RECONSTITUTION

The recommended daily dose of OSTAC i.v. must be added aseptically to 500 mL of 0.9% w/v sodium chloride injection, USP or 5% w/v dextrose, USP. **Note**: No other diluent should be used and no other drugs or nutrients may be added.

STORAGE OF DILUTED SOLUTION:

Protect the diluted solution from temperatures below 15^{o}C and above 30^{o}C. The reconstituted solution of OSTAC i.v. should be administered within 12 hours of preparation by slow intravenous infusion over a period of 2 to 6 hours.

OVERDOSAGE

There is a lack of documented experience on acute overdosing with clodronate disodium. An overdose of the intravenous preparation could provoke renal damage. Renal function should be monitored. Overdosage may result in hypocalcemia. Careful monitoring for several days for signs and symptoms of hypocalcemia is recommended in cases where the dose given was too high in relation to initial serum calcium (see PRECAUTIONS). Oral or parenteral calcium supplementation may be required to restore plasma calcium levels.

Gastric lavage may be used to remove unabsorbed drug following acute oral overdosage.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

OSTAC (clodronate disodium) belongs to the class of bisphosphonates which act primarily on bone. This tissue specificity is due to the high affinity of bisphosphonates for calcium phosphate crystals. Clodronate disodium forms complexes with the hydroxyapatite of bone, altering the crystalline structure in such a way that dissolution of the crystals is inhibited.

The major effect of clodronate disodium is to inhibit osteoclast-mediated bone resorption without an inhibitory effect on mineralization. In responsive patients, inhibition of abnormal bone resorption by clodronate disodium leads to the management of osteolytic bone metastases and, if present, reduction of hypercalcemia.

In patients with bone metastases, clodronate prevents the progression of bone destruction. Prevention of the progression and dissemination of existing metastases, as well as the formation of new skeletal metastases has been demonstrated both by scintigraphy and by radiography. In normocalcemic patients, the anti-osteolytic action of clodronate disodium is also clearly shown in reduced urinary calcium and hydroxyproline excretion. During and also after intravenous administration of clodronate disodium, the elevated serum calcium decreases, in some rare instances to hypocalcemic levels.

Pharmacodynamics

Several variables interfere with a precise assessment of the duration of the effect. Variations in the tumour load, in the amount and type of osteolytic mediators produced by the tumour cells, concomitant anticancer therapy and the renal handling of calcium can influence the duration of action.

In hypercalcemic patients, after successful treatment patients remain normocalcemic for some days up to several weeks. In general they become hypercalcemic again within 2 -3 weeks after termination of therapy with clodronate disodium.

Clodronate disodium is not metabolized and is excreted unchanged by the kidneys. In calcium homeostasis the kidneys have a prominent role. Skeletal osteolysis may be accompanied by the pathogenesis of hypercalcemia and renal dysfunction may occur. 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 clodronate disodium, the state of negative fluid balance requires vigorous and adequate hydration with isotonic saline (0.9% w/v).

Normalization of blood calcium levels by clodronate disodium in adequately hydrated patients may also normalize suppressed plasma parathyroid hormone (PTH) levels and decrease urinary calcium, hydroxyproline and phosphate excretion.

Pharmacokinetics

Clodronate disodium is rapidly cleared from the blood. The mean value for plasma half-life after oral administration of clodronate disodium is 5.6 h. About 20% of the quantity absorbed is bound to bone. Since no biotransformation occurs, the drug is exclusively cleared by the kidneys at a rate of about 80 mL/min., when kidney function is normal. As with all bisphosphonates, the intestinal absorption and bioavailability of clodronate disodium after oral administration is low (1 - 3%).

After i.v. dose, clodronate disodium exhibits a plasma concentration profile which fits a two-compartment model with a t½α approximately 0.3 h and a t½ß approximately 2 h, and terminal elimination phase with t½ approximately 13 h. The latter accounts for 10 - 15% of renal excretion. Total clearance is about 110 mL/min. and renal clearance is approximately 90 mL/min. Volume of distribution is approximately 20 L.

The clinical effect of clodronate disodium is based on its concentration at the site of action, i.e. in bone tissue. Its half-life is dependent on the rate of skeletal turnover. When the bound substance is released from bone tissue during bone resorption, high local concentrations develop at the site of osteolysis, which has a direct action on the bone-resorbing osteoclasts.

STORAGE AND STABILITY

OSTAC (clodronate disodium) i.v. (concentrate for intravenous infusion) and white gelatin capsules should be stored at room temperature (15-30^{o}C). Protect from high humidity.

STORAGE OF DILUTED SOLUTION:

Protect the diluted solution from temperatures below 15^{o}C and above 30^{o}C. The reconstituted solution of OSTAC i.v. should be administered within 12 hours of preparation by slow intravenous infusion over a period of 2 to 6 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

OSTAC (clodronate disodium) i.v. (concentrate for intravenous infusion) is supplied in 10 mL sterile ampoules containing 300 mg of clodronate disodium per ampoule. OSTAC is available in boxes of 5 ampoules. The non-medicinal ingredients are disodium hydrogen carbonate (3.200 - 5.700 mg/10 mL) and water for injection.

OSTAC (clodronate disodium) white gelatin capsules are supplied as 400 mg of clodronate disodium per capsule. OSTAC capsules are available in blister packs of 120 capsules per box. Boxes of 120 capsules contain 12 blister strips (10 capsules/blister strip). The non-medicinal ingredients are: gelatine, iron oxide, magnesium stearate, maize starch, polydimethyl siloxane, shellac, sodium starch glycolate, soya lecithin, talc, and titanium oxide.

PART II: SCIENTIFIC INFORMATION

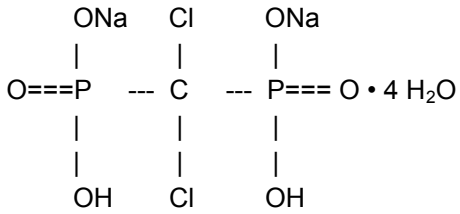
PHARMACEUTICAL INFORMATION

Clodronate disodium belongs to the group of bisphosphonates (formerly known as diphosphonates), which is characterized by two C-P bonds. Since these two bonds are bound to the same carbon atom to form a P-C-P bond, clodronate disodium is classified as a geminal bisphosphonate.

Drug Substance

Proper name:	Clodronate Disodium
Chemical name:	Anhydrous, clodronate disodium (as tetrahydrate)
Molecular formula:	$CH_2Cl_2Na_20_6P_2$. 4 H_20
Molecular weight:	360.92

Structural formula:



Physicochemical properties:

Description:	white to yellowish-white crystalline powder	
Solubility:	**Water:**	Freely soluble
	Methanol:	Very slightly soluble
	Ethanol:	Practically insoluble
	Acetone:	Practically insoluble
pH: (0.5 % (m/v) in water)	3.8 to 4.8	
PKa III: (25^oC, 0.02 mol/L in water)	5.84	
PKa IV: (25^oC, 0.02 mol/L in water)	8.68	
Melting Point:	Sintering is observed just above 50^oC. No melting is noted up to 250^oC.	

CLINICAL TRIALS

To date, results from several controlled clinical trials have shown that clodronate disodium can normalize plasma calcium in the majority of hypercalcemic, rehydrated cancer patients in whom increased bone resorption is the prevailing disturbed calcium flux. In these patients, clodronate disodium, given intravenously either as a single infusion or as repeated daily (300 mg/d) administrations, normalized serum calcium, usually 3 to 5 days after the onset of therapy. In responding patients, long-term oral maintenance treatment resulted in sustained normocalcemia. The dose range was 1600 - 3200 mg daily with treatment period extending up to 18 months.

In patients displaying a good response to clodronate disodium, the fall in plasma calcium is accompanied by an increase in the calcium regulating hormones, parathyroid hormone and 1,25-dihydroxyvitamin D_3. This homeostatic reaction probably explains why hypocalcemia rarely occurs in clodronate disodium-treated patients.

The data supporting the clinical efficacy and safety of clodronate disodium for the indication of osteolysis is compiled from three (3) controlled and several non-controlled clinical trials. These studies report on the use of clodronate disodium in normocalcemic patients with osteolytic/osteoporosis/osteosclerosis, bone metastases. In total, 448 patients received clodronate disodium for periods ranging from several days to 18 months.

Efficacy in these studies was demonstrated by improvement in bone related parameters.

- Incidence of vertebral fractures
- Incidence of non-vertebral fractures
- Progression of bone metastases/Incidence of new bone metastases
- Biochemical parameters relating to bone metabolism (urinary calcium/creatine excretion, urinary hydroxyproline/creatine excretion and serum calcium levels and/or hypercalcemic episodes)

No serious side effects have been reported in cancer patients receiving oral clodronate disodium, except for the occasional occurrence of mild and transient gastrointestinal upset.

DETAILED PHARMACOLOGY

PRECLINICAL PHARMACODYNAMICS:

Inhibition of calcification - *in vivo* action:

Bisphosphonates inhibit calcification *in vivo*. They have an inhibitory effect on various experimental soft tissue calcifications, including arteries, kidneys, skin, muscle and heart. This inhibitory action is found after administration of the bisphosphonate by either the parenteral or oral routes.

There is a close correlation between the inhibition of calcium phosphate formation *in vitro* by the various bisphosphonates and their inhibitory effect on ectopic calcifications *in vivo*. This evidence has led to the conclusion that the inhibition of calcification *in vivo* is physicochemical in nature.

The inhibition of soft tissue calcification by bisphosphonates does not parallel the inhibition of hard tissue calcification. Clodronate disodium has been shown to be an excellent inhibitor of calcification in soft tissue, with only a slight effect on bone and cartilage. At doses of 46.6 mg/kg given subcutaneously, which corresponds to 10 mg/kg of phosphorous, clodronate disodium did not have any effect on normal bone calcification. By contrast, the equivalent dose of etidronate disodium corresponding to 10 mg/kg phosphorus always produced inhibition of normal bone calcification. The long-term administration (2 years) of etidronate disodium, even at lower doses (0.5 mg/kg s.c.), results in the inhibition of calcification and ultimately to fractures, which is not the case with clodronate disodium. Finally, at doses of 2.5 mg/kg s.c., clodronate disodium does not have any negative action on the healing of fractures, particularly on traction resistance, in dogs.

Inhibition of bone resorption

Bisphosphonates proved to be very powerful inhibitors of bone resorption when tested in a variety of conditions, both *in vitro* and *in vivo*.

Using different *in vitro* models it has been shown that bone resorption may be inhibited by binding to the mineral component of the bone matrix, preventing its resorption by osteoclasts. Studies with osteoclasts isolated from bone and incubated with clodronate disodium (10^{-5} to 10^{-9}) show a dose dependant inhibition of bone resorption and supports the requirement of binding to the mineralized matrix.

In vivo models have shown clodronate disodium as able to inhibit bone lysis induced by different tumour models. High doses of clodronate disodium, reduce the number of osteoclasts induced by the tumour and therefore inhibit bone resorption without affecting bone formation (mineralization).

There is also evidence, that clodronate disodium may not only prevent osteolysis, but bone mass/strength may even increase depending on the total amount of drug administered.

Preclinical Pharmacokinetics:

In animals, the intestinal absorption of clodronate disodium is low. It is reported to be 4 to 10% in rats and 10 to 55% in dogs. Absorption of bisphosphonates is generally higher in younger animals and in rats and chicken occurs predominantly in the small intestine. Bisphosphonates are not metabolized and are excreted unchanged in the urine.

Clinical Pharmacology:

In man, the intestinal absorption of clodronate disodium after oral administration is low (1 to 3%). The absolute bioavailability is 1 to 2%. Of the quantity absorbed, about 80% is excreted within 24 hours via the kidney and the remaining 20% is bound to bone. Because of its high affinity for calcium phosphate, clodronate disodium acts selectively on bone. The binding of clodronic acid to bone structures occurs preferentially in regions of increased bone turnover (osteoclast activity). The drug is not metabolized but is excreted unchanged in the urine.

After i.v. dose, clodronate disodium exhibits a plasma concentration profile which fits a two-compartment model with a $T_{½\alpha}$ approximately 0.3 h and a $t_{½\beta}$ approximately 2 h, and terminal elimination phase with $t_{½}$ approximately 13 h. The latter accounts for 10 - 15% of renal excretion. Total clearance is about 110 mL/min and renal clearance is approximately 90 mL/min. Volume of distribution is approximately 20 L.

The biological effect of clodronate disodium is based on its concentration at the site of action, i.e. in bone tissue. Its half-life is dependent on the rate of skeletal turnover. If the bound substance is released from bone tissue on bone breakdown, there is a high local concentration at the site of osteolysis, which has a direct action on the bone-resorbing osteoclasts, their mononuclear precursors and other bone-disintegrating cells.

TOXICOLOGY

As a bisphosphonate, clodronate disodium has a high affinity for hydroxyapatite of the bone. This simultaneously explains its low toxicity. The good tolerability and relatively low toxicity of clodronate disodium on parenteral administration with respect to pharmacologically active doses has been confirmed both in acute experiments and in subchronic toxicity tests. On i.v. administration, the doses of 30 mg/kg/day in the dog and 100 mg/kg/day in the rat are still within the tolerated range.

Clodronate disodium exhibits relatively little toxicity either on single oral administration or after daily oral administration for a period of up to 9 months. In the chronic toxicity test in rats, a dose of 200 mg/kg/day is at the limit of tolerability. In dogs, 40 mg/kg/day chronically are within the tolerated range.

On daily oral administration of 500 mg/kg for 6 weeks to rats, signs of renal failure with a clear rise in blood urea nitrogen and initial liver parenchymal reaction with rises of SGOT, SGPT and AP occurred. No significant hematological changes were found in the toxicological investigations.

Acute toxicity

Acute toxicity (LD_{50}) in mice, rats and guinea pigs was studied after oral, intramuscular (i.m.) and intravenous (i.v.) administration.

Species	Route	LD_{50} mg/kg	
		Male	Female
Mouse	Oral	>2000	>2000
	i.m.	711*	893
	i.p.	722	793
	i.v.	238	236
Rat	Oral	635	1798
	i.p.	399	465
	i.v.	65.2	-----
Guinea Pig	Oral	>2000	>2000
	i.m.	316	346

* *Range*

Subacute toxicity

Subacute toxicity in rats and dogs was studied after oral, intramuscular (i.m.) and intravenous (i.v.) administration.

Species	Route	Doses mg/kg/day	Duration days (wks)	Observation
Rat	Oral	500/300	42(6)	All doses well tolerated. No deaths. No hematological disorders. Rise in BUN, slight rise in SGOT and SGPT, and rise in AP in high dose groups.
	i.m.	20/10	42(6)	All doses well tolerated. No deaths. Normal weight gain. Slight fall in hemoglobin in males. Leukopenia in high dose groups. No significant electrolyte changes.
	i.v.	100/50/25	30(6)[1]	From 5th week onward, animals in high dose groups showed respiratory insufficiency with dyspnea and deterioration in general well-being. Pneumonia demonstrated in autopsy. Dose dependent decrease in body weight and food intake. High dose groups showed increase in prothrombin time and reduced leukocyte count, hemoglobin and hematocrit. High dose groups showed significant rise in BUN and slight increase in SGOT and LDH.
	i.v.	750(450)/ 150/30	28(4)	Highest dose was highly toxic. 25/50 animals died, body weight gain was reduced, food consumption decreased along with haematological parameters haemoglobin, erythrocytes, lymphocytes and haematocrit. Increased values for reticulocytes and platelets, plasma glucose, blood urea, plasma ALAT, ASAT, LDH and aP. Histopathology revealed pathological findings in GI tract, kidneys, liver, testicles. At mid dose, reduction in body wgt gain, haemoglobin, erythrocytes, lymphocytes, haematocrit. Increase values for reticulocytes, platelets, activity of ALAT, ASAT, LDH in plasma. Lowest dose caused slight, not significant increase of ALAT and ASAT activity.
Dog	Oral	100/50	63(9)	All doses well tolerated. No deaths. No drug induced hematological, biochemical or urinary changes.
	i.m.	10/5	60(10)[2]	All doses well tolerated. No deaths. No changes in behaviour. Normal body weight development. No drug induced hematological or biochemical changes. Increased excretion of in-organic phosphate, calcium and chloride in males.
	i.v.	30/6	30(5)[3]	All doses well tolerated. No deaths. No drug induced hematological or biochemical changes. Increased excretion of inorganic phosphate in all dose groups. Increased calcium excretion in high dose groups.
	i.v.	100/45/20	28(4)	Highest dose was highly toxic. Mid dose lies at limit of tolerance, producing drug-related clinical changes/ biochemical changes in blood parameters. Lowest dose produced no substance-related effects.

[1] The substance was administered for 6 weeks, 5 times a week.
[2] Administered 6 days/week for 10 weeks.
[3] Administered 6 days/week for 5 weeks

Chronic toxicity

Chronic toxicity in rats and dogs was studied after oral administration.

Species	Route	Doses mg/kg/day	Duration weeks (mths)	Observation
Rat	Oral	200/100	26 (6)	All doses well tolerated. No deaths. Slight delay in body weight gain in high dose groups. No drug induced hematological changes. No significant increase in BUN, serum protein, cholesterol, inorganic phosphate or potassium levels. No significant reduction of total lipids, calcium or sodium levels. Slight rise in SGPT and AP.
	Oral	300/200 /100	26 (6)	All doses well tolerated. No deaths. For high dose groups, slight increase in leukocyte count and AP. Significant decrease in packed cell volume neutrophils (female), and serum phosphate.
	Oral	400/250 /100	52(12)	Highest dose was toxic. Trabeculae extension not reversible in high dose group. Leukocytosis was dose dependant and appeared in mid and high dose group and disappeared during recovery period. Liver was affected in dose-dependent manner (increase in S-ALAT and S-ASAT). No evidence that kidney was affected. Mid dose was at limit of tolerable range. Lowest dose was within tolerated range.
Dog	Oral	40/20	9	All doses well tolerated. No deaths. No drug induced biochemical or urinalysis changes.
Mini Pig	Oral	600/300 /150	52(12)	Highest dose was highly toxic. Changes in stomach and enzymes related to liver. Mid dose was at limit of tolerance ie. produced marginal changes in enzyme levels. Low dose was well tolerated. Only pharmacodynamic changes in bone were observed illustrating intended action of drug. All changes normalized during recovery period.

Teratological and reproduction studies

Orally administered clodronate disodium at doses of 100 or 300 mg/kg/day to pregnant rats, or at doses of 200 mg/kg/day to pregnant rabbits, is neither embryotoxic, fetotoxic or has teratogenic effects.

In combined fertility and peri- and post-natal toxicity studies in Wister rats, subcutaneously administered clodronate disodium at a dose of 20 mg/kg/day was shown to have no effect on reproduction. In pregnant rats, clodronate disodium was neither embryotoxic nor fetotoxic. There was no evidence of any teratogenic effect on any of the offspring which ultimately produced an F_2 generation without any signs of impaired fertility.

Carcinogenicity

Carcinogenicity studies were performed in rats and mice after daily gavage administration.

Species	Route	Doses mg/kg/day	Duration weeks (mths)	Observation
Mouse	Gavage	45/150 /400	80	An 80-week carcinogenicity study in the mouse was performed. Disodium clodronate was administered daily by gavage at doses of 45, 150 & 400 mg/kg. The incidence of tumors in the animals treated with disodium clodronate did not differ significantly from that of the controls and there was no trend for dose-response relationship in the incidence of neoplastic changes. The data also indicated that mortality in animals treated with sodium clodronate did not differ from that in controls. It was concluded that disodium clodronate was not carcinogenic at the doses administered and does not increase mortality.
Rat	Gavage	50/100/200	104	A 104-week carcinogenicity study in the rat was performed. Disodium clodronate was administered daily by gavage at doses of 50, 100, 200 mg/kg. The spectrum of neoplastic changes and their incidence did not differ notably between control group and the test article treated groups. Positive trend towards basal cell tumour of the skin in males. Positive trend towards C-cell carcinoma in thyroid glands and theca-granulosa cell tumour in ovary in females. Frequency did not exceed non-treated control groups. Test article increased trabecular extension (an elongation and increase in the number of columns of calcified cartilage) in femur and sternum bone both in males and females in a dose dependent fashion. The data also indicated that mortality in animals treated with sodium clodronate did not differ from that in controls. It was concluded that disodium clodronate was not carcinogenic at the doses administered and does not increase mortality.

Mutagenicity

In vitro mutagenicity has been evaluated in the following test systems:

- The Ames Test using salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 in the presence and absence of a rat liver S9 homogenate.
- The micronucleus test in bone marrow erythrocytes of NMRI mice.
- The DNA synthesis test (repair test in human cells) with and without rat liver homogenates.
- The 5 - Loci mutation test in Schizosaccharomyces pombe in the presence and absence of a metabolic activity system.

- Mutation test at HPRT locus of V79 Chinese hamster cells (resistance to 6-thioguanine) in presence and absence of a rat liver S9 homogenate.
- Test for chromosomal abberations by means of metaphase analysis on cultured human lymphocytes in presence and absence of rat liver S9 homogenate.

No mutagenic effect was found with any of the in vitro test systems. In vivo mutagenicity was investigated by means of the micronucleus test using adult Swiss mice. The results of the micronucleus test indicated that clodronate disodium, at the doses used, did not induce the formation of micronuclei in the marrow of Swiss mice and therefore was not mutagenetic in this test system.

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PART III: CONSUMER INFORMATION

OSTAC
clodronate disodium

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

ABOUT THIS MEDICATION

What the medication is used for:
OSTAC belongs to a class of compounds known as bisphosphonates which slow down the removal and replacement of calcium on the bone tissue.

This medication is for adult use only.

What it does:
In certain cancers, the speed of bone loss is occurring faster than the new production of bone. This is called osteolysis. This can be accompanied by an increased release of calcium into the blood. When the level of calcium in the blood is too high, this is called hypercalcemia. OSTAC works by attaching itself to the bone and therefore prevents osteolysis. In cases where there is bone breakdown and an increased release of calcium into the blood, OSTAC reduces the high calcium blood levels by stopping the release of calcium into the blood. Although effective in the treatment of osteolysis and hypercalcemia as a result of the cancer, the use of OSTAC will not provide a cure for cancer.

When it should not be used:
If the answer is YES to any of the following questions, do not take this medicine until you have talked to your doctor about it.
- **Do you have any kidney problems?**
- **Are you pregnant or breast feeding?**
- **Do you have stomach pain or a bowel disturbance?**
- **Have you been allergic to similar medicines before?**

What the medicinal ingredient is:
OSTAC contains the active ingredient clodronate disodium.

What the nonmedicinal ingredients are:
For the capsules, the nonmedicinal ingredients are gelatine, iron oxide, magnesium stearate, maize starch, polydimethyl siloxane, shellac, sodium starch glycolate, soya lecithin, talc, and titanium oxide.

For the injection, the nonmedicinal ingredients are disodium hydrogen carbonate and water for injection.

The medication should not be used if you are allergic to any ingredient in the formulation or any component of the container.

What dosage forms it comes in:
30 mg/mL solution for injection to be given as a slow intravenous infusion only. An intravenous line or I.V. is a thin, plastic tube placed in a vein in your hand or arm.

and

400 mg white gelatin capsules

WARNINGS AND PRECAUTIONS

Osteonecrosis of the jaw
Osteonecrosis (pronounced OSS-tee-oh-ne-KRO-sis) of the jaw is a rare condition that involves the loss, or breakdown, of the jaw bone. It is not known if biphosphonates play any role in the loss or breakdown of the jaw but it has occurred in some cancer patients receiving bisphosphonates.

Symptoms include, but are not limited to:

Pain, swelling, or infection of the gums
Loosening of teeth
Poor healing of the gums
Numbness or the feeling of heaviness in the jaw

If you experience any of the above symptoms or any other symptom of possible dental problems, tell both your oncologist and your dentist immediately. Be sure to inform your dentist that you are being treated with OSTAC. Also consult with your oncologist if any dental procedure is required.

INTERACTIONS WITH THIS MEDICATION

Please DO NOT take the capsules with milk. If OSTAC is taken with drinks containing milk, it is more difficult for the medicine to enter the blood and so it is not as effective. For the same reason, DO NOT take OSTAC with antacid indigestion tablets or mineral supplements as these may also make the medicine less effective.

Before starting treatment with OSTAC, talk to your doctor about any other medicines that you are using or intending to use. It is especially important that your doctor knows that you are being treated with another bisphosphonate, calcitonin, calcium tablets, or vitamin supplements.

PROPER USE OF THIS MEDICATION

Things to Remember About OSTAC
1. **Take your medicine as advised by your doctor and carefully read the label.**
2. **Please do not take this medicine with milk.**
3. **This medicine has been prescribed for your current medical problem. Do not give it to other people.**
4. **Keep your medicine out of the reach of children.**

Usual dose:
When in hospital, you may have received this medication as an intravenous infusion. These instructions are for taking the OSTAC 400 mg white gelatin capsules and should be followed exactly, because the success of your treatment depends very much on how carefully and consistently you follow your doctor's instructions.

Your doctor will tell you how much OSTAC to take each day. The dosage is prescribed to suit your particular needs. The doctor will also tell you how to divide your dosage through the day. For example, he or she might prescribe a total dosage of 1600 mg per day, to be taken as one or two equally divided doses. Therefore, you must take the exact amount which has been prescribed for you.

Your dose of OSTAC capsules, to be taken once or twice daily, simply consists of removing the number of capsules that are required to make up the dose that your physician has prescribed for you. Swallow the capsules whole, with liquid (except milk). Do not take the capsules with food or within one hour before or after food or milk. Please take the capsules even if you are not eating at present.

The success of treatment with OSTAC depends very much on how CAREFULLY and consistently you follow the doctor's instructions about taking OSTAC.

Follow instructions exactly and ask your doctor or hospital pharmacist if you are unsure. It is very important not to miss any of the tests which your doctor orders, including blood tests and tests to determine the function of your kidneys.
Based on blood tests and other tests, your doctor might make changes in the amount of OSTAC you must take. NEVER MAKE DOSE CHANGES ON YOUR OWN.

Always take your medication on time and never allow your medication to run out. If you plan a holiday, please remember to take enough supplies to cover your needs.

Overdose:
If you take more than the scheduled dose, contact your doctor to find out what needs to be done.

Missed Dose:
If you forget to take a scheduled dose, most doctors will suggest that you take it at the time you remember and then go on with your normal schedule. (Check with your doctor to see if this procedure is acceptable).

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

The most common side effects are associated with the digestive system and include nausea and diarrhea.

Drug related allergies such as skin rashes have been reported less commonly.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	diarrhea	✓		
	nausea	✓		
Uncommon	skin rashes			✓

Loss or breakdown of the jaw bone has occurred in some cancer patients receiving bisphosphonates.

Other side effects not listed above may also occur in some patients. If you notice any other effects, tell your doctor immediately.

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

HOW TO STORE IT

OSTAC capsules should be stored at room temperature (15-30°C) and should be protected from high humidity.

REPORTING SUSPECTED SIDE EFFECTS

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

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Hoffmann-La Roche Limited at: www.rochecanada.com.

This leaflet was prepared by Hoffmann-La Roche Limited

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