

PRODUCT MONOGRAPH

^{Pr}**CLASTEON**[®]

clodronate disodium

clodronate disodium capsules, 400 mg

Bone Metabolism Regulator

Sunovion Pharmaceuticals Canada Inc.
6790 Century Ave.
Mississauga, Ontario
Canada
L5N 2V8

Date of Preparation:
September 12, 2017

Licensed by ABIOTEN PHARMA S.p.A Italy

Control # : 194371

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CLASTEON®
clodronate disodium

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule / 400mg	gelatin <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

CLASTEON (clodronate disodium) 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, 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.

CONTRAINDICATIONS

- Renal functional impairment (serum creatinine exceeding 440 µmol/L (5.0 mg/dL).
- Patients who are hypersensitive to clodronate disodium or other bisphosphonates, or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Severe inflammation of the gastrointestinal tract.
- Pregnancy and lactation.

WARNINGS AND PRECAUTIONS

General

CLASTEON (clodronate disodium) should not be given together with other bisphosphonates since the combined effects of these agents are unknown.

Endocrine, Metabolism and Fluid Balance

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: 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 the 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.

Gastrointestinal

Oral bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations, oesophageal perforation and gastroduodenal ulcerations. Thus caution should be used in patients who have a history of oesophageal disorders which delay oesophageal transit and gastric emptying, e.g. stricture or achalasia, those who are unable to stay in the upright position for at least 30 minutes after taking the capsule, if the medicinal product is given to patients with active or recent oesophageal or upper gastrointestinal problems. Prescribers should emphasize to patients the importance of paying attention to the dosing instructions and be alert to any signs and symptoms of possible oesophageal reaction. The patients should be instructed to seek timely medical attention if they develop symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain or new/worsened heartburn.

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.

Skeletal/Muscle

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

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

- Cumulative dose of bone resorption therapy
- Co-morbid conditions (e.g. anaemia, coagulopathies) and smoking
- Periodontal disease, poorly fitting dentures, history of dental disease.

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

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

Low-energy fractures: 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 or short oblique in orientation without evidence of comminution. Atypical femur 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 thigh 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.

Renal

Administration of clodronate disodium may aggravate renal function in some patients. The effect of the drug on the renal function of patients with serum creatinine in excess of 220 $\mu\text{mol/L}$ (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 (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Respiratory

CLASTEON should be given with caution in patients with acetylsalicylic-acid-sensitive asthma. Impairment of respiratory function in these patients treated with CLASTEON has been reported.

CLASTEON can cause hypersensitivity reactions manifesting as dyspnea and other respiratory disorders.

Special Populations

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

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

Pediatrics: The safety and efficacy of CLASTEON 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, anorexia and diarrhea are the most frequent adverse events reported during clodronate disodium therapy. A reduction in dosage or a temporary interruption of therapy may assist in the management of patients where these symptoms are relevant.

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 CLASTEON (clodronate disodium) 400 mg capsules.

ADVERSE EVENT	(N=390) %(N)
Digestive System	
Nausea	3.1(12)
Diarrhea	1.8(7)
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: Adverse events affecting the cardiovascular system were all assessed as unrelated to clodronate disodium therapy since alternative causalities were evident (e.g. heart failure prior to clodronate disodium therapy).

Endocrine and Metabolism: 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.

Immune: 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.

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

Musculoskeletal: Adverse events reported as spontaneous fractures were all assessed as unrelated to clodronate disodium therapy since alternative causalities were evident (e.g. deficient immune state in patients suffering from advanced malignant diseases).

Respiratory: Adverse events affecting the respiratory system were all assessed as unrelated to clodronate disodium therapy since alternative causalities were evident (e.g. pneumonia).

Abnormal Hematologic and Clinical Chemistry Findings

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.

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.

Post-Market Adverse Drug Reactions

Eye disorders: Uveitis has been reported with CLASTEON during post-marketing experience (see **WARNINGS AND PRECAUTIONS**).

Gastrointestinal disorders: Oral bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations, oesophageal perforation and gastroduodenal ulcerations.

Infections and infestations: Conjunctivitis has been reported with CLASTEON during post-marketing experience (see **WARNINGS AND PRECAUTIONS**).

Injury, poisoning and procedural complications: During post-marketing experience the following reactions have been reported rarely: atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

Immune system disorders: Hypersensitivity reactions manifesting as dyspnea and other respiratory disorders have also been reported.

Musculoskeletal and connective tissue disorders: Cases of osteonecrosis (primarily involving the jaws) have been reported in patients treated with bisphosphonates such as zoledronate and pamidronate. The majority of the reported cases are in cancer patients attendant to a dental procedure. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anemia, coagulopathies, infection, pre-existing oral disease).

Severe bone, joint and/or muscle pain has been reported in patients taking CLASTEON. The onset of symptoms varies from days to several months after therapy starting with CLASTEON.

Although causality cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged (see **WARNINGS AND PRECAUTIONS**, **Skeletal/Muscle**).

Very rarely, osteonecrosis of the external auditory canal has been reported (bisphosphonate class adverse reaction).

Renal and urinary disorders: Impairment of renal function (increases of serum creatinine and proteinuria) and severe renal damage especially after rapid intravenous infusion of high doses of clodronate disodium have been reported. Single cases of renal impairment, rarely with fatal outcome, have been reported in particular with concomitant use of NSAIDs, most often diclofenac.

Respiratory, thoracic and mediastinal disorders: Impairment of respiratory function in patients with acetylsalicylic acid-sensitive asthma has been reported with CLASTEON use (see **WARNINGS AND PRECAUTIONS, Respiratory**).

DRUG INTERACTIONS

Drug-Drug Interactions

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 clodronate disodium.

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

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

It has been reported that the concomitant use of estramustine phosphate with clodronate disodium increases the serum concentration of estramustine phosphate by 80% at the maximum.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Since clodronate disodium binds to bone, CLASTEON (clodronate disodium) may interfere with bone scintigraphy examinations.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Recommended dosage: The recommended daily dose 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).

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

CLASTEON (clodronate disodium) 400 mg blue and white gelatin capsules should be administered whole with copious fluids, but not with milk. The patient should not lie down for at least 30 minutes after CLASTEON intake and until after their first food of the day. The patient should not eat one hour before or after CLASTEON intake.

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.

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 with a higher oral dosage (up to 3200 mg/day).

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.

OVERDOSAGE

There is a lack of documented experience on acute overdosing with clodronate disodium. One case of total kidney failure, liver damage and unconsciousness has been reported after accidental ingestion of 20,000 mg (50 x 400 mg) of clodronate. 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 **WARNINGS**

AND RECAUTIONS, Monitoring and Laboratory Tests). Oral or parenteral calcium supplementation may be required to restore plasma calcium levels.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

CLASTEON (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.

Pharmacodynamics

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.

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 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 administration is low (1 - 3%).

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

CLASTEON (clodronate disodium) blue and white gelatin capsules should be stored at room temperature (15-30°C). Protect from high humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CLASTEON (clodronate disodium) blue and white gelatin capsules are supplied as 400 mg of clodronate disodium per capsule. CLASTEON capsules are available in blister packs of 120 capsules per box. Boxes of 120 capsules contain 12 blister strips (10 capsules/blister strip).

Quantitative composition of the capsules:

CAPSULES
Maize starch
Sodium starch glycolate
Talc
Magnesium stearate
Gelatin
Titanium oxide
Indigotin

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.

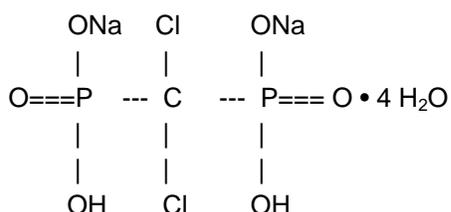
Drug Substance

Proper name: Clodronate Disodium

Chemical name: Anhydrous, clodronate disodium (as tetrahydrate)

Molecular formula and molecular mass: $\text{CH}_2\text{Cl}_2\text{Na}_2\text{O}_6\text{P}_2 \cdot 4 \text{H}_2\text{O}$; 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
PKAIII: (25°C, 0.02 mol/L in water)	5.84
PKa IV: (25°C, 0.02 mol/L in water)	8.68
Melting Point:	Sintering observed just above 50°C. No melting is noted up to 250°C.

CLINICAL TRIALS

To date, results from six clinical trials, including 87 patients who received oral clodronate disodium at doses of 800 to 3200 mg/day for 5 days to 4 months, have shown that oral clodronate disodium can normalize plasma calcium in patients with hypercalcemia due to malignancy. In these patients, clodronate disodium normalized serum calcium, usually 5 to 10 days after the onset of therapy. In responding patients, long-term treatment resulted in sustained normocalcemia.

The data supporting the clinical efficacy and safety of oral clodronate disodium for the indication of osteolysis is compiled from seven randomized, controlled clinical trials with 642 patients receiving oral clodronate disodium at doses of 400 to 4000 mg/day for 4 weeks to 4 years. These studies report on the use of clodronate disodium in patients with osteolysis resulting from bone metastases of malignant tumors.

Efficacy in these studies was demonstrated by improvement in bone related parameters including the following:

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

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.

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.

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 (LD₅₀) 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.

Species	Route	Doses mg/kg/day	Duration days (wks)	Observation
	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 F₂ 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 <u>males</u> . Positive trend towards C-cell carcinoma in thyroid glands and theca-granulosa cell tumour in ovary in <u>females</u> . 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 <u>males</u> and <u>females</u> 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 mutagenic in the test system.

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PART III: CONSUMER INFORMATION**Pr CLASTEON®
clodronate disodium**

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

ABOUT THIS MEDICATION**What the medication is used for:**

- As an additional therapy in the management of bone destruction resulting from cancerous tumours.
- Management of abnormally high blood calcium levels caused by cancer.

What it does:

CLASTEON belongs to a class of compounds known as bisphosphonates which act to reduce the rate of removal and replacement of bone tissue. In certain cancers, there is a greater breakdown of bone than there is new production which is called osteolysis. This can be accompanied by an increased release of calcium into the blood which is called hypercalcemia. CLASTEON attaches specifically to bone and effectively prevents osteolysis. In cases where there is bone breakdown and an increased release of calcium into the blood, CLASTEON effectively reduces high calcium blood levels hence preventing or delaying some of the consequences of hypercalcemia. Although effective in the treatment of osteolysis and hypercalcemia of malignancy, the use of CLASTEON will not provide a cure for cancer.

When it should not be used:**Before taking your medicine:**

- 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 clodronate and/or bisphosphonates or the nonmedicinal ingredients (see what the important nonmedicinal ingredients are) before?

If the answer is **YES** to any of these questions, do not take this medicine until you have talked to your doctor about it.

What the medicinal ingredient is:

clodronate disodium

What the important nonmedicinal ingredients are:

Gelatin, indigotin, magnesium stearate, maize starch, sodium starch glycolate, talc, titanium oxide

What dosage forms it comes in:

The blue and white gelatin form is supplied in 400 mg capsules. Packs of 120 capsules contain 12 full aluminum blister strips of 10 capsules each.

WARNINGS AND PRECAUTIONS**BEFORE you use CLASTEON, talk to your doctor or pharmacist if you:**

- have sores in the mouth. This can lead to osteonecrosis of the jaw.

Your doctor may check if you:

- smoke
- have or have had 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.

Your doctor may tell you to stop taking CLASTEON until all sores in your mouth are healed.

Drugs like CLASTEON may cause problems in your esophagus (i.e., the tube connecting the mouth and the stomach), stomach and intestines, including ulcers. Before you use CLASTEON, talk to your doctor or pharmacist if you have had problems or disease in your esophagus (i.e., the tube connecting the mouth and the stomach), stomach or intestines.

Drugs like CLASTEON can cause eye disorders and infections.

CLASTEON can cause breathing difficulties in patients with asthma who are allergic to acetylsalicylic acid (ASA) that may be severe.

Oral hygiene is very important for patients living with cancer. Some patients have experienced problems with their jaw bones while being treated with drugs like CLASTEON. Please talk to your doctor before undergoing invasive dental procedures such as tooth extractions or when you experience pain in your jaw or poor wound healing in your mouth.

CLASTEON can cause a broken leg or a thigh bone.

When you take CLASTEON, your kidneys may not work as well or they may stop working. This is called kidney failure.

INTERACTIONS WITH THIS MEDICATION

Before starting treatment with CLASTEON, talk to your doctor about any other medications that you are using or intending to use. It is especially important that your doctor knows that you are being treated with:

- another bisphosphonate (such as alendronate, risedronate, etidronate, pamidronate or zoledronic acid)
- phosphate
- calcitonin
- calcium tablets
- vitamin supplements
- mithramycin
- thiazides
- aminoglycosides

- corticosteroids
- NSAIDS (non-steroidal anti-inflammatory drugs)
- antacids
- any drug containing iron, magnesium or aluminum
- estramustine phosphate

PROPER USE OF THIS MEDICATION

Things to remember:

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.

Usual adult dose:

Your doctor will tell you how much CLASTEON 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.

The success of the treatment with CLASTEON depends on how CAREFULLY and consistently you follow the doctor’s instructions about taking CLASTEON.

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 CLASTEON you must take. NEVER MAKE 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.

Pay close attention to the amount of drug you are taking. Make sure it is the amount your doctor has prescribed for you.

These instructions should be followed exactly, because the success of your treatment depends very much on how carefully you follow your doctor’s instructions.

Your dose of CLASTEON 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). You should not lie down for at least 30 minutes after taking the medication. 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.

Please DO NOT take CLASTEON capsules with milk. If CLASTEON 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 CLASTEON with antacid indigestion tablets or mineral supplements as these may also make the medicine less effective.

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, CLASTEON 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.

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

CLASTEON can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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	Nausea	X		
	Diarrhea	X		
	Loss of Appetite	X		
Uncommon	Allergic reactions (i.e skin rashes)		X	
	Mouth pain		X	
Very Rare	Abnormal thigh bone fractures		X	
Very Rare	Ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.		X	

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
Unknown	Difficulty breathing with wheezing or coughing in asthma patients who are allergic to acetylsalicylic acid		X	
Unknown	Jaw problems: mouth or gums heal poorly after dental work such as pulling a tooth Ongoing infections Pain in the mouth		X	
Unknown	Eye disorders and infections: redness, irritation, swelling		X	
Unknown	Severe bone, joint, and/or muscle pain (the onset of symptoms varied from days to several months after starting CLASTEON)		X	
Unknown	Severe kidney damage (especially after rapid intravenous infusion of high doses of clodronate)		X	

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
Unknown	Problems in your esophagus (i.e., the tube connecting the mouth and the stomach), stomach and intestines		X	

Please consult your doctor prior to dental procedures (except dental cleaning) such as tooth extractions and dental surgery. Movable dentures should fit properly and be removed at night.

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

HOW TO STORE IT

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

Keep out of reach of children.

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: cadmp@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 at: www.sunovion.ca

or by contacting the sponsor, Sunovion Pharmaceuticals Canada Inc. at: 1-866-260-6291

This leaflet was prepared by Sunovion Pharmaceuticals Canada Inc., 6790 Century Ave., Mississauga, ON, Canada L5N 2V8

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Last revised: September 12, 2017