DRUG NAME: Clodronate

SYNONYM(S): Clodronate disodium, clodronic acid, Cl_2MDP, dichloromethylene bisphosphonate, disodium clodronate, sodium clodronate

COMMON TRADE NAME(S): CLASTEON®, BONEFOS®; OSTAC®

CLASSIFICATION: Bone metabolism regulator

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Clodronate is a first-generation bisphosphonate, which inhibits bone resorption.[1] Bisphosphonates are analogues of endogenous pyrophosphate and characterized by a P-C-P bond, which is resistant to enzymatic hydrolysis.[2] The mechanism of action of bisphosphonates has not been fully elucidated. Available data suggest that they bind strongly to hydroxyapatite crystals in the bone matrix, preferentially at the sites of increased bone turnover and inhibit the formation and dissolution of the crystals. Other actions may include direct inhibition of mature osteoclast function, promotion of osteoclast apoptosis, and interference with osteoblast-mediated osteoclast activation.[3] Clodronate does not interfere with bone mineralization.[4] On a molar basis, clodronate is 10 times less potent than pamidronate.[2] In malignancy-related hypercalcemia, clodronate decreases serum calcium by inhibiting tumour-induced bone resorption and reducing calcium flow from the resorbing bone into the blood. Clodronate also reduces morbidity of osteolytic bone metastases by inhibiting tumour-induced bone resorption.[3,5]

PHARMACOKINETICS:

Interpatient variability	large interpatient and intrapatient variability in oral absorption[6]	
Oral Absorption	1-3% of dose absorbed, mostly in the small intestine; unabsorbed drug is excreted unchanged in the feces. Food reduces bioavailability, with better bioavailability when given 0.5-1 h before breakfast than 2 h after breakfast.[6]	
	time to peak plasma concentration[6]	0.5-1 h
Distribution	20% of absorbed oral dose is bound to bone.[5] 40% of IV dose is bound to bone and eliminated slowly.	
	cross blood brain barrier?	no information found
	volume of distribution	20 L
	plasma protein binding	2-36%
Metabolism	not metabolized	
Excretion	mainly renal excretion	
	feces	5% of IV dose; 50 % of oral dose[4]
	urine	60-80% of IV dose within 48 h[4,7]
	terminal half life	13 h
	clearance	110 mL/min

Adapted from reference[8] unless specified otherwise.

USES:

Primary uses:

*Malignancy-related hypercalcemia

*Osteolytic bone metastases

Other uses:

*Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Contraindications[5,7]:

- history of hypersensitivity reaction to clodronate or other bisphosphonates
- severe renal dysfunction (serum creatinine > 440 μmol/L)
- patients with severe inflammation of the GI tract.

Caution:

- For acute malignancy-related hypercalcemia, patients must be adequately ***hydrated*** with intravenous ***normal saline*** before and during clodronate treatment to expand intracellular volume and to increase renal calcium clearance.[7,9] Optimum saline infusion rate is determined by the severity of hypercalcemia, the degree of dehydration, and the ability of the patient to tolerate fluid. Infusion rates of 200-300 mL/h have been commonly used; however, these infusion rates may require adjustment if signs and symptoms of fluid overload occur.[9]

Carcinogenicity: Not carcinogenic in animal studies at doses 45-400 mg/kg/day.[5]

Mutagenicity: Not mutagenic in Ames test or in mammalian *in vitro* mutation test. Not clastogenic in mammalian *in vitro* or *in vivo* chromosome tests.[7]

Fertility: No information found.

Pregnancy: Animal studies showed decreased maternal weight gains, decreased fetal weights and delayed fetal ossification. The safety and efficacy in humans have not been established.[7] Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding is not recommended due to the potential secretion into breast milk.[7]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
allergy/immunology	hypersensitivity (rare)[5]
dermatology/skin	*extravasation hazard:* none[10]
	rash (rare)[11]
endocrine	increased parathyroid hormone level (0.6%)
gastrointestinal	*emetogenic potential:* nonemetogenic

ORGAN SITE	SIDE EFFECT
	gastrointestinal disturbances with oral route, including nausea, vomiting, gastric pain, diarrhea (2-10%)[3,7]
metabolic/laboratory	hypocalcemia (3%)[12]
musculoskeletal	osteonecrosis of the jaw[13,14]
renal/genitourinary	acute renal failure (rare)[4]
	transient proteinuria (rare)[5,7]
	transient increase of serum creatinine (0.6%)[12]

Adapted from reference[8] unless specified otherwise.

Osteonecrosis of the jaw (ONJ) is a rare, but serious event that has been associated with antiresorptive agents such as bisphosphonate therapy. Osteonecrosis of other anatomical sites (e.g., femur, hip, auditory canal, metatarsal bones, etc.) have also been rarely reported.[15] ONJ is more commonly observed with increasing bisphosphonate potency, dose intensity, and duration of treatment, particularly when treatment exceeds four years.[16-18] The risk of ONJ is higher with intravenous than with oral bisphosphonate treatment.[19,20] Multiple risk factors may play a role, including invasive dental procedures and pre-existing dental disease, concomitant therapy with angiogenesis inhibitors, corticosteroids, and radiation to the head and neck, as well as certain comorbid medical conditions (e.g., anemia[19,21], cancer, coagulopathies, and diabetes).[17-22] For further details and management of ONJ, refer to *Bisphosphonates and Osteonecrosis of the Jaw in* ***Oral & Dental Care: Osteonecrosis of the Jaw.***

Bronchoconstriction was described in one case report. A patient with a history of acetylsalicylic acid-sensitive asthma developed dyspnea and wheezing 10 minutes after starting clodronate 200 mg IV infusion. The infusion was stopped and the patient recovered after inhalation of salbutamol. When rechallenged with oral clodronate 400 mg, her forced expiratory values decreased significantly from baseline. The mechanism of bronchoconstriction is unclear.[23]

Gastrointestinal disturbances such as nausea, vomiting, gastric pain, and diarrhea, are generally associated with higher oral doses and may be minimized by reducing or dividing the total daily dose, or temporarily interrupting treatment.[4,5]

Hypocalcemia: Symptomatic hypocalcemia is rare.[12] Symptoms include abdominal cramps, confusion, muscle spasms, lethargy and irritability.[24] Risk factors include concurrent use of aminoglycosides[25] or other calcium-lowering agents such as corticosteroids, phosphate, calcitonin, mithramycin and loop-diuretics.[7] Patients with a history of small bowel resection or Crohn's disease may also be more prone to hypocalcemia with oral clodronate.[24] Symptomatic hypocalcemia can be treated with oral or IV calcium supplement.[5,24]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
antacids; calcium, iron, magnesium or aluminum-containing preparations[7]	decreased therapeutic effect of oral clodronate	decreased absorption of oral clodronate	avoid concurrent administration, take at least 2 hours apart
aminoglycosides (eg, amikacin, gentamycin, tobramycin)[25,26]	increased hypocalcemic effect of clodronate	additive	use with caution during concurrent therapy and in patients with prior therapy of clodronate or aminoglycosides
vitamin D-containing preparations[27]	may decrease hypocalcemic effect of clodronate	antagonistic	avoid concurrent therapy

AGENT	EFFECT	MECHANISM	MANAGEMENT
calcium-lowering agents (eg, corticosteroids, phosphate, calcitonin, mithramycin, loop-diuretics)[5,7]	increased hypocalcemic effect of clodronate	additive	use with caution during concurrent therapy
estramustine[28]	increased serum concentration of estramustine	possibly by increasing oral bioavailability of estramustine	avoid concurrent therapy outside clinical trials

SUPPLY AND STORAGE:

Oral: Sunovion supplies clodronate as 400 mg capsules. Store at room temperature.[29]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:

1600 mg (range 800-3200 mg) ***PO in single or two divided doses daily***[3,7,30]

Maximal recommended daily dose is 3200 mg.[5,7] Round dose to the nearest 400 mg.

Administer on empty stomach at least 1 hour before or 1-2 hours after food.[5,7,31] For patients who are awake in the middle of the night, clodronate may be taken at that time as long as the drug is taken 1 hour before or 1-2 hours after eating. Clodronate may also be taken 30 minutes before eating if necessary as the bioavailability is comparable to that taken 1 hour before eating.[6]

For patients with swallowing problems, capsules may be opened and mixed with a small amount of water for administration. However, capsule content is acidic and may cause burning in the esophagus; bioavailability of this administration route has not been determined.[31,32]

Dosage in renal failure:

Reduce dose by 50% with CrCl 10-30 mL/min.[4] Clodronate is contraindicated in patients with CrCl < 10 mL/min or serum creatinine > 440 μmol/L.[4,7]

Dosage in hepatic failure:

no adjustment required

Dosage in dialysis:

no information found

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