DRUG NAME: Clodronate

SYNONYM(S): Clodronate disodium, clodronic acid, Cl\(_2\)MDP, dichloromethylene bisphosphonate, disodium clodronate, sodium clodronate

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

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:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interpatient variability</strong></td>
<td>large interpatient and intrapatient variability in oral absorption(^6)</td>
</tr>
<tr>
<td><strong>Oral Absorption</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>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%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>not metabolized</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>mainly renal excretion</td>
</tr>
<tr>
<td>feces</td>
<td>5% of IV dose; 50 % of oral dose(^4)</td>
</tr>
<tr>
<td>urine</td>
<td>60-80% of IV dose within 48 h(^5,7)</td>
</tr>
<tr>
<td>terminal half life</td>
<td>13 h</td>
</tr>
<tr>
<td>clearance</td>
<td>110 mL/min</td>
</tr>
<tr>
<td>Gender</td>
<td>no information found</td>
</tr>
<tr>
<td>Elderly</td>
<td>no information found</td>
</tr>
<tr>
<td>Children</td>
<td>no information found</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>no information found</td>
</tr>
</tbody>
</table>

Adapted from reference\(^8\) unless specified otherwise.
USES:

Primary uses:
- Malignancy-related hypercalcemia\(^9\)-\(^12\)
- Osteolytic bone metastases\(^13\)-\(^16\)
- Health Canada Therapeutic Products Programme approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Contraindicated in patients who have a history of hypersensitivity reaction to clodronate or other bisphosphonates and in patients with severe renal dysfunction (serum creatinine > 440 \(\mu\)mol/L). Oral clodronate is also contraindicated in patients with severe inflammation of the GI tract.\(^5\),\(^7\)

Hydration: For acute malignancy-related hypercalcemia, patients must be adequately hydrated with intravenous NS before and during clodronate treatment to expand intracellular volume and to increase renal calcium clearance.\(^7\),\(^17\) The optimum NS infusion rate is determined by the severity of hypercalcemia, the degree of dehydration and the ability of the patient to tolerate fluid. Infusion rate of 200-300 mL/h has been commonly used. However, these infusion rates may require adjustment if signs and symptoms of fluid overload occur.\(^17\)

Carcinogenicity: Not carcinogenic in animal studies at doses 45-400 mg/kg/day.\(^5\)

Mutagenicity: Not mutagenic in Ames test or in mammalian \textit{in vitro} mutation test. Not clastogenic in mammalian \textit{in vitro} or \textit{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.

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>allergy/immunology</td>
<td>hypersensitivity (rare)(^5)</td>
</tr>
<tr>
<td>dermatology/skin</td>
<td>extravasation hazard: none(^18)</td>
</tr>
<tr>
<td></td>
<td>rash (rare)(^19)</td>
</tr>
<tr>
<td>endocrine</td>
<td>increased parathyroid hormone level (0.6%)</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>emetogenic potential: nonemetogenic</td>
</tr>
<tr>
<td></td>
<td>gastrointestinal disturbances with oral route, including nausea, vomiting, gastric pain, diarrhea (2-10%)(^17)</td>
</tr>
<tr>
<td>metabolic/laboratory</td>
<td>hypocalcemia (3%)(^20)</td>
</tr>
</tbody>
</table>
ORGAN SITE | SIDE EFFECT
--- | ---
musculoskeletal | osteonecrosis of the jaw\(^{21,22}\)
renal/genitourinary | acute renal failure (rare)\(^4\)
 | transient proteinuria (rare)\(^5,7\)
 | transient increase of serum creatinine (0.6%)\(^{20}\)

Adapted from reference\(^8\) unless specified otherwise.

**Osteonecrosis of the jaw (ONJ)** has been reported\(^{21,22}\). 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\(^{20}\). Symptoms include abdominal cramps, confusion, muscle spasms, lethargy and irritability\(^24\). Risk factors include concurrent use of aminoglycosides\(^25,26\) 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:**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>antacids; calcium, iron, magnesium or aluminum-containing preparations(^7)</td>
<td>decreased therapeutic effect of oral clodronate</td>
<td>decreased absorption of oral clodronate</td>
<td>avoid concurrent administration, take at least 2 hours apart</td>
</tr>
<tr>
<td>aminoglycosides (eg, amikacin, gentamycin, tobramycin)(^{25,26})</td>
<td>increased hypocalcemic effect of clodronate</td>
<td>additive</td>
<td>use with caution during concurrent therapy and in patients with prior therapy of clodronate or aminoglycosides</td>
</tr>
<tr>
<td>vitamin D-containing preparations(^27)</td>
<td>may decrease hypocalcemic effect of clodronate</td>
<td>antagonistic</td>
<td>avoid concurrent therapy</td>
</tr>
<tr>
<td>calcium-lowering agents (eg, corticosteroids, phosphate, calcitonin, mithramycin, loop-diuretics)(^5,7)</td>
<td>increased hypocalcemic effect of clodronate</td>
<td>additive</td>
<td>use with caution during concurrent therapy</td>
</tr>
<tr>
<td>estramustine(^{28})</td>
<td>increased serum concentration of estramustine</td>
<td>possibly by increasing oral bioavailability of estramustine</td>
<td>avoid concurrent therapy outside clinical trials</td>
</tr>
</tbody>
</table>
SUPPLY AND STORAGE:

**Oral:**
BONEFOS®: 400 mg; inactive ingredients include lactose. Store at room temperature.7

OSTAC®: 400 mg; inactive ingredients do not include lactose. Store at room temperature. Protect from high humidity.5

CLASTEON®: 400 mg; inactive ingredients do not include lactose. Store at room temperature and protect from high humidity.29

**Injection:**
BONEFOS®: 5 mL ampoule; each mL contains 60 mg of anhydrous disodium clodronate. Store at room temperature.7

OSTAC®: 10 mL ampoule; each mL contains 30 mg of anhydrous disodium clodronate. Store at room temperature and protect from high humidity.5

CLASTEON®: 10 mL ampoule; each mL contains 30 mg of anhydrous clodronate disodium. Store at room temperature and protect from high humidity.29

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

**Compatibility:** Clodronate should not be mixed with calcium-containing IV solutions such as Ringer’s solution.7

PARENTERAL ADMINISTRATION:

<table>
<thead>
<tr>
<th>Route</th>
<th>BCCA administration guideline noted in <strong>bold, italics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>investigational, 1500 mg in 1L NS by SC infusion over 12 or 24 h¹⁸,³⁰</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>investigational, has been used in clinical trials at lower dosages³¹-³³</td>
</tr>
<tr>
<td>Direct intravenous</td>
<td>not recommended since severe local reactions and thrombophlebitis may occur due to high local concentration; also rapid bolus injection may cause acute renal failure.⁷</td>
</tr>
<tr>
<td><strong>Intermittent infusion</strong></td>
<td>≤ 300 mg in 500 mL NS or D5W over 2 h⁶; &gt; 300 mg in 500 mL NS or D5W over 3-4 h⁶,³⁴</td>
</tr>
<tr>
<td></td>
<td>• can also be given over 3-9 h⁶,³⁴,³⁵</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>no information found</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>no information found</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>no information found</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>no information found</td>
</tr>
</tbody>
</table>
DOSAGE GUIDELINES:
Refer to protocol by which patient is being treated.

**Adults:**

**Oral:**

Osteolytic bone metastases

**Cycle Length:**

1600 mg (range 800-3200 mg) **PO in single or two divided doses daily**\textsuperscript{3,7,13}

Maximal recommended daily dose is 3200 mg.\textsuperscript{5,7} Round dose to the nearest 400 mg.

Administer on empty stomach at least 1 hour before or 1-2 hours after food.\textsuperscript{5,7,36}

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.\textsuperscript{8}

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.\textsuperscript{36,37}

Maintenance for malignancy-related hypercalcemia

same as above

**Intravenous:**

Osteolytic bone metastases

4 weeks: 1500 mg **IV for one dose**\textsuperscript{38,39}

Malignancy-related hypercalcemia

300 mg IV once daily for 5 consecutive days (range 3-10 days)\textsuperscript{3,5}; **OR**

1500 mg IV for one dose\textsuperscript{5,9}

**Dosage in renal failure:**

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

**Dosage in hepatic failure:**

no adjustment required

**Dosage in dialysis:**

hemodialysis: No adjustment required with single IV dose if given at the beginning of dialysis.\textsuperscript{40,41} No information on oral clodronate.

CAPD: Reduce IV dose by \(\geq 50\%\), as CAPD removes clodronate poorly. Long-term treatment may cause pronounced clodronate deposition in skeleton.\textsuperscript{42} No information on oral clodronate.

REFERENCES: