Indications: Hypercalcemia of malignancy, Paget's disease, prevention/treatment of osteoporosis, prophylactic use to reduce the incidence of skeletal-related events in patients with osteolytic lesions from multiple myeloma, metastatic breast cancer and other solid tumors; †bone pain.

Pharmacology

The bisphosphonates are stable analogs of naturally occurring pyrophosphate compounds that inhibit bone dissolution by interfering with osteoclast function and/or inducing their apoptosis (programmed cell death). Nitrogen-containing bisphosphonates (**ibandronic acid** (not USA), **pamidronate disodium**, **zoledronic acid**) inhibit the mevalonate pathway and impair post-translational protein modification important in cell signaling and non-nitrogen-containing bisphosphonates (**clodronate disodium** (not USA), **etidronate disodium**) form cytotoxic ATP analogs.[1,2] These cellular effects also extend to macrophages, reducing the production of pro-inflammatory cytokines, and may help explain the analgesic effect of bisphosphonates.[3] *In vitro* and in animals, bisphosphonates also have a direct anticancer effect via inhibition of matrix metalloproteinase, altered cell adhesion, anti-angiogenic activity and induction of apoptosis.[4,5] Bisphosphonates have no impact on the effect of parathyroid-related protein (PTHrP) or on renal tubular re-absorption of calcium.

Bisphosphonates are poorly absorbed PO and this is reduced further by food. They are rapidly taken up by the skeleton, particularly at sites of bone resorption and where the mineral is more exposed, and they remain there for weeks–months.[6] Most of the remainder is bound to plasma proteins. Bisphosphonates are not metabolized and are excreted unchanged via the kidneys. The plasma proportion of the drug is eliminated generally within 24h. Thereafter, elimination is much slower as the remainder gradually seeps out of bone.[7] Comparison of the halflives of different bisphosphonates is complicated by this multiphasic elimination (Table 7.1).

Hypercalcemia of malignancy

Bisphosphonates given IV are the treatment of choice for hypercalcemia of malignancy.[8] The initial response is highest with **zoledronic acid** (~90%), with **ibandronic acid** equal to **pamidronate disodium** (~75%). A longer duration of response can be obtained with **zoledronic acid** and **ibandronic acid** compared with **pamidronate disodium**.[9,10] The PI for **pamidronate disodium** recommends higher doses for higher initial calcium levels, but one systematic review suggests that the higher dose should be given irrespective of the initial calcium level to increase the likelihood of a response and prolong its duration.[8]

Prophylactic use in patients with myeloma or bone metastases

Pamidronate disodium and **zoledronic acid** IV or **ibandronic acid** PO/IV given *long-term* decrease the incidence of new skeletal events in patients with bone metastases. Benefit is most evident for patients with breast cancer or myeloma and is less clear for other types of cancers.[11-14] Only studies ≥ 6 months in duration have shown a reduction in vertebral and non-vertebral fractures, hypercalcemia and the need for radiotherapy. Studies ≥ 2 years duration have also shown a reduced need for orthopedic surgery. The incidence and severity of pain is reduced with a number needed to treat (NNT) of 11 at 4 weeks and 7 at 12 weeks. There is no impact on

survival or the occurrence of spinal cord compression. The ability of bisphosphonates to prevent the development of bone metastases is being investigated.[15]

Bisphosphonates as adjuvant analgesics

Bisphosphonates have been used for metastatic bone pain and several regimens have been recommended for use when more conventional methods have been exhausted.[3,16-19] An effect is generally seen within 14 days. The evidence stems mainly from studies with **pamidronate disodium** or **clodronate disodium**, and suggests that benefit is more likely in patients with breast cancer or myeloma, and with an IV bisphosphonate.[19]

Renal toxicity and other rare undesirable effects of bisphosphonates

Bisphosphonates can affect renal function. High-dose (200–1500mg/day for 2–5 days), short-duration (<2h) IV infusions of **clodronate disodium** and **etidronate disodium** can cause oliguria, tubulo-interstitial damage and acute renal failure, possibly via the formation of an insoluble calcium-bisphosphonate complex in the blood.[20,21] **Pamidronate disodium** can also rarely cause collapsing focal segmental glomerulosclerosis, particularly in high doses, e.g. 180mg every 2–4 weeks. The probable mechanism is a direct toxic effect on glomerular capillary podocytes and renal tubules.[22] The more potent third-generation bisphosphonates are given in much smaller doses and reach lower concentrations in the renal tubules. Nevertheless, renal impairment has occurred with **zoledronic acid** (see p.299) and **ibandronic acid**.[23-27] Other risk factors for bisphosphonate-induced renal damage include dehydration, an increased baseline serum creatinine concentration, multiple treatments and concurrent use of other nephrotoxic drugs. The risk of renal toxicity is reduced by ensuring adequate hydration and adhering to the recommended dose and infusion rate. Renal function should be monitored and the dose of bisphosphonate adjusted as appropriate.

Bisphosphonates have recently been implicated as a risk factor for osteonecrosis of the jaw.[28,29] Others include dental procedures, poor dental health, blood clotting disorders, anemia, chemotherapy and corticosteroids. It is recommended that patients should undergo preventive dental treatment before commencing bisphosphonates and avoid invasive dental procedures during treatment. Another rare undesirable effect is ocular inflammation, causing eye pain, redness or abnormal vision.[30,31]

Table 7.1 Bisphosphonates and the initial treatment of hypercalcemia [9,10,32]

	Zoledronic acid	Ibandronic acid	Pamidronate disodium	Clodronate disodium
IV dose	4mg	2–6mg	30–90mg	(a) 1500mg (b) 300–600mg daily for 5 days
Onset of effect	<4 days	<4 days	<3 days	<2 days
Maximum effect	4–7 days	7 days	5–7 days	3–5 days
Duration of effect	4 weeks	2.5 weeks (4mg) 4 weeks (6mg)	2.5 weeks	(a) 2 weeks (b) 3 weeks
Restores normocalcemia	90%	75%	70–75%	40–80%

Cautions

***Serious drug interactions*:** concurrent use with aminoglycoside antibiotics may produce symptomatic hypocalcemia if given with long-term oral **clodronate disodium** therapy;[33] prolonged hypocalcemia and hypomagnesemia may occur with aminoglycosides and **ibandronic acid** or **zoledronic acid**. Risk of renal impairment increased by concurrent use with other nephrotoxic drugs.

Renal impairment; correct hypovolemia before treatment and monitor renal function. Hypocalcemia, hypophosphatemia or hypomagnesemia. Invasive dental procedures (osteonecrosis of the jaw).

Undesirable effects

For full list, see manufacturer's PI.

Very common (>10%): transient pyrexia and influenza-like symptoms (more common with IV nitrogen-containing bisphosphonates), fatigue, headache, anxiety, hypertension, anemia, thrombocytopenia, cough, dyspnea, arthralgia, myalgia, bone pain, asymptomatic hypocalcemia, hypomagnesemia, hypophosphatemia. Oral preparations in particular may cause anorexia, dyspepsia, nausea, vomiting, abdominal pain, diarrhea or constipation.

Common (<10%, >1%): sleep disturbance, psychosis, tachycardia, atrial fibrillation or flutter, syncope, leucopenia, infusion site reactions, deterioration in renal function, increased serum creatinine, hypokalemia.

Rare (<0.1%, >0.01%): ocular inflammation, angioedema, collapsing focal segmental glomerulosclerosis (**pamidronate disodium**), nephrotic syndrome (**pamidronate disodium**), symptomatic hypocalcemia (e.g. tetany).

Very rare (<0.01%): anaphylaxis, bronchospasm, osteonecrosis of the jaw.

Dose and use

For **zoledronic acid**, see p.299.

Hypercalcemia of malignancy

The PI for **pamidronate disodium** recommends a dose dependent on the initial corrected plasma calcium concentration (Box 7.A and Table 7.2). However, it has been suggested that the higher dose should be given irrespective of the initial calcium level to increase the likelihood of a response and prolong its duration:[8]

- patients should be well hydrated, using 0.9% saline if necessary
- maximum recommended dose is 90mg IV/treatment
- dilute the dose in 1L of 0.45% saline, 0.9% saline or 5% glucose; the UK PI advises that the concentration should not exceed *60mg/250ml*
- infuse over at least 2h; the UK PI advises that the infusion rate should not exceed *1mg/min* in patients with normal renal function; patients with mild–moderate renal impairment (creatinine clearance 30–90ml/min) do *not* require dose reduction but the infusion rate should not exceed *20mg/h*
- repeat after 1 week if initial response inadequate
- repeat every 3–4 weeks according to plasma calcium concentration
- measure serum creatinine before each dose. No dose adjustment is required in mild–moderate renal impairment. In palliative care, treatment with bisphosphonates will probably not be initiated in patients with hypercalcemia and

severe renal impairment. If it is considered appropriate, see advice in bisphosphonates and bone metastases below.

If the IV route is inaccessible, bisphosphonates can be administered by CSCI, together with SC hydration:[34,35]

- **pamidronate disodium** 90mg in 1L 0.9% saline over 12–24h
- **clodronate disodium** 1500mg in 50–250ml 0.9% saline or 5% glucose over 2–3h.

Box 7.A Correcting plasma calcium concentrations

Corrected calcium (mg/dl) = measured calcium (mg/dl) + (0.8 x (4 –albumin g/dl))
e.g. measured calcium = 9.8mg/dl; albumin = 3.2mg/dl
corrected calcium = 9.8 + (0.8 x 0.8) = 10.44mg/dl

Table 7.2 IV pamidronate disodium for hypercalcemia[a]

Corrected plasma calcium concentration (mg/dl)	Dose (mg)
12–13.5	60–90
>13.5	90

a. manufacturer's recommendations.

Prophylactic use to reduce the incidence of skeletal-related events in patients with multiple myeloma or breast cancer

Recommendations differ slightly for patients with multiple myeloma as they are at greater risk of renal impairment/renal toxicity:

- patients should be well hydrated, using 0.9% saline if necessary
- recommended dose, dilution and frequency (*multiple myeloma*); 90mg/500ml of 0.45% saline, 0.9% saline or 5% glucose given IVI over 4h every 4 weeks
- recommended dose, dilution and frequency (*breast cancer*); 90mg/250ml of 0.45% saline, 0.9% saline or 5% glucose given IVI over 2h every 3–4 weeks
- serum creatinine should be measured before each dose. Treatment should be withheld if creatinine increases by:
  - 0.5mg/dl in patients with a normal baseline creatinine concentration (i.e. <1.4mg/dl), *or*
  - 1.0mg/dl in patients with a raised baseline creatinine concentration (i.e. >1.4mg/dl)
- treatment may be resumed at the same dose as before when serum creatinine returns to within 10% of the baseline value.

Metastatic bone pain

Several regimens have been recommended for when more conventional methods have been exhausted:

- **pamidronate disodium** 90mg IV (50% of patients respond, usually within 7–14 days); if helpful repeat 60–90mg every 3–4 weeks for as long as benefit is maintained[3]
- **pamidronate disodium** 120mg IV, repeated p.r.n. every 2–4 months[18]

- **pamidronate disodium** 90–120mg IV or **clodronate disodium** 600–1500mg IV, repeated p.r.n. In patients not responding to a first treatment, a second can be tried. If still no response, discontinue[19]
- **clodronate disodium** 1.5g IV initially; plus maintenance therapy 1600mg PO q.d.[16,17]

Supply
Pamidronate disodium (generic)
Injection 30mg/10ml vial =$290 (AWP); 60mg/10ml vial = $560 (AWP); 90mg/10ml vial = $872 (AWP).

Aredia Dry Powder® (Novartis)
Injection (powder for reconstitution) 30mg vial = $280 (AWP); 90mg vial = $840.

Clodronate disodium
Not USA.

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