Therapeutic Reviews

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Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. Additional content is available via www.medicinescomplete.com. The series editors welcome feedback on the articles (hq@palliativedrugs.com).

Bisphosphonates AHFS 92:24

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Indications: Authorized indications vary between products and among countries; consult PI for details. They include tumor-induced hypercalcemia; prevention of skeletal-related events (SRE) and pain in adults with advanced malignancies involving bone; †adjuvant analgesic in moderate–severe bone pain; †treatment of bone loss in patients at high risk of fracture receiving hormone deprivation therapy for early prostate or breast cancer; †prevention of bone metastases in post-menopausal women with early breast cancer; osteoporosis in post-menopausal women and men ± long-term corticosteroid; Paget's disease.

Contra-indications: Hypocalcemia. *PO*: Esophageal abnormality (e.g. stricture or achalasia), inability to sit upright for 60min.

Pharmacology

The bisphosphonates are stable analogues of pyrophosphate, a naturally occurring regulator of bone metabolism. They have a high affinity for calcium ions, and bind rapidly to hydroxyapatite crystals in mineralized bone. Bisphosphonates are subsequently released and taken up by osteoclasts, interfering with their function and/or inducing their apoptosis (programmed cell death). Nitrogen-containing bisphosphonates (e.g. alendronate, ibandronic acid, pamidronate disodium, zoledronic acid) inhibit the mevalonate pathway vital for normal cellular function (e.g. vesicular trafficking, cell signalling, cytoskeleton function) and non-nitrogen-containing bisphosphonates (sodium clodronate, disodium etidronate) form cytotoxic adenosine triphosphate (ATP) analogues.[1,2] Nitrogen-containing bisphosphonates are more potent.

These cellular effects also extend to macrophages, reducing the production of cytokines. This anti-inflammatory effect may contribute to the analgesic effect of bisphosphonates. Bisphosphonates interfere with the cancer-related increase in the number and activity of osteoclasts which cause bone pain by:

- producing an increasingly acidic environment (stimulating acid-sensing receptors on sensory nerves)
- destroying sensory nerves (producing neuropathic pain)
- causing mechanical instability as a result of the loss of bone mineral (stimulating mechanoreceptors on sensory nerves in the periosteum).

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In vitro and in animals, bisphosphonates also have a direct anticancer effect via inhibition of matrix metalloproteinase, altered cell adhesion, anti-angiogenic activity, reduction in release of local growth factors from bone and induction of apoptosis.[3] However, a cancer-promoting effect has been seen in some animal studies.[4] Bisphosphonates have no impact on the effect of parathyroid hormone-related protein (PTHrP) or on renal tubular resorption 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.[5] 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.[6] Comparison of the halflives of different bisphosphonates is complicated by this multiphasic elimination.

Tumor-induced hypercalcemia

Bisphosphonates given IV are the treatment of choice for tumor-induced hypercalcemia (Table 1).[7]

Table 1
Bisphosphonates and the initial treatment of tumor-induced hypercalcemia[8,9]

	Zoledronic acid	Pamidronate disodium	Ibandronic acid
IV dose	4mg	30–90mg	2–6mg
Onset of effect	<4 days	<3 days	<4 days
Maximum effect	4–7 days	5–7 days	7 days
Duration of effect	4 weeks	2.5 weeks	2.5 weeks (4mg) 4 weeks (6mg)
Restores normocalcemia	90%	70–75%	75%

Zoledronic acid 8mg has been given to patients who do not respond to 4mg or to pamidronate disodium, and those who relapse within a few days of treatment. With the higher dose, normocalcemia is achieved in 50% of the non-responders.[8] However, the median duration of response is only 2 weeks. Further, the incidence of renal impairment doubles with 8mg, so its use was abandoned in clinical trials and it is unauthorized.[10]

Prevention of skeletal-related events (SRE) in patients with advanced malignancies involving bone

IV pamidronate disodium, IV zoledronic acid and PO/IV ibandronic acid are given long-term to patients with bone metastases to decrease the incidence of SRE. Onset of benefit is 2–3 months. SRE can include pathological fracture, radiotherapy to bone, spinal cord compression, surgery to bone and pain (see below). However, the SRE used as outcomes in studies vary (e.g. radiological vs. clinical pathological fracture) and can limit direct comparison of study findings.

Various national guidelines recommend with provisos the routine use of bisphosphonates for the treatment and prevention of SRE in patients with:

- symptomatic myeloma, whether or not bone lesions are evident[11]
- breast cancer with bone metastases[12,13]
- hormone-relapsed prostate cancer with bone metastases.[14]

There is no consensus on the use of bisphosphonates in other cancers, although it has been suggested that in any patient with a prognosis of >3 months and multiple bone metastases, it is reasonable to consider their use.[15,16]

Only studies ≥6 months in duration have shown a reduction in fractures, hypercalcemia, and the need for radiotherapy. Studies ≥1 year in duration have also shown a reduced need for orthopedic surgery. There is no impact on the occurrence of spinal cord compression.[17-19]

The optimal dosing schedule is not clearly established. Although zoledronic acid is generally given every 4 weeks, treatment every 12 weeks over 2 years in patients with bone metastases from breast or prostate cancer or myeloma appears to be equally effective.[20] The optimal duration of treatment is unclear, but bisphosphonates are generally continued for as long as they are tolerated or there is a substantial decline in the patient's performance status.

Multiple myeloma

In patients with myeloma, bisphosphonates reduce SRE, including vertebral fracture, and are recommended for all patients with symptomatic myeloma. They may also reduce pain, both through prevention of painful SRE and through a possible direct anti-tumor effect. Meta-analyses are not wholly consistent but zoledronic acid is probably the most effective and may prolong overall survival. Both zoledronic acid and pamidronate disodium are more effective than disodium clodronate.[11,21-23] There is no consensus on duration of treatment, but treatment may be stopped when there is a complete response to therapy or no evidence of active bone disease.[11,21] Denosumab, another osteoclast inhibitor, is no more effective than IV bisphosphonates in myeloma but costs more.[24] Thus, guidelines favour IV bisphosphonates but consider denosumab an alternative, particularly in patients with impaired renal function.

Breast cancer

In patients with breast cancer and bone metastases, bisphosphonates delay time to developing SRE, reduce the risk and rate of developing SRE and improve quality of life. Zoledronic acid 4mg IV given every month for 1 year reduces the risk of an SRE by about 40%.[25] Treatment every 2 weeks provides no greater benefit.[26] After 1 year, a 12-weekly regimen has been shown to maintain benefit, and may be satisfactory from the start of treatment.[20,27]

Zoledronic acid is more effective than PO ibandronic acid; it may also be more effective than pamidronate disodium and IV ibandronic acid.[19,23,28] Conversely, denosumab is more effective than zoledronic acid.[24] However, some have questioned the cost-effectiveness of the modest health gains at substantial additional cost.[29] Guidelines suggest that either IV zoledronic acid or SC denosumab should be started in all patients with breast cancer and bone metastases, whether or not they are symptomatic.[16,30]

Prostate cancer

In early and metastatic prostate cancer controlled by androgen ablation, there is little or no benefit from bisphosphonates in relation to SRE, quality of life, or survival.[31-35]

In patients with metastatic hormone-relapsed prostate cancer, zoledronic acid (but not pamidronate) given for >15 months may reduce the risk and rate of developing SRE.[36,37] Compared with zoledronic acid, denosumab reduces SRE risk and increases the time to first SRE (21 vs. 17 months respectively).[24,38] However, the question of cost-effectiveness remains.[39] Neither zoledronic acid nor denosumab improve survival.

Further, the pivotal trials of both zoledronic acid and denosumab predate approval of newer treatment options for hormone-relapsed prostate cancer, e.g. abiraterone, enzalutamide, all of which reduce SRE. Thus, the place of denosumab and zoledronic acid in conjunction with these treatments is still to be determined.[14,23,40] As a result, bisphosphonates and denosumab are used more frequently in some regions (e.g. USA) than others (e.g. Europe).[39]

Bisphosphonates as analgesics

Bisphosphonates are used in two ways:

Prophylactic use

IV/PO bisphosphonates given over months—years are recommended in myeloma and breast cancer (and, by some, in metastatic hormone-relapsed prostate cancer; see above), to reduce the risk and rate of developing potentially painful SRE. This could lead to a delay in the development and/or worsening of bone pain. However, evidence in support of this is mixed. For example, in a systematic review, *no* analgesic benefit of bisphosphonates was seen in 22 of 28 RCTs, mostly involving patients with breast cancer, prostate cancer or myeloma.[41] Generally, bone pain was not the focus of these studies; few used it as a primary end-point and others did not require it as an inclusion criteria. Further, even when assessed, the use of differing and often non-validated measures of pain and analgesic use make comparisons difficult.

Of the studies showing benefit, most were in patients with breast cancer or myeloma and mild—moderate pain, with moderate relief obtained from an IV bisphosphonate given over several months.[19,22] A direct anti-cancer effect of bisphosphonates, seen particularly in breast cancer and myeloma, may be relevant. Thus, in the prophylactic use setting, the 'analgesic effect' is limited to preventing the development of more painful SRE.

Adjuvant analgesics for moderate—severe bone pain

The role of bisphosphonates as adjuvant analgesics for bone pain is unclear. IV bisphosphonates are given as adjuvant analgesics for moderate—severe bone pain, not responding to usual analgesic and anticancer approaches, with the expectation of a more rapid analgesic effect, potentially from their anti-inflammatory effect

(see Pharmacology).[42] Onset of pain relief is about 2 weeks, and is most likely in patients with moderate pain receiving IV bisphosphonates.[25,43-47] Denosumab is an alternative and has similar, modest benefit.[24,30] However, supporting data are limited/low quality. Thus, for patients with painful bone metastases despite optimized analgesia and systemic anticancer therapy, *PCF* advises:

- if localized, consider palliative radiotherapy;[12,32] reserve the use of a bisphosphonate (see below) for when this is ineffective or inappropriate
- if more widespread, consider:
  - ➢ a radionuclide, e.g. radium-223, in patients with prostate cancer[14,48]
  - ➢ IV zoledronic acid or, if unavailable, IV pamidronate (see Dose and use) in patients with a prognosis of >2 weeks and not already receiving prophylactic bisphosphonates or denosumab.

†Treatment of bone loss in patients at high risk of fracture receiving hormone deprivation therapy for early prostate or breast cancer

Androgen and oestrogen deprivation therapy accelerates bone turnover leading to a reduction in bone mineral density (BMD) and a 40−50% increase in fracture incidence. Thus, specialty guidelines generally suggest that in early stage prostate or breast cancer, men treated with androgen deprivation therapy or women treated with an aromatase inhibitor or ovarian suppression (including premenopausal women rendered prematurely postmenopausal, e.g. by chemotherapy) should have their bone health monitored, e.g. every 1−2 years, for fracture risk.[16,49,50]

An overall fracture risk is determined based on BMD and the presence of additional risk factors, e.g. age >65 years, current or past smoker, personal or family history of fragility fracture, long-term corticosteroid use. Correctable risk factors should be addressed and all advised to consume a calcium enriched diet, to exercise moderately and take vitamin D supplements, with bisphosphonate or denosumab therapy reserved for those at greatest risk.

In early prostate cancer, in patients with a high fracture risk, zoledronic acid every 6−12 months is an accepted treatment.[14,16,51,52] Although denosumab is authorized for this indication, generally it is used when bisphosphonates are poorly tolerated, or in severe renal impairment.[14,24,32]

In early breast cancer, in patients with a high fracture risk, both PO and IV bisphosphonates can be used, e.g.:[13,50,53,54]

- risedronate 35mg PO once a week
- zoledronic acid 4mg IV every 6 months.

Denosumab may be an alternative.[50,55] Note. Certain groups of women may already be receiving zoledronic acid to reduce the risk of bone metastases (see below).

†Prevention of bone metastases in post-menopausal women with early breast cancer

In *post-menopausal* women with early breast cancer *without* bone metastases, bisphosphonates reduce the incidence of bone metastases and lead to a small improvement in survival.[19,56,57] There are insufficient data to show if denosumab increases survival.[55,58] Consequently, some guidelines recommend bisphosphonates (e.g. zoledronic acid 4mg IV every 6 months) as an adjuvant therapy for post-menopausal women with early invasive breast cancer at high risk of recurrence (e.g. node-positive), regardless of their fracture risk.[49]

Cautions

Renal impairment (see Dose and use). Vitamin D deficiency (increased risk of hypocalcemia).[59] Invasive dental procedures (risk of osteonecrosis of the jaw).

Drug interactions

Concurrent use increases the risk of:

- prolonged hypocalcemia and hypomagnesemia with an aminoglycoside[60]
- hypocalcemia and dehydration with loop diuretics
- renal impairment with other nephrotoxic drugs
- renal impairment with thalidomide in multiple myeloma.

For PO bisphosphonates, avoid taking PO products containing calcium, antacids (and other products containing aluminum, magnesium and iron) for 1−2h after each dose.

Undesirable effects

Very common (>10%): transient pyrexia and flu-like symptoms (see below), fatigue, headache, anxiety, hypertension, anemia, thrombocytopenia, cough, arthralgia, myalgia, bone pain, *asymptomatic* hypocalcemia, hypomagnesemia, hypophosphatemia.

Oral products in particular may cause anorexia, dyspepsia, nausea, vomiting, abdominal pain, diarrhea or constipation.

Common (<10%, >1%): sleep disturbance, psychosis, tachycardia, atrial fibrillation or flutter,[61] hypertension, syncope, breathlessness, leucopenia, infusion site reactions, renal impairment (see below), hypokalemia, osteonecrosis of the jaw (see below).

Rare (<0.1%, >0.01%): ocular inflammation (see below), angioedema, acute renal failure, nephrotic syndrome (pamidronate disodium), *symptomatic* hypocalcemia (e.g. tetany), atypical femoral fractures (see below).

Very rare (<0.01%): osteonecrosis of the external auditory canal (see below).

Acute systemic inflammatory reactions after IV bisphosphonates

Bone pain sometimes occurs <12h after IV bisphosphonates. Systemic reactions, more common with IV nitrogen-containing bisphosphonates, manifest as mild fever (occasionally rigors), myalgia, arthralgia, nausea and vomiting in 25−50% of patients, generally <2 days after IV infusion and lasting 1−2 days. Can be treated with acetaminophen (paracetamol) or NSAIDs. Generally lessen with repeat doses or with prophylactic acetaminophen or NSAID.[62]

Renal toxicity

Bisphosphonates can affect renal function. Rarely, pamidronate disodium causes acute renal failure, particularly at high doses, e.g. 180mg every 2−4 weeks, probably as a direct toxic effect.

The more potent third-generation bisphosphonates are given in much smaller doses and reach lower concentrations in the renal tubules. Renal impairment has occurred with zoledronic acid but is uncommon with ibandronic acid.[10,63-65] In direct comparisons, the incidence of decreased renal function with zoledronic acid 4mg (about 10%) is similar to pamidronate disodium 90mg over 2h.[8]

With zoledronic acid 4mg, increases in plasma creatinine lead to treatment delay or discontinuation in about 1% and 3% of patients respectively.[66] Increases in creatinine levels >3 times the upper limit of normal were seen in 0.4% of patients.[67] There have been reports of life-threatening renal failure caused by toxic acute tubular necrosis in patients treated with zoledronic acid, e.g. 72 cases among >430,000 patients (<0.02%).[18,68,69] Other risk factors were often present, including dehydration, pre-existing renal impairment, and concurrent use of other nephrotoxic drugs.

Renal impairment often manifests <2 months after starting treatment. Mild impairment tends to recover a few days−several months after discontinuing zoledronic acid but, in those with renal failure, the damage is generally permanent.[19]

The risk of renal toxicity is reduced by adhering to the recommended dose and infusion rate, ensuring adequate hydration, monitoring renal function and adjusting the dose of bisphosphonate as appropriate or discontinuing treatment if there is deterioration, and avoiding the concurrent use of other nephrotoxic drugs.

Osteonecrosis of the jaw and external auditory canal

All bisphosphonates PO and IV (and denosumab) have been implicated as a risk factor for osteonecrosis of the jaw (ONJ).[70,71] The true incidence of ONJ is difficult to identify, but some studies put it as high as 10% of patients receiving long-term zoledronic acid and 4% of those receiving pamidronate disodium.[72] Most reports involve the long-term IV use of zoledronic acid or pamidronate disodium for metastatic bone disease.[72] Although osteonecrosis has been reported after 4 months, generally, patients have been receiving bisphosphonates for years (median duration 2−3 years). Additional risk factors for ONJ include dental procedures (reported in about 60% of patients), poor dental health, blood clotting disorders, anemia, and possibly chemotherapy, angiogenesis inhibitors and corticosteroids.

The jaw bones may be particularly susceptible to osteonecrosis because of the combination of repeated low-level local trauma (e.g. from chewing, dentures) and ease of infection from microbes. Trauma and infection increase the demand for bone repair which the bisphosphonate-inhibited bone cannot meet, resulting in localized bone necrosis; the anti-angiogenic effect of bisphosphonates may also contribute.[72]

ONJ can present as an asymptomatic bony exposure in one or more sites in the mandible or maxilla, or with orofacial pain, trismus, offensive discharge from a cutaneous fistula, chronic sinusitis because of an oro-antral fistula and numbness in the mandible or maxilla.[62] If probed, the necrotic bone is usually non-tender and may not bleed. There may be osteomyelitis with oral-cavity flora or *Actinomyces* species. ONJ may show as mottled bone on a plain radiograph and be confused with bone metastases on a bone scan. Pathological fracture can occur.

Management is based on clinical experience. Long-term outcomes are generally poor with relatively few patients experiencing improvement or resolution. Thus, prevention is an important part of the recommended approach (see Box A).

Box A. Prevention and management of ONJ[62,72,73]

For PO bisphosphonates, advise patients to maintain good oral hygiene, attend routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist.
For IV bisphosphonates:

- explain the risk of ONJ and give the patient a reminder card (supplied by manufacturers)
- undertake preventive dental treatment before commencing long-term bisphosphonates, e.g. treat infection, teeth extractions
- delay bisphosphonate treatment (unless a medical emergency) if there are unhealed oral lesions
- encourage good dental hygiene including regular dental cleaning by a dental hygienist
- avoid invasive dental procedures during treatment and advise patients to inform their dentist of bisphosphonate treatment
- minimize trauma, e.g. patients with dentures should wear soft liners
- advise patients to inform their doctor or dentist immediately if oral symptoms develop, e.g. loose teeth, pain, swelling, discharge or non-healing sores.

If urgent treatment precludes dental examination before starting a bisphosphonate, a dental referral and any treatment should be undertaken within 1−2 months for patients expected to receive long-term bisphosphonates.

If ONJ occurs:

- seek specialist advice from a dentist or oral surgeon with expertise in ONJ regarding temporary/permanent discontinuation; however, new lesions may continue to appear even after discontinuation
- treat infection, e.g. antimicrobials, chlorhexidine mouthwash, periodic minor debridement and wound irrigation
- major debridement is avoided because it may exacerbate the situation
- avoid major surgery unless there is no alternative, e.g. due to sequestered bone, pathological fracture, or oro-antral fistula.

Bisphosphonates PO or IV (and denosumab) can also very rarely cause osteonecrosis of the external auditory canal. Reports are for both cancer-related and osteoporosis indications, although generally in patients treated for >2 years.[74] Possible risk factors include corticosteroid use, chemotherapy ± local infection or trauma. Patients should be counselled to report ear pain, discharge, or infection during treatment.[74]

Hypocalcemia

Hypocalcemia is a risk with all bisphosphonates, although less than with denosumab.[24] Patients who have undergone thyroid surgery may be at increased risk. Although asymptomatic hypocalcemia is classified as very common, symptomatic hypocalcemia is rare. However, life-threatening cases have been reported with zoledronic acid. For all indications, other than tumor-induced hypercalcemia:

- pre-existing hypocalcemia must be corrected before the initial dose of zoledronic acid
- patients should receive daily oral supplementation with calcium and vitamin D (see below).

Ocular toxicity

A rare undesirable effect is ocular inflammation, causing eye pain, redness, swelling, abnormal vision or impaired eye movement (due to rectus muscle edema).[75] Typically, the onset is <2 days after the first or second infusion and affects both eyes. There may be other symptoms of an acute systemic reaction (see above). An urgent ophthalmology assessment is required, followed by appropriate treatment.

Patients with mild reactions, e.g. those which settle quickly without treatment, can generally continue to receive the same bisphosphonate. Those with more severe reactions, e.g. uveitis or scleritis, should not receive the same bisphosphonate again. Some tolerate a switch to a non-nitrogen-containing bisphosphonate, but specialist advice should be sought from the ophthalmologist ± endocrinologist.[62]

Other toxicities

Atypical femoral fractures: reported rarely and usually in patients treated for >5 years for osteoporosis. The absolute number of atypical fractures reported is far lower than the number of osteoporotic fractures prevented. They are often bilateral and can occur with no/minimal trauma. Patients should be advised to report new or unusual thigh, hip or groin pain.[76,77]

Musculoskeletal pain: Severe (sometimes incapacitating) musculoskeletal pain has been reported after days, months or years of bisphosphonate treatment. It is particularly associated with PO bisphosphonates used for osteoporosis and Paget's disease. The pain is distinct from the arthralgia/myalgia associated with an acute systemic reaction (see above), and may respond to temporary or permanent discontinuation of the bisphosphonate.[78]

Dose and use

Because zoledronic acid is more effective, *PCF* favours it over pamidronate disodium as the bisphosphonate of first choice for tumor-induced hypercalcemia and prevention of SRE in patients with advanced malignancies involving bone.

Generally, either a single bisphosphonate or denosumab is used, but not both concurrently.[24]

Tumor-induced hypercalcemia

Tumour-induced hypercalcemia can occur as a terminal event in a patient expected to die soon from progressive cancer. Stop and think! Are you justified in correcting a potentially fatal complication in a moribund patient?

All plasma calcium values should be albumin-corrected, see Box B.

Box B. Correcting plasma calcium concentrations[a]

If the mean normal albumin for the local laboratory is 4g/dL

Corrected calcium (mg/dL) = measured calcium (mg/dL) + (0.8 x (4 − albumin g/dL))

e.g. measured calcium = 9.8mg/dL; albumin = 3.2g/dL

corrected calcium = 9.8 + (0.8 x 0.8) = 10.44mg/dL

(*normal range = 8.5–10.2mg/dL*)

[a]most pathology laboratories automatically report an albumin-corrected plasma calcium concentration based on locally validated data.

For zoledronic acid the PI recommends treatment for an albumin-corrected plasma calcium ≥12mg/dL (see Box B):

- patients should be well hydrated, using sodium chloride 0.9% IV if necessary
- give 4mg IVI in 100mL sodium chloride 0.9% or dextrose 5% over 15min
- if plasma calcium does not normalize, repeat after 1 week[7]
- in refractory hypercalcemia 8mg has been used, but is unauthorized because of concerns about renal impairment (see Pharmacology)
- no dose adjustment is needed in mild–moderate renal impairment for patients being treated for tumor-induced hypercalcemia; if possible, avoid use in severe renal impairment (see below).

For pamidronate disodium the PI recommends a dose dependent on the initial albumin-corrected plasma calcium concentration (Box B and Table 2). However, it has been suggested that 90mg should be given irrespective of the initial calcium level to increase the probability of a response and to prolong its duration:[7]

- patients should be well hydrated, using sodium chloride 0.9% IV if necessary
- standard and maximum recommended dose is 90mg IVI in 500mL sodium chloride 0.9% over 4h
- repeat after 1 week if initial response inadequate
- repeat every 3–4 weeks according to plasma calcium concentration
- no dose adjustment is needed in mild–moderate renal impairment for patients being treated for tumor-induced hypercalcemia; if possible, avoid use in severe renal impairment (see below).

Table 2
IV pamidronate disodium for tumor-induced hypercalcemia[a]

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

[a]based on USA manufacturer's recommendations. Irrespective of the initial calcium level, many centers use 90mg to increase the probability of a response and to prolong its duration.[7]

Prevention of skeletal-related events (SRE) in patients with advanced malignancies involving bone

Onset of benefit is 2–3 months. Pre-existing hypocalcemia must be corrected before starting bisphosphonate therapy. Daily oral supplements of elemental calcium ≥500mg and vitamin D 400 units are recommended, e.g. Caltrate® 600+D.

Baseline assessment and monitoring

Patients should be well hydrated, using sodium chloride 0.9% IV if necessary. Plasma creatinine should be measured before each dose of zoledronic acid or pamidronate disodium. Withhold treatment if:

- creatinine increases by ≥0.5mg/dL in patients with a *normal* baseline creatinine concentration (i.e. <1.4mg/dL), *or*
- creatinine increases by ≥1mg/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 plasma creatinine returns to within 10% of the baseline value. Discontinue treatment permanently if plasma creatinine fails to improve after 4–8 weeks.

Plasma calcium should be within the normal range before starting treatment the initial dose of zoledronic acid. To reduce the risk of ONJ, follow the guidelines in Box A.

For zoledronic acid:

- patients should be well hydrated, using sodium chloride 0.9% IV if necessary
- give 4mg IVI in 100mL sodium chloride 0.9% or dextrose 5% over 15min every 3–4 weeks; with appropriate support, this can be given at home[13]
- for dose in patients with mild–moderate renal impairment, see Table 3; avoid use in severe renal impairment (see below).

Table 3
Dose reduction for zoledronic acid in cancer patients and mild–moderate renal impairment[a,b,c]

Baseline creatinine clearance (mL/min)	Recommended dose (mg)
>60	4 (no reduction)
50–60	3.5
40–49	3.3
30–39	3

[a]manufacturer's recommendations for patients with multiple myeloma or bone metastases
[b]no data exist for severe renal impairment (creatinine clearance <30mL/min) because these patients were excluded from the studies
[c]reduced doses are diluted in 100mL sodium chloride 0.9% or dextrose 5% and given IVI over 15min; see PI for preparation details.

For pamidronate disodium:

- patients should be well hydrated, using sodium chloride 0.9% IV if necessary
- in *breast cancer with bone metastases*, give 90mg IVI in 250mL sodium chloride 0.9% over 1.5–2h every 3–4 weeks
- in *multiple myeloma*, give 90mg IVI in 500mL sodium chloride 0.9% *over 4h* every 4 weeks because of greater risk of renal toxicity
- no dose adjustment is needed in mild–moderate renal impairment for prophylactic use to reduce the incidence of SRE, but the infusion rate should not exceed 90mg/4h; avoid use in severe renal impairment (see below).

†Adjuvant analgesics for moderate–severe bone pain

High quality data are lacking and such use is unauthorized (see Pharmacology). Consider when analgesics and radiotherapy are unsatisfactory and the patient is not already receiving prophylactic bisphosphonates or denusomab. Zoledronic acid is the drug of choice (see Prevention of SRE above). If not available:

- give pamidronate disodium 90mg IVI (50% of patients respond, generally within 1–2 weeks); if helpful repeat 60–90mg every 3–4 weeks for as long as benefit is maintained.

Renal or hepatic impairment

For use in mild–moderate renal impairment, see above according to indication.

The use of bisphosphonates in severe renal impairment or ESKD can be complex and specialist renal/endocrinology advice should be sought. Reasons include the need for caution with fluid administration, the presence of other potentially contributing factors, e.g. tertiary hyperparathyroidism, use of vitamin D analogues, calcium-based phosphate binders, and the risk of further renal toxicity (see Undesirable effects). 'Renally safer' options include denosumab or reduced doses of ibandronic acid (Box C; not USA).[24] Although not authorized/available in the USA, in the UK, both denosumab and ibandronic acid are authorized for the prevention of SRE in patients with bone metastases from breast cancer/solid tumors in patients with severe renal impairment.

No dose adjustment is needed for pamidronate disodium in mild-moderate hepatic impairment, there are no data in severe hepatic impairment or for zoledronic acid; caution is advised by the manufacturer. No dose adjustment is necessary for ibandronic acid in patients with hepatic impairment (Box C; not USA).

Box C. Ibandronic acid

Ibandronic acid is a third-generation bisphosphonate which is available PO and IV and authorized in the UK for the indications below (not USA; see Supply).

IV ibandronic acid may be as effective as zoledronic acid in reducing SRE in patients with myeloma or metastatic bone disease.[28,81] It can be used PO for this indication in patients wanting to avoid IV treatment or at risk of renal impairment but is less effective than IV.[68,69,82] The PO tablet is smaller and more easily swallowed than sodium clodronate tablets.

The incidence of undesirable events is low (see main text).[7,44] Renal impairment is no more frequent than with placebo, and it is the only bisphosphonate authorized for use in reduced doses in severe renal impairment (creatinine clearance <30mL/min). Dose adjustment is not needed in hepatic impairment.

Dose and use

For full details, see UK SPC.

Tumor-induced hypercalcemia

- patients should be well hydrated, using sodium chloride 0.9% IV if necessary
- if the albumin-corrected plasma calcium:
  - ➢ is ≥12mg/dL give 4mg IVI
  - ➢ is <12mg/dL give 2mg IVI
- for both, the dose is given in 500mL sodium chloride 0.9% *or* dextrose 5% over 2h.

Prevention of skeletal related events in patients with bone metastases from breast cancer (PO/IV) or moderate-severe bone pain (IV)

Plasma calcium should be within the normal range before starting treatment; daily supplementation with calcium and vitamin D and steps to reduce the risk of ONJ are recommended as for other bisphosphonates (see above).

For oral use:

- give 50mg PO once daily
  - ➢ in moderate renal impairment, give 50mg PO *alternate days*
  - ➢ in severe renal impairment, give 50mg PO *once a week*.

To maximize absorption and to minimize undesirable gastro-esophageal effects, patients should take ibandronic acid tablets whole after an overnight fast with a glass of *plain tap water*, followed by a further fast while sitting upright for 1h.

For parenteral use:

- give 6mg IVI in 100mL sodium chloride 0.9% *or* dextrose 5% over 15min every 3–4 weeks
  - ➢ in moderate renal impairment, give 4mg in 500mL *over 1h* every 3–4 weeks
  - ➢ in severe renal impairment, give 2mg in 500mL *over 1h* every 3–4 weeks.

†Subcutaneous administration

If the IV route is inaccessible, the following bisphosphonates can be administered by CSCI, together with SC hydration.[79,80]

- pamidronate disodium 90mg in 1L sodium chloride 0.9% over 12–24h
- sodium clodronate (not USA or UK) 1,500mg in 50–250mL sodium chloride 0.9% or dextrose 5% over 2–3h. Denosumab, a SC injection, is an alternative.[24]

Supply

Pamidronate disodium (generic)

Injection (concentrate for dilution and use as an infusion) 3mg/mL, 10mL vial = $17; 6mg/mL, 10mL vial = $34, 9mg/mL, 10mL vial = $43.

Zoledronic acid (generic)

Injection (concentrate for dilution and use as an infusion) 4mg/5mL, 5mL vial = $53–$967.

Infusion 4mg/100mL, 100mL bag, vial, or bottle = $72–$216.

Note. Zoledronic acid 5mg/100mL is available but authorized for the treatment of Paget's disease and as an annual dose for osteoporosis in women (post-menopausal) or men.

Ibandronic acid (generic)

Note. Ibandronic acid 150mg tablets and 1mg/mL, 3mL pre-filled syringe are available but authorized for the prevention and treatment of post-menopausal osteoporosis.

Abbreviations/key

†	Off-label use
BMD	Bone mineral density
ESKD	End-stage kidney disease
min	Minute(s)
ONJ	Osteonecrosis of the jaw
PCF	Palliative Care Formulary
PI	Package insert (USA), equivalent to SPC (UK)
PO	Per os, by mouth
IV	Intravenous
IVI	Intravenous infusion
RCT	Randomized controlled trial
SC	Subcutaneous
SRE	Skeletal-related event

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