

Yorkshire Palliative Medicine Clinical Guidelines Group

**GUIDELINES ON THE USE OF
BISPHOSPHONATES IN PALLIATIVE CARE**

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Overall objective: To provide evidence-based guidance for the use of bisphosphonates in specialist palliative care, with particular reference to hypercalcaemia of malignancy and bone pain.

Search strategy: Medline and Embase databases were searched using the words cancer, neoplasm and the generic and trade names for individual drugs. Searches were limited to papers published in English relating to adult humans in clinical trials to February 2007. References obtained were hand searched for additional materials relevant to this review.

Level of evidence: Evidence regarding medications included in this review has been graded according to criteria described by Keeley [2003] on behalf of the SIGN research group (see appendix 2).

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Disclaimer: These guidelines are the property of the Yorkshire Palliative Medicine Clinical Guidelines Group and are intended for qualified, specialist palliative medicine professionals as an information resource. They should be used in the clinical context of each individual patient's needs and reference to appropriate prescribing texts / literature should also be made. The Clinical Guidelines Group takes no responsibility for any consequences of any actions taken as a result of using these guidelines.

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INTRODUCTION

The bisphosphonates are a group of drugs which share a common structure of two phosphate groups linked to a carbon molecule, hence the name bisphosphonate. Additional side chains create the differences between the bisphosphonates. Those that contain nitrogen e.g. pamidronate, ibandronic acid and zoledronic acid are more potent than those which do not e.g. clodronate.

Bisphosphonates bind to hydroxyapatite crystals on the surface of bone and are reabsorbed by osteoclasts. Once internalised by osteoclasts they reduce their activity, thereby slowing bone resorption. A number of other effects have been postulated, including a reduction in the invasion of tumour cells, antiangiogenic activity and direct tumour cytotoxicity.

Bisphosphonates are considered standard treatment for hypercalcaemia of malignancy (HCM) and for the prevention and treatment of skeletal related complications of bone metastases in some malignancies. Although associated with almost every type of malignancy, bone metastases are most frequently associated with prostate and breast cancer with an incidence of 65-90% [Wu 2007].

Bone metastases can lead to fractures, spinal cord compression and pain. Metastatic bone pain, in particular movement-related pain, can be difficult to manage despite a number of treatment options. Bisphosphonates offer a further treatment modality for bone pain, particularly when refractory to standard treatments, including analgesics, radiotherapy and surgery.

These guidelines explore the most efficacious type, dose and frequency of bisphosphonate to prescribe for bone pain or HCM in the palliative setting, along with information on bisphosphonate use for the prophylaxis of skeletal related events (SRE).

PREScribing INFORMATION

This section contains background information on all the bisphosphonates discussed in the guidelines. It includes information on the manufacturers' recommendations for use, monitoring, side effects and interactions, usual doses and changes recommended in renal impairment. Only common or significant drug interactions and side effects for each medication reviewed have been included. Prescribers should refer to such sources as the current edition of the British National Formulary [BNF] or the Electronic Medicines Compendium [www.medicines.org.uk] for full and up-to-date guidance. Cost for each bisphosphonate [BNF March 2007] has also been included.

ORAL SODIUM CLODRONATE (Bonafos®)

Licensed indications

Management of osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with carcinoma of the breast or multiple myeloma.

Maintenance of clinically acceptable serum calcium levels in patients with hypercalcaemia of malignancy initially treated with intravenous sodium clodronate.

Monitoring and supplementation

It is recommended that monitoring of renal function be carried out during treatment. Serum calcium should be monitored periodically.

Side effects

Gastrointestinal disturbances e.g. nausea, vomiting and diarrhoea. Dividing the dose may improve gastrointestinal tolerance.

Renal dysfunction, including failure reported.

Asymptomatic hypocalcaemia infrequently reported. Symptomatic hypocalcaemia is rare.

Osteonecrosis of the jaw.

Drug interactions

Caution with non steroidal anti-inflammatory drugs (NSAIDs) due to possible risk of renal impairment. As aminoglycosides can cause hypocalcaemia, concomitant clodronate should be administered with caution. Simultaneous administration with food, antacids and mineral supplements may impair absorption.

Usual dose

1600 mg sodium clodronate daily taken as a single dose or in two divided doses (800 mg bd). Taken with a little fluid, but not milk, at least 1 hour before or 1 hour after food.

Renal impairment

In patients with moderate renal impairment (creatinine clearance 10 - 30 ml/min), the daily dose should be reduced to 800 mg sodium clodronate. Sodium clodronate is contraindicated in patients with a creatinine clearance below 10 ml/min.

Form

400mg capsules or 800mg tablets.

Cost

1600mg od sodium clodronate for 30 days costs £161.97 (capsules) or £169.62 (tablets).

INTRAVENOUS SODIUM CLODRONATE (Bonefos Concentrate®)**Licensed indications**

Hypercalcaemia of malignancy.

Monitoring and supplementation

It is recommended that appropriate monitoring of renal function be carried out during treatment.

Side effects

Osteonecrosis of the jaw.

Drug interactions

Caution with NSAIDs due to possible risk of renal impairment. As aminoglycosides can cause hypocalcaemia concomitant clodronate should be administered with caution.

Usual dose

Single Infusion: 1500 mg sodium clodronate in 500 ml of 0.9% saline or 5% glucose IV over 4 hours following adequate hydration.

Multiple Infusions: 300 mg sodium clodronate in 500 ml of 0.9% saline or 5% glucose administered IV over at least 2 hours on successive days until normocalcaemia is achieved or to a maximum of 7 days following adequate hydration.

Renal impairment

No published data to base recommendations for dose reduction in renal impairment when considering a single 1500 mg infusion in hypercalcaemia.

Sodium clodronate should be reduced in renal impairment according to creatinine clearance when using divided intravenous doses of 300 mg. In mild renal impairment (creatinine clearance 50 - 80 ml/min) a 25% reduction in dose is recommended, in moderate renal impairment (10 - 50 ml/min) a 25 - 50% reduction in dose is recommended. Sodium clodronate is contra-indicated in patients with a creatinine clearance below 10 ml/min.

Form

Sodium clodronate 60mg/ml concentrate for infusion.

Cost

1500mg IV sodium clodronate costs £64.10.

ORAL IBANDRONIC ACID (Bondronat®)**Licensed indications**

Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

Monitoring and supplementation

Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ibandronic acid. Adequate intake of calcium and vitamin D is important in all patients. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.

Clinical studies have not shown any evidence of deterioration in renal function with long term ibandronic acid. Nevertheless, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored.

Side effects

Dysphagia, oesophagitis, oesophageal or gastric ulcers, abdominal pain, nausea.

Asymptomatic hypocalcaemia.

Osteonecrosis of the jaw.

Drug interactions

Products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk and food, are likely to interfere with absorption. Bioavailability is reduced by approximately 75% when ibandronic acid is administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (at least 6 hours) and fasting should continue for at least 30 minutes after the dose has been taken.

NSAIDs are associated with gastrointestinal irritation therefore caution should be taken during concomitant oral medication with ibandronic acid.

Caution is advised when administered with aminoglycosides, since both agents can lower serum calcium levels for prolonged periods.

Usual dose

50 mg daily.

Taken after an overnight fast (at least 6 hours) in an upright position with a glass of water, before the first food or drink of the day. Other medication (including calcium) should be avoided prior to taking ibandronic acid. Fasting should be continued for at least 30 minutes and patients should not lie down within 60 minutes of taking the tablet.

Renal impairment

No dose adjustment is necessary for patients with mild or moderate renal impairment (creatinine clearance ≥ 30 ml/min). Below 30 ml/min, the recommended dose is 50 mg once weekly.

Form

50 mg tablets.

Cost

50mg od ibandronic acid for 28 days costs £195.

INTRAVENOUS IBANDRONIC ACID (Bondronat concentrate for infusion®)

Licensed indications

Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
Treatment of hypercalcaemia.

Monitoring and supplementation

Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ibandronic acid. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.

Clinical studies have not shown any evidence of deterioration in renal function with long term ibandronic acid therapy. Nevertheless, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored.

Side effects

Flu-like syndrome consisting of fever, bone and/or muscle aches.

Asymptomatic hypocalcaemia and hypophosphataemia.

Gastrointestinal upset.

Osteonecrosis of the jaw.

Drug interactions

Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia.

Usual dose

- **Prevention of skeletal related events**

6 mg IV every 3-4 weeks infused over at least 15 minutes in 100 ml 0.9% saline or 5% glucose.

- **Treatment of Hypercalcaemia**

Prior to treatment the patient should be adequately rehydrated.

In most patients with severe hypercalcaemia (calcium ≥ 3 mmol/l), 4 mg is an adequate single dosage. In patients with moderate hypercalcaemia (calcium < 3 mmol/l) 2 mg is an effective dose. The drug should be administered in 500ml 0.9% saline or 5% glucose over 2 hours.

Renal impairment

For the prevention of skeletal events in patients with breast cancer and bone metastases the following recommendations should be followed:

Creatinine clearance (ml/min)	Dose	Infusion time	Infusion volume
≥ 50	6mg	15 min	100 ml
30 – 50	6mg	1 hr	500 ml
< 30	2mg	1 hr	500 ml

Form

Ibandronic acid 2mg/2ml concentrate for infusion. Ibandronic acid 6mg/6ml concentrate for infusion.

Cost

6mg IV ibandronic acid costs £195. 2mg IV ibandronic acid costs £94.86.

PAMIDRONATE

Licensed indications

(These may vary depending on the particular brand used. For full details consult SPC)

Hypercalcaemia of malignancy.

Osteolytic lesions and bone pain in patients with bone metastases associated with breast cancer or multiple myeloma.

Monitoring and supplementation

Serum electrolytes, calcium and phosphate should be monitored following initiation of therapy.

Patients receiving multiple infusions over a prolonged period of time should have periodic monitoring of renal function, especially those with predisposing factors (e.g. multiple myeloma, hypercalcaemia).

Side effects

Fever, bone pain and flu like symptoms usually within the first 48 hours of infusion. Nausea and vomiting.

Renal dysfunction, including failure reported.

Asymptomatic hypocalcaemia, hypophosphataemia and hypomagnesaemia are common.

Symptomatic hypocalcaemia is rare.

Osteonecrosis of the jaw.

Drug interactions

Nil specific reported.

Usual dose

Note the infusion rate should never exceed 60mg/hour (1mg/min), and the concentration of pamidronate in the infusion should not exceed 60mg/250ml.

- **Hypercalcaemia of malignancy**

It is recommended that patients be rehydrated before or during treatment.

Dose depends on the patient's initial serum calcium levels. The following guidelines are derived from clinical data on uncorrected calcium values but are also applicable to corrected calcium values.

Initial serum calcium (mmol/l)	Recommended total dose (mg)
< 3.0	15 – 30
3.0 to 3.5	30 – 60
3.5 to 4.0	60 – 90
> 4.0	90

- **Osteolytic lesions and bone pain**

90mg every four weeks (or every three weeks to coincide with chemotherapy in breast cancer).

Renal Impairment

Pharmacokinetic studies indicate that no dose adjustment is necessary in patients with any degree of renal impairment. However, until further evidence is available in patients with

established or suspected renal impairment (e.g. those with hypercalcaemia of malignancy or multiple myeloma) it is recommended that the infusion rate does not exceed 20mg/hr.

Note: The SPC for Aredia® states that it should not be administered to patients with severe renal impairment (creatinine clearance < 30 ml/min) unless in cases of life-threatening hypercalcaemia of malignancy where the benefit outweighs the potential risk. Renal monitoring is recommended prior to each dose of Aredia®. In patients receiving Aredia® for bone metastases who show evidence of deterioration in renal function, Aredia® treatment should be withheld until renal function returns to within 10% of the baseline value.

Form

Pamidronate 3mg/ml concentrate or dry powder for reconstitution (Aredia®).

Cost

90mg IV pamidronate costs £165 (Generic) or £170.45 (Aredia®).

Note: Leeds Teaching Hospitals Trust (LTHT) contract price for 90mg pamidronate ready made infusion £18.99.

ZOLEDRONIC ACID (Zometa®)

Licensed indications

Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or hypercalcaemia of malignancy) in patients with advanced malignancies involving bone.

Hypercalcaemia of malignancy.

Monitoring and supplementation

Serum levels of calcium, phosphate and magnesium should be carefully monitored. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary.

Creatinine levels should be assessed prior to each dose.

Side effects

Flu-like symptoms, bone pain, fever and gastrointestinal disturbance.

Asymptomatic hypophosphataemia, hypomagnesaemia and hypocalcaemia.

Renal dysfunction, including failure reported. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic drugs.

Osteonecrosis of the jaw.

Drug interactions

As aminoglycosides can cause hypocalcaemia concomitant zoledronic acid should be administered with caution.

Caution when used with other potentially nephrotoxic drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates are used in combination with thalidomide.

Usual dose

- **Prevention of skeletal related events**

4 mg zoledronic acid in 100 ml 0.9 % sodium chloride or 5 % glucose IV infused over ≥15 minutes every 3 to 4 weeks.

Patients should also be prescribed an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

- **Treatment of hypercalcaemia**

4 mg zoledronic acid in 100 ml 0.9 % sodium chloride or 5 % glucose infused over ≥15 minutes. Adequate hydration should be maintained pre and post administration.

Renal impairment

- **Hypercalcaemia**

Zoledronic acid for HCM in patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In clinical studies, patients with serum creatinine > 400 µmol/l were excluded. The SPC states that no dose adjustment is necessary in hypercalcaemic patients with serum creatinine < 400 µmol/l. However, in clinical practice the use of a potentially less nephrotoxic bisphosphonate is recommended (e.g. pamidronate or ibandronic acid).

- **Prevention of skeletal related events**

When initiating zoledronic acid, serum creatinine and creatinine clearance (CrCl) should be determined. Zoledronic acid is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CrCl < 30 ml/min. In clinical trials, patients with serum creatinine > 265 µmol/l were excluded.

In patients presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CrCl 30–60 ml/min, the following zoledronic acid dose is recommended:

Baseline creatinine clearance (ml/min)	Zoledronic acid recommended dose
>60	4.0 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3.0 mg

Following initiation of therapy, serum creatinine should be measured prior to each dose of zoledronic acid and treatment should be withheld if renal function has deteriorated. In clinical trials, renal deterioration was defined as follows:

- An increase of 44 µmol/l from a baseline serum creatinine of < 124 µmol/l
- An increase of 88 µmol/l from a baseline creatinine of > 124 µmol/l

Treatment was resumed only when the creatinine level returned to within 10 % of the baseline value and was resumed at the same dose as that prior to interruption.

Form

Zoledronic acid 4mg/5ml concentrate for infusion.

Cost

4mg IV zoledronic acid costs £195

(Note; LHT contract price for 4mg zoledronic acid £132)

HYPERCALCAEMIA OF MALIGNANCY

INTRODUCTION

Hypercalcaemia is the commonest life threatening metabolic complication of malignancy, affecting approximately 10-20% of patients with advanced cancer. Incidence varies widely between cancer types, but it occurs most frequently in patients with multiple myeloma, lung, breast, renal and head and neck cancers. It is associated with a poor prognosis, with a median survival of 3-4 months.

Patients with or without bone metastases can develop hypercalcaemia. It is caused by factors secreted by tumour cells and the immune system such as parathyroid hormone related protein (PTHrP), prostaglandins and cytokines. These factors stimulate excess bone reabsorption. PTHrP also increases renal reabsorption of calcium, resulting in further increases in serum calcium [Bower 2005].

The current mainstay of treatment for hypercalcaemia of malignancy (HCM) is rehydration followed by bisphosphonate administration.

REHYDRATION

Rehydration prior to administration of bisphosphonates is standard practice in clinical trials. Fluids partly correct the increased renal reabsorption of calcium seen in HCM and may minimise renal damage both from hypercalcaemia and the administration of a potentially nephrotoxic drug [Ralston 1985].

Fluids alone can achieve normocalcaemia but the response is variable. One small randomised study reported normocalcaemia in 22% by day 6, for a median duration of 6 days [Gucalp 1994]. This followed treatment with 3L 0.9% saline followed by >2L daily for 7 days. As the duration of response is short a bisphosphonate is usually required for a more prolonged duration of action.

Trials of bisphosphonates for the treatment of HCM often involve pre-hydration with a minimum of 2L 0.9% saline and continued rehydration until normocalcaemia is achieved. This should be taken into account when considering the response rates discussed below.

BISPHOSPHONATES

Bisphosphonates have been shown to be an effective treatment for HCM and are more effective than hydration alone [Gucalp 1994]. Clodronate, ibandronic acid, pamidronate and zoledronic acid are all licensed for this use.

Clodronate

A dose response study randomised 67 patients with non haematological malignancies and HCM to various doses of intravenous clodronate, dependant on the corrected serum calcium level (CSC) [Shah 2002]. The response rate (CSC <2.6 mmol/L at days 6-9) was

49% with no statistically significant difference between the four doses of clodronate used (600mg, 900mg, 1200mg, 1500mg). A pooled analysis of three separate studies with different treatment criteria reported a response rate (CSC <2.68 mmol/L at day 5) of 76% for 1500mg of clodronate and 60% for 900mg ($p>0.15$) [Atula 2003].

The nadir for CSC following clodronate infusion occurs at approximately day 4 [Purohit 1995, Vinholes 1997, J Clin Oncol].

Ibandronic acid

A dose response study randomised 125 patients with HCM to ibandronic acid 2, 4 or 6mg. The response rate (CSC <2.7 mmol/L) was 50%, 76% and 78% respectively, with a median duration of normocalcaemia for 11-12 days with all 3 doses [Ralston 1997]. Based on a logistic regression analysis of the results the authors suggest that in patients with CSC <3mmol/l a dose of 2mg is used, as it is equally as likely to give a complete response as 4mg or 6mg, while 4mg should be used for serum calcium levels above 3mmol/l.

The nadir for CSC following ibandronic acid infusion occurs at day 5 [Ralston 1997].

Pamidronate

A number of studies have investigated the use of pamidronate for the treatment of HCM using a variety of doses and regimens and often intensive rehydration [Body 1986, Thiebaud 1988, Nussbaum 1993, Gucalp 1994]. They report the achievement of normocalcaemia in 40-100% of patients, with higher doses of pamidronate achieving higher response levels. The manufacturer's guidelines recommend that the dose of pamidronate should be adjusted to the pre treatment CSC level. This is based on a small study which reported that higher doses of pamidronate were more efficacious both in lowering the calcium level and the duration of response, but led to an increased incidence of asymptomatic hypocalcaemia [Thiebaud 1988]. Higher doses were not associated with increased renal impairment [Thiebaud 1988, Nussbaum 1993]. A further study suggested that for calcium levels >3mmol/L, 90mg should be used [Body 1994]. A number of more recent comparative trials of bisphosphonates have used 90mg of pamidronate, irrespective of calcium level, with no apparent adverse effect [Purohit 1995, Vinholes 1997 J Clin Oncol]. As a result of the longer duration of response and lack of adverse effects, the use of 90mg of pamidronate for any level of HCM is recommended [Saunders 2004].

The nadir for CSC following pamidronate infusion occurs at approximately day 7 [Purohit 1995, Vinholes 1997, J Clin Oncol]

Zoledronic Acid

A pooled analysis evaluated 275 patients with HCM, randomised to zoledronic acid 4 or 8mg, or pamidronate 90mg in 2 double blind studies [Major 2001]. The response rate (CSC <2.7 mmol/L) was 83% in both zoledronic acid groups at day 7, and 88% for 4mg and 87% for 8mg at day 10 (p non significant). The response was quicker for the higher dose, 56% vs. 45% at day 4 (p ns), and of longer duration, 43 days vs. 32 days (p unreported) [Major 2001]. Grade 3 or 4 renal adverse events (creatinine increase more than 3 times upper limit of normal) occurred in 5 patients treated with zoledronic acid 8mg compared to 2 patients treated with zoledronic 4mg acid and 4 patients given pamidronate

90mg . An open label study of 25 patients with HCM treated with 4mg zoledronic acid reported a similar response rate of 84% by day 10 with a median time to relapse of 23 days [Kawada 2005].

The nadir for CSC following zoledronic acid infusion occurs at approximately day 6-11 [Major 2001, Kawada 2005].

Comparative studies

Pamidronate has been directly compared with each of clodronate, ibandronic acid and zoledronic acid.

In a double blind study 41 patients with HCM were randomised to pamidronate 90mg or clodronate 1500mg. The response rate (CSC <2.65 mmol/L at any point) was 100% for pamidronate and 80% for clodronate ($p >0.1$). Median time to normocalcaemia was 3 days for clodronate and 4 days for pamidronate. Median duration of normocalcaemia (time from bisphosphonate to CSC >2.6 mmol/l) was 14 days for clodronate and 28 days for pamidronate ($p=0.01$) [Purohit 1995]. A second study of 32 patients treated with pamidronate 90mg or clodronate 1500mg exactly replicated these findings ($p<0.01$) [Vinholes 1997]. A pooled analysis of 3 separate studies including 51 patients, of clodronate 1500mg and 900mg compared with pamidronate 90mg found no significant difference between the 3 groups in the achievement of normocalcaemia within 5 days [Atula 2003].

In an open label, randomised trial of ibandronic acid in 58 patients compared to pamidronate, normocalcaemia was achieved within 4 days in 76% of patients in both groups (dose of bisphosphonate dependent on CSC as per SPCs) [Pecherstorfer 2003]. The median duration of normocalcaemia was 14 days for ibandronic acid compared to only 4 days for pamidronate. However, further analysis of the 60mg and 90mg pamidronate groups showed a median duration of response of 14 days. In a subgroup analysis of 11 patients with an initial CSC >3.5 mmol/l there was a greater reduction in calcium at day 4 in the ibandronic acid group vs. pamidronate ($p=0.046$).

A pooled analysis evaluated 275 patients with HCM, randomised to zoledronic acid 4 or 8mg, or pamidronate 90mg in 2 double blind studies. Normocalcaemia was achieved in 44% of patients receiving 4mg zoledronic acid compared to 33% receiving 90mg pamidronate within 4 days (p ns) and 88% of patients compared to 70% within 10 days ($p=0.02$) [Major 2001]. The median duration of normocalcaemia was 32 days for zoledronic acid compared with 18 days for pamidronate (p unreported, however the median time to relapse was reported as 30 vs. 17 days, $p=0.001$).

REFRACTORY OR RELAPSING HYPERCALCAEMIA

It is difficult to compare data in refractory and relapsing HCM as these clinically different scenarios are often combined in clinical studies due to small numbers. In the largest study 69 patients with relapsed or refractory hypercalcaemia received further treatment with 8mg zoledronic acid. Normocalcaemia was achieved within 10 days in 52%, compared to 87% first line [Major 2001]. In another study of 7 patients with relapsed or

refractory hypercalcaemia, retreatment with Zoledronic acid 4mg resulted in 4 patients achieving normocalcaemia [Kawada 2005].

In refractory HCM alone responses have been shown to either the same or a different bisphosphonate; two of five patients responded to further ibandronate and two of four to further pamidronate [Pecherstorfer 2003], two patients responded to 90mg pamidronate when 1500mg clodronate had failed [Purohit 1995]. In relapsing HCM two of three patients responded to re-treatment with 90mg pamidronate and four of eight responded to re-treatment with 1500mg clodronate [Purohit 1995].

Theoretically, patients with frequently relapsing hypercalcaemia may benefit from zoledronic acid as it has the longest reported duration of response and doses of 8mg could also be considered for the same reason. However, the reported median duration of response was much shorter when 8mg was used in refractory and relapsing HCM; 10.5 versus 43 days initially [Major 2001], and concerns over renal impairment with 8mg should be noted.

Oral clodronate is licensed for the maintenance of clinically acceptable serum calcium levels in patients with HCM initially treated with an intravenous infusion of clodronate. In a study of 173 patients with breast cancer and bone metastases, patients were randomized to receive either 1600mg daily of oral clodronate or placebo for 3 years [Paterson 1993]. There were no significant differences in side effects between groups. In the clodronate group 20 patients developed HCM compared with 31 in the placebo group, with a significant decrease in the total number of hypercalcaemic episodes in the clodronate-treated patients compared to placebo (28 vs. 52; $p < 0.01$).

CONCLUSIONS

- Clodronate, ibandronic acid, pamidronate and zoledronic acid all have proven efficacy in the treatment of HCM.
- Many studies of these drugs prehydrate patients with at least 2 litres of fluid before treatment and this practice may improve outcomes. Therefore prehydration prior to bisphosphonate treatment of HCM should be considered.
- There are few comparative studies between bisphosphonates for the treatment of HCM. The results of these suggest that ibandronic acid and pamidronate (doses of at least 60mg) are of equal efficacy and that clodronate 1500mg achieves the same rate of normocalcaemia as pamidronate 90mg but for a shorter duration. Zoledronic acid appears to be more effective than pamidronate in a single trial, with an 18% greater response rate after 10 days and 14 day longer median duration of normocalcaemia.
- For patients with frequently relapsing hypercalcaemia, zoledronic acid may give a longer time period between treatments as trial data suggests that this has the longest duration of action. However, the reported median duration of response was much shorter when 8mg was used in refractory and relapsing HCM; 10.5 versus 43 days initially. Maintenance with oral clodronate could also be considered.

- In refractory and relapsing HCM, retreatment with any bisphosphonate has been associated with at least 50% achievement of normocalcaemia, based on small numbers. Theoretically zoledronic acid may elicit a response where other bisphosphonates have failed due to its higher response rate.
- The nadir for clodronate is day 4, ibandronic acid day 5, pamidronate approximately day 7 and zoledronic acid day 6-11. By day 4, 76% of patients will be normocalcaemic with ibandronic acid, 33-50% with pamidronate and 45% with zoledronic acid. Approximately another 40% will be normocalcaemic by day 10 with pamidronate or zoledronic acid. When rechecking CSC in patients who remain symptomatic, these figures should be taken into account.
- Zoledronic acid has the advantage of a faster infusion time over other agents but many patients receiving treatment for HCM will require rehydration, making the infusion time of the drug less significant.
- Currently the cost of zoledronic acid and ibandronic acid are comparable, and approximately £30 more expensive than pamidronate. Clodronate is approximately 1/3 of the cost. However, local costs may vary significantly from this e.g. 90mg pamidronate £19, 4mg zoledronic acid £132, via LTHT. If this price is comparable across the region and considering available evidence for the efficacy of the drugs, it would seem reasonable to use pamidronate first line in patients with HCM.
- The SPC recommends modifying the dose of pamidronate which dependant on the uncorrected serum calcium level. Several comparative studies use pamidronate 90mg to treat HCM in all patients regardless of level of hypercalcaemia and without significant adverse effects (renal or symptomatic hypocalcaemia). Pamidronate 90mg is also standard treatment for prevention of SRE (when calcium levels prior to treatment are likely to be within normal range). Using pamidronate 90mg for any level of hypercalcaemia in patients with cancer is likely to increase the response rate and duration of response and is therefore recommended (although outside product licence). This practice is supported by a recent systematic review of bisphosphonates in the treatment of HCM [Saunders 2004].

PREVENTION OF SKELETAL RELATED EVENTS

CLODRONATE

Summary

There is evidence that oral clodronate decreases bone disease progression and fractures in multiple myeloma. Clodronate is no better than placebo for preventing bone disease progression in prostate and breast cancer.

Breast cancer

Studies of oral clodronate have reported conflicting results with regards to survival and the development of bone metastases in breast cancer. A recent meta-analysis of studies published up to and including 2006 involving oral clodronate 1600mg daily for 2 or 3 years found no statistically significant difference in overall survival, bone metastasis-free survival or non-skeletal metastasis-free survival in advanced or early breast cancer patients receiving clodronate therapy compared with those who did not receive any active treatment [Ha 2007].

Multiple Myeloma

In randomised placebo controlled trials of patients with newly diagnosed multiple myeloma, oral clodronate 1.6 - 2.4g daily, has been associated with reductions in bone disease progression (24% vs. 12%, $p=0.026$), vertebral fractures (38% vs. 55%, $p=0.01$) and non vertebral fractures (6.8% vs. 13.2%, $p=0.04$) [Lahtinen 1992, McCloskey 1998]. There was no difference in overall survival [McCloskey 2001].

Prostate cancer

A double blind randomised placebo controlled trial of 311 patients where oral clodronate 2080mg daily was added to usual treatment found no statistically significant difference in symptomatic bone progression free survival, time to symptomatic bone progression or survival over 3 years [Dearnaley 2003].

Bone metastases of any origin

No evidence.

IBANDRONIC ACID

Summary

In metastatic breast cancer intravenous ibandronic acid reduces the number of SREs and delays time to first SRE. Both oral and intravenous ibandronic acid decrease skeletal event rates. Hazard ratios for the two preparations suggest equal efficacy. There is no evidence for the use of ibandronic acid in the prevention of SREs in prostate cancer and it is no better than placebo in multiple myeloma (low dose in the latter).

Breast cancer

A double blind randomised placebo controlled trial of 3-4 weekly IV ibandronic acid, either 6mg or 2 mg, over 96 weeks in 466 patients, found significant improvements for the 6mg group over placebo in the mean number of SRE per patient (2.65 vs. 3.64, $p=0.032$), median time to first SRE (50.6 vs. 33.1 weeks, $p=0.018$) and the skeletal morbidity period rate (SMPR) (no. of 12 week periods with a SRE divided by the total observation time, 1.19 vs. 1.46, $p=0.004$) [Body 2003]. Multiple events analysis found a 40% reduction in risk of SRE for 6mg compared to placebo (hazard ratio 0.6, $p=0.003$). No statistically significant difference was found for the 2mg group compared to placebo.

Oral ibandronic acid 50mg significantly reduced the mean SMPR in patients with metastatic breast cancer compared with placebo (0.95 vs. 1.18, $p=0.004$) [Body 2004, B J Cancer]. Median time to first new SRE was 90.3 weeks for ibandronic acid vs. 64.9 weeks for placebo ($p=0.089$). Multiple events analysis showed the risk reduction for a SRE in the ibandronic acid group was significantly lower than placebo (hazard ratio 0.62, $p<0.0001$).

Multiple Myeloma

A double blind, randomised, placebo controlled trial of monthly IV ibandronic acid 2mg in 198 patients for 12-24 months reported no significant difference between groups for SRE per patient year or time to first SRE (median 438 and 462 days for the ibandronic acid and placebo groups respectively) [Menssen 2002].

Prostate cancer

No evidence.

Bone metastases of any origin

No evidence.

PAMIDRONATE

Summary

Intravenous pamidronate has been shown to decrease SRE's and delay the time to an event in both multiple myeloma and breast cancer. It is no better than placebo in prostate cancer. Oral pamidronate also decreases SRE's in breast cancer but its use is limited by GI toxicity.

Comparative trials have found no significant difference between zoledronic acid and pamidronate in multiple myeloma. In breast cancer there was no difference between the two drugs in the proportion of patients developing a SRE although multiple event analysis reports a 20% reduction in the risk of SRE for zoledronic acid over pamidronate. In subgroup analysis there is a risk reduction of 30% for zoledronic acid in patients on hormone therapy and those with lytic lesions but no difference to pamidronate in patients on chemotherapy or with no lytic lesions.

Breast cancer

2 double blind randomised placebo controlled studies of 754 patients in total showed 90mg IV pamidronate 3-4 weekly for 24 cycles significantly decreased the SMR (2.4 vs. 3.7 events per year, not including hypercalcaemia, $p<0.001$), percentage of patients having a SRE (51% vs. 64%, $p<0.001$) and delayed the median time to first SRE (7 vs. 12.7 months, $p<0.001$) [Lipton 2000].

A randomised, double blind, dose response study of 280 breast and myeloma patients treated with either 0.4mg/2mg/4mg zoledronic acid or 90mg pamidronate over 10 months reported that the 0.4mg zoledronic acid dose was significantly less effective than pamidronate 90mg (no. of patients with at least 1 SRE 35% vs. 46% ($p<0.05$), median time to first SRE 167 vs. 254 days ($p<0.05$)) but differences between the other zoledronic acid groups and pamidronate were not reported [Berenson 2001].

A double blind randomised controlled study compared 3-4 weekly pamidronate 90mg with zoledronic acid 4mg and 8mg in 1648 patients with breast cancer and multiple myeloma over 12 months, extended to 24 months [Rosen 2001, 2003, 2004]. The 8mg group was discontinued due to concerns over renal safety. In the 1130 patients with breast cancer, similar numbers developed at least 1 SRE with both pamidronate and zoledronic acid (49% vs. 46% at 24 months, p unreported). Median time to first SRE, including HCM, was unreported for the breast cancer group as a whole but subgroup analyses found a significant advantage with zoledronic acid over pamidronate for those on hormone therapy (415 vs. 370 days, $p=0.047$) but not those on chemotherapy (349 vs. 366 days, $p=0.826$) and those with lytic metastases (310 vs. 174 days, $p=0.013$) but not with non lytic metastases. The SMR was not significantly different for the breast cancer group as a whole (0.9 vs. 1.49 at 24 months, $p=0.125$) but again subgroup analyses found a significant advantage with zoledronic acid for those on hormone therapy (0.83 vs. 1.37 at 24 months, $p=0.039$) but not those on chemotherapy and those with lytic metastases (1.2 vs. 2.4 at 12 months, $p=0.008$) but not with non lytic metastases ($p=0.904$). Hazard ratios show a 20% risk reduction of developing a SRE for zoledronic acid compared with pamidronate over 12 months (excluding HCM, $p=0.037$), extending to 24 months (including HCM, $p=0.025$). Subgroup analyses identified these risk reductions to comprise a 30% benefit for zoledronic acid for those on hormone therapy ($p=0.009$) or with lytic metastases

($p=0.01$) but no reduction if on chemotherapy ($p=0.75$) or having non lytic metastases (p unreported).

In randomised controlled studies, oral pamidronate (300mg - 600mg daily) decreased the proportion of skeletal complications by 38% but did not prevent or delay the development of bone metastases (300mg daily) [Val Holten-Verzantvoort 1993,1996]. Gastrointestinal side effects led to a drop out rate of 23% [Val Holten-Verzantvoort 1993].

Multiple Myeloma

A double blind randomised placebo controlled trial of monthly IV pamidronate 90mg in 377 patients reported a significant decrease in the number of patients having a SRE at all time points from 3-21 months compared to placebo (38% vs. 51% at 21 months, $p=0.015$) [Berenson 1996, 1998]. Pamidronate decreased the number of vertebral (16% vs. 27%, $p=0.05$) but not non-vertebral fractures. It conferred no survival benefit. A randomised controlled trial of IV pamidronate 60mg in 46 patients for a median duration of 48 months, found initial differences similar to above but over the entire study the number of patients developing SRE's was no different (52% vs. 56%, $p=0.42$), suggesting that pamidronate effects may become less pronounced during extended treatment [Kraj 2004].

A double blind randomised controlled study compared 3-4 weekly pamidronate 90mg with zoledronic acid 4mg and 8mg in 1648 patients with breast cancer and multiple myeloma over 12 months, extended to 24 months [Rosen 2001, 2003]. The 8mg group was discontinued due to concerns over renal safety. In the 513 patients with multiple myeloma, no significant difference was found between pamidronate and zoledronic acid in number of patients with SREs excluding HCM (49% vs. 47%, p unreported), median time to first SRE including HCM (286 vs. 380 days, $p=0.54$) or risk reduction of developing a SRE over 24 months (risk ratio 0.93, $p=0.59$).

See also under breast cancer [Berenson 2001].

Oral pamidronate has been shown to have no benefit over placebo in a placebo controlled trial [Brincker 1998].

Prostate Cancer

A combined analysis of 2 double blind randomised placebo controlled studies found that 3 weekly IV pamidronate 90mg was no better than placebo for prevention of SRE's (25% in both groups after 27 weeks) [Small 2003].

Bone metastases of any origin

No evidence.

ZOLEDRONIC ACID

Summary

Zoledronic acid reduced the number of patients with SREs, SMR, the risk of developing a SRE and delayed the time to first SRE in breast cancer, prostate cancer, and renal cell carcinoma. In trials involving metastatic solid tumours of any origin, zoledronic acid significantly decreased the risk of SREs and prolonged the time to first SRE compared to placebo, only when HCM was included in the analysis. There are no placebo controlled trials of zoledronic acid in multiple myeloma. Comparative trials have found no significant difference between zoledronic acid and pamidronate in multiple myeloma. In breast cancer there was no difference between the two drugs in the proportion of patients developing a SRE although multiple event analysis reports a 20% reduction in the risk of SRE for zoledronic acid over pamidronate. Subgroup analyses report a risk reduction of 30% for zoledronic acid in patients on hormone therapy and those with lytic lesions but no difference to pamidronate in patients on chemotherapy or with no lytic lesions.

Breast cancer

A randomised, double blind, placebo controlled trial of monthly 4mg zoledronic acid IV over 12 months in 228 patients reported a significant decrease in the percentage of patients with a SRE (29.8% vs. 49.6%, $p=0.03$) and prolonged time to first SRE (median not reached vs. 364 days; $p=0.007$) compared to placebo [Kohno 2005]. In multiple event analysis the risk of SRE was reduced (risk ratio 0.59; $p=0.019$) compared with placebo.

A randomised, double blind, dose response study of 280 breast and myeloma patients treated with either 0.4mg/2mg/4mg zoledronic acid or 90mg pamidronate over a 10 month period reported that the 0.4mg zoledronic acid dose was significantly less effective than pamidronate 90mg (no. of patients with at least 1 SRE 35% vs. 46% ($p<0.05$), median time to first SRE 167 vs. 254 days ($p<0.05$)) but differences between the other zoledronic acid groups and pamidronate were not reported [Berenson, Cancer 2001].

A double blind randomised controlled study compared 3-4 weekly pamidronate 90mg with zoledronic acid 4mg and 8mg in 1648 patients with breast cancer and multiple myeloma over 12 months, extended to 24 months [Rosen 2001, 2003, 2004]. The 8mg group was discontinued due to concerns over renal safety. In the 1130 patients with breast cancer, similar numbers developed at least 1 SRE with both pamidronate and zoledronic acid (49% vs. 46% at 24 months, p unreported). Median time to first SRE, including HCM, was unreported for the breast cancer group as a whole but subgroup analyses found a significant advantage with zoledronic acid over pamidronate for those on hormone therapy (415 vs. 370 days, $p=0.047$) but not those on chemotherapy (349 vs. 366 days, $p=0.826$) and those with lytic metastases (310 vs. 174 days, $p=0.013$) but not with non lytic metastases. The SMR was not significantly different for the breast cancer group as a whole (0.9 vs. 1.49 at 24 months, $p=0.125$) but again subgroup analyses found a significant advantage with zoledronic acid for those on hormone therapy (0.83 vs. 1.37 at 24 months, $p=0.039$) but not chemotherapy and those with lytic metastases (1.2 vs. 2.4 at 12 months, $p=0.008$) but not non lytic metastases ($p=0.904$). Hazard ratios show a 20% risk reduction of developing a SRE for zoledronic acid compared with pamidronate over 12 months (excluding HCM, $p=0.037$), extending to 24 months (including HCM, $p=0.025$).

Subgroup analyses identified these risk reductions to comprise a 30% benefit for zoledronic acid for those on hormone therapy ($p=0.009$) or with lytic metastases ($p=0.01$) but no reduction if on chemotherapy ($p=0.75$) or non lytic lesions (p unreported).

Multiple Myeloma

A double blind randomised controlled study compared 3-4 weekly pamidronate 90mg with zoledronic acid 4mg and 8mg in 1648 patients with breast cancer and multiple myeloma over 12 months, extended to 24 months [Rosen 2001, 2003]. The 8mg group was discontinued due to concerns over renal safety. In the 513 multiple myeloma patients, no significant difference was found between the 2 drugs for number with SREs excluding HCM (49% vs. 47%, p unreported), median time to first SRE including HCM (286 vs. 380 days, $p=0.54$) or risk reduction of a SRE over 24 months (risk ratio 0.93, $p=0.59$).

See also under breast cancer [Berenson 2001].

Prostate cancer

A randomised, placebo controlled trial compared zoledronic acid 4mg or 8mg, 3 weekly, in 643 patients over 15 months [Saad 2002]. The 8mg dose was discontinued due to concerns over renal safety. At least 1 SRE occurred in 44% patients on placebo vs. 33% on zoledronic acid ($p=0.021$). 186 patients entered a 24 month extension phase [Saad 2004]. Reduction in SREs was stable (38% vs. 49%, $p=0.028$). Median time to first SRE was significantly increased with zoledronic acid compared to placebo (488 vs. 321 days, $p=0.009$). Skeletal morbidity rate was 0.77 for zoledronic acid vs. 1.47 for placebo ($p=0.005$). Multiple event analysis showed a 36% reduction in risk of SRE (hazard ratio 0.64, $p=0.002$) for patients treated with zoledronic acid compared with placebo.

Renal cell carcinoma

A retrospective analysis of 74 patients with renal cell carcinoma involved in a randomised placebo controlled trial of zoledronic acid 4mg given 3 weekly for 9 months reported a significant reduction in the proportion of patients with a SRE (37% vs. 74%, $p=0.015$), the mean SMR (2.68 vs. 3.38, $p=0.014$) and prolonged time to first event (median not reached vs. 72 days, $p=0.006$) compared to placebo [Rosen 2003 JCO, Lipton 2003]. A multiple event analysis demonstrated that the risk of developing a SRE was reduced by 61% compared with placebo (hazard ratio of 0.39; $p=0.008$).

Bone metastases of any origin

A double blind, randomised, placebo controlled trial of 3 weekly IV zoledronic acid, 4mg or 8mg, over 9 months extended to 21 months was undertaken in 773 patients with bone metastases secondary to lung cancer (50%) or other solid tumours not including breast and prostate [Rosen 2003 JCO, 2004 Cancer]. The 8mg dose was reduced to 4mg due to concerns over renal safety. Compared with placebo, zoledronic acid decreased the number of patients with at least 1 SRE (38% vs. 47% at 9 months, $p=0.039$), the SMR (1.74 vs. 2.71 at 21 months, $p=0.012$) and prolonged the median time to first SRE (236 vs. 155 days at 21 months, $p=0.009$). Multiple events analysis reported a reduction in risk of a SRE of 27% ($p=0.017$) and 31% ($p=0.003$) after 9 and 21 months respectively. However, all these results were not statistically significant when HCM was excluded from analyses.

SUMMARY OF EVIDENCE FOR PREVENTION OF SRE BY TUMOUR TYPE

BREAST CANCER

- The Cochrane Review of bisphosphonates for breast cancer calculated that, overall, bisphosphonates reduce the risk of developing a SRE (including hypercalcaemia) by 17% (RR 0.83, 95% CI 0.78-0.89, $p < 0.00001$) [Pavlakakis 2005]. Of all the bisphosphonates, both IV and oral, zoledronic acid 4mg was the most effective in reducing the risk of a SRE by 41% (RR 0.59 95% CI 0.42-0.82). Pamidronate 90mg reduced the risk of developing a SRE by 33% (RR 0.77, 95% CI 0.69-0.87) compared with 18% for ibandronic acid 6mg IV (RR 0.82 95% CI 0.67-1.00), 14% for oral ibandronic acid 50mg (RR 0.86 95% CI 0.73 to 1.02) and 16% for oral clodronate 1600mg (RR 0.84 95% CI 0.72-0.98). Women with advanced breast cancer and clinically evident bone metastases treated with bisphosphonates showed significant delays in median time to a skeletal event and a reduction in the skeletal event rate (median reduction 29%, range 14 - 48%). Treatment did not seem to affect survival and in 3 studies of patients with breast cancer without bone metastases treatment did not significantly reduce the incidence of SRE.
- The American Society of Clinical Oncology (ASCO) 2003 guidelines for the role of bisphosphonates in breast cancer recommend the use of pamidronate 90mg IV over 2 hours or zoledronic acid 4mg IV over 15 minutes for women with evidence of bone destruction [Hillner 2003].
- Direct comparative trials report no significant difference between zoledronic acid and pamidronate in the proportion of patients developing a SRE. Multiple events analysis reports a 20% greater reduction in the risk of developing a SRE for zoledronic acid over pamidronate. Subgroup analyses report a risk reduction of 30% for zoledronic acid in patients on hormone therapy and those with lytic lesions but no difference to pamidronate in patients on chemotherapy or with no lytic lesions.

MULTIPLE MYELOMA

- The Cochrane Review of bisphosphonates in multiple myeloma published in 2002 included articles up to 2001. It reported a beneficial effect on prevention of pathological vertebral fractures (OR 0.59 95% CI 0.45-0.78 $p = 0.0001$) [Djubegovic 2002] with a NNT of 10 (95% CI 7-20). There was no effect on mortality, non vertebral fractures or the incidence of hypercalcaemia.
- Recently published ASCO guidelines for bisphosphonates in multiple myeloma recommend pamidronate 90mg over at least 2 hours or zoledronic acid 4mg over at least 15 minutes every 3 to 4 weeks, for any patient with evidence of lytic destruction of bone or compression fracture of the spine from osteopenia [Kyle 2007]. They state clodronate to be an alternative although this is not currently available in the USA.

- Oral clodronate and intravenous pamidronate and zoledronic acid are effective in the prevention of SRE. No effect was observed for intravenous ibandronic acid, although the 2mg dose used in the trial is lower than effective doses used in breast cancer and HCM.
- In the only comparative trial of pamidronate and zoledronic acid that included breast and multiple myeloma patients over 25 months, no significant difference was found between the 2 drugs for the myeloma subgroup [Rosen 2003].

PROSTATE CANCER

- The Cochrane Review of bisphosphonates for advanced prostate cancer calculated a SRE rate of 37.8% and 43.0% for the treatment group and controls respectively. The OR for skeletal events was 0.79 (95% CI 0.62-1.00, p=0.05). There was insufficient data to guide the choice of bisphosphonates or the dose and route of administration.
- Zoledronic acid is the only bisphosphonate that has been shown to reduce SRE in prostate cancer.

MISCELLANEOUS CANCERS

- Few studies have evaluated the use of bisphosphonates in metastatic cancers other than myeloma, breast and prostate cancers but of note:
 - Zoledronic acid significantly reduced the risk of SREs and prolonged median time to first SRE compared with placebo in a trial involving various metastatic cancers, but this did not reach statistical significance when HCM was excluded from the analysis.
 - In renal cell carcinoma, zoledronic acid significantly decreased SREs, and conferred a 61% reduction in the risk of developing a SRE.
- Despite the absence of direct evidence, bisphosphonate therapy may still be appropriate for patients with metastatic bone disease from solid tumours considering the benefit in breast and prostate cancers, which encompass a wide range of osteolytic and osteoblastic lesions [Wu 2007].

BONE PAIN

CLODRONATE

Summary

Clodronate appears to be no better than placebo for bone pain in prostate cancer and multiple myeloma. There is conflicting evidence in breast cancer and in trials investigating bone metastases of any origin. An IV loading dose followed by oral clodronate appears to be inferior to monthly IV pamidronate in the latter group.

Breast cancer

A randomised placebo controlled study of 300mg IV clodronate daily for 7 days in 38 patients, found no difference in pain intensity but a decrease in analgesic use of unreported magnitude over the study period [Martoni 1991]. A randomised placebo controlled trial of 100 patients reported no significant effect on physician rated pain or analgesic consumption with 800mg oral clodronate bd compared to placebo over 2 years [Kristensen 1999]. However, the Cochrane review [Pavlakakis 2006] reports on a French double blind placebo controlled trial of 144 patients, where 1600mg oral clodronate was significantly better than placebo in reducing pain intensity over 12 months ($p=0.01$) although no further details available [Tubiana – Hulin 2001]. In those trials reporting the use of radiotherapy for pain control, no significant difference was found when compared to placebo [Kanis 1996, Paterson 1993].

Multiple Myeloma

In randomised placebo controlled trials no significant difference in pain control, or radiotherapy required for pain, was found for oral clodronate over placebo [Lahtinen 1992, McCloskey 1998] except for prevalence of lower back pain at a single time point of 24 months (10.9% vs. 19.9%, $p<0.05$) [McCloskey 1998].

Prostate cancer

Open label studies of 300mg IV clodronate for 8-14 days followed by oral maintenance have reported a significant reduction in pain e.g. decrease of >5points on a 10 point VAS, in 37-94%, lasting for 7-9 weeks with a response by day 4 [Heidenreich 2001, Vorreuther 1993, Adami 1989, Cresswell 1995]. A similar reduction in pain has been reported with a response rate of 91% using monthly infusions of 1500mg alone, with effects lasting over 6 months [Rodrigues 2004]. However, double blind randomised placebo controlled studies have not replicated these findings: 300mg IV clodronate for 3-5 days then oral maintenance in 57 and 55 patients was no better than placebo [Kylmala 1997, Strang 1997] and oral clodronate was also no better than placebo in 311 patients [Dearnaley 2003].

Bone metastases of any origin

There is conflicting data for oral clodronate from 2 small double blind randomised placebo controlled trials. One investigating doses from 400 – 3200mg in 80 patients found no

difference to placebo over 4 weeks [O'Rourke 1995]. However, another study of 1600mg oral clodronate compared to placebo over 12 months in 55 patients reported a significant improvement in median pain score (-0.9 from 3.2 vs. +0.4 from 4.8 on a 10 point VAS at 12 months, $p=0.03$), evident within the first month [Robertson 1995].

A single infusion of clodronate 600mg has been shown to improve pain by 0.89 from a baseline of approx. 4.2 on a 10 point scale over 1 week compared to placebo in a double blind crossover trial of 24 patients ($p=0.004$) [Ernst 1992]. A similarly designed study of 1500mg or 600mg of IV clodronate compared to placebo in 60 patients found no difference in pain scores but an improvement in dose equivalent of daily morphine (DEDM) by 30mg (mean DEDM 451mg, $p=0.03$) [Ernst 1997].

A comparative trial randomised 43 patients to receive oral clodronate 1600mg alone, IV clodronate 1500mg stat then oral clodronate as above or IV pamidronate 90mg monthly [Jagdev 2001]. No difference was found between the clodronate groups and they were combined for analysis with pamidronate. Mean amalgamated score of pain, analgesia and performance status, marked out of 15, worsened from baseline in the clodronate groups from 7 by approx. 1 – 2.5 but improved in the pamidronate group from 8 by approx. 0.8, significantly different at 3 months ($p<0.01$) and last value ($p<0.05$). 22% of patients responded to clodronate vs. 56% for pamidronate where a response was defined as improvement in score at 2 consecutive time points.

IBANDRONIC ACID

Summary

Oral and intravenous ibandronic acid 6mg significantly improves pain scores by approx 0.3 on a 5 point scale in patients with metastatic breast cancer, maintained over 2 years in placebo controlled trials. In patients with myeloma and breast cancer, ibandronic acid 2mg IV was no different to placebo. Two small open label studies have demonstrated that loading doses of ibandronic acid are of benefit in treating pain in prostate cancer and bone metastases of any origin.

Breast cancer

In a double blind placebo controlled trial of 50mg oral ibandronic acid daily in 564 patients with metastatic breast cancer, bone pain was reduced below baseline throughout the study in the ibandronic acid group, almost reaching its maximum reduction of 0.3 within 8-12 weeks of treatment initiation [Body 2004, Pain]. Bone pain scores increased progressively in the placebo group. At week 96, mean bone pain scores were significantly reduced (on a 5 point scale) in the ibandronic acid group compared with placebo (-0.1 vs. 0.2, $p=0.001$). Mean analgesic use increased in both groups, however the mean increase from baseline to week 96 was significantly less in the ibandronic acid group ($p=0.032$). The mean number of 12 week periods requiring radiotherapy to bone was significantly reduced with ibandronic acid compared with placebo (0.73 vs. 0.98, $p<0.001$).

In a double blind placebo controlled trial of 2mg and 6mg doses of IV ibandronic acid in 466 patients with metastatic breast cancer given 3-4 weekly over 60-96 weeks, mean bone pain (on a 5 point scale) increased from baseline to the end of study in the 2mg and placebo groups but was significantly reduced in patients receiving 6mg ibandronic acid (-0.28 ± 1.11 , $p<0.001$ compared to placebo $+0.21\pm0.09$) [Diel 2004]. Benefits of ibandronic acid on bone pain scores were seen within 6 weeks of therapy. Analgesic requirements increased in all treatment groups with no significant differences between groups.

Multiple Myeloma

A double blind randomised placebo controlled trial of monthly ibandronic acid 2mg IV in 198 patients for 12-24 months reported no significant difference between groups in terms of bone pain or analgesic use [Menssen 2002].

Prostate cancer

25 patients with painful bone metastases from hormone refractory prostate cancer were treated with ibandronic acid 6mg IV daily for 3 days, then 6mg every 4 weeks in an open label uncontrolled study [Heidenreich 2002]. A significant reduction in pain score (on an 11 point VAS) from 6.5 (5-10) to 2.0 (0-4) ($p<0.001$) was achieved in 23 patients, 9 patients were pain free. Analgesic effect was first observed at day 3 (1-5), with a mean duration of analgesic action of 24 weeks (16-43 weeks).

Bone metastases of any origin

18 patients with moderate to severe pain from bone metastases secondary to a variety of tumours were treated with 4mg IV ibandronic acid on 4 consecutive days in an open label study [Mancini 2004]. At baseline all patients had a pain score of 5-6 on an 11 point VAS and were receiving the equivalent of approximately 400mg oral morphine per day. Treatment with ibandronic acid significantly reduced pain scores by approximately 2-3 points within 7 days ($p<0.001$), continuing to day 21 ($p<0.001$) and day 42 ($p<0.05$). Analgesic requirements did not change significantly.

PAMIDRONATE

Summary

Open label studies have reported a significant improvement in pain in all types of cancer. However placebo controlled studies suggest a significant effect for breast cancer patients (approximately 1 point on 9 point scale) but no benefit in prostate and multiple myeloma. Dose response studies suggest that 90mg has a more rapid onset of action than 60mg.

Comparative studies suggest equal efficacy on bone pain with zoledronic acid and superiority to oral clodronate (with or without an IV loading dose). The magnitude of effect is approximately 1-17% on heterogenous pain scales.

Breast cancer

In double blind randomised placebo controlled trials involving 754 patients, 90mg IV pamidronate 3-4 weekly improved bone pain by 0.07 compared to a deterioration of 1.14 for placebo using a 9 point composite score after 24 cycles ($p=0.015$) [Lipton 2000]. In an open label study of IV pamidronate 60mg fortnightly in 69 patients pain improved after 1 month (49 to 39 on a 100 VAS, $p=0.02$), and at the last visit (49 to 36, $p=0.001$, median duration treatment 4.5 months) [Tyrrell 1995]. A randomised study in 61 patients comparing different doses using a 9 point composite score reported that pamidronate 90mg IV monthly significantly decreased mean pain scores after 2 weeks (from 6.1 by approx. 2, $p<0.05$) as did 60mg monthly after 6 weeks (from 5.4 by approx. 3, $p<0.05$) [Glover 1994].

A randomised double blind dose response study of 280 breast and multiple myeloma patients treated with either 0.4mg/2mg/4mg zoledronic acid or 90mg pamidronate over 10 months showed that among the 232 patients with pain at study entry, a decrease in pain score was reported for a greater proportion of patients in the 4mg zoledronic acid group (67%) than in the 0.4mg and 2mg zoledronic acid groups and the pamidronate group (51%, 48% and 50% respectively, not statistically significant). The mean change from baseline on a 0-10 scale was -0.3/-0.6/-0.7/-0.1 for the 0.4mg/2mg/4mg zoledronic acid/90mg pamidronate groups (p unreported) [Berenson, Cancer 2001].

A randomised double blind study compared 4mg zoledronic acid with 90mg pamidronate given every 3-4 weeks for 12 months in 1648 patients with breast cancer (69%) or myeloma with bone metastases [Rosen 2001, Cancer Journal]. In patients with pain at baseline (scale 0-10), 53-69% experienced a reduction in pain but no significant difference was found between the two drugs. Pain decreased in the first 3 months and remained stable at approx. 0.5 below baseline (mean baseline score 3, p value unreported).

In a randomised placebo controlled trial in 144 patients, oral pamidronate, 300mg daily significantly improved bone pain compared to placebo (approximately 0.5 from 1.07 on 3 point scale, $p=0.007$) after 3 months of treatment but then pain scores increased in both groups, slower in the treatment group [Val Holten-Verzantvoort 1991].

Multiple Myeloma

A randomised controlled trial of 46 patients where 60mg monthly IV pamidronate was added to chemotherapy treatment found that an amalgamation of pain score, performance

status and analgesic use decreased from baseline in both groups. This was significantly better in those receiving pamidronate (magnitude of response unreported, $p < 0.05$) but the effect was lost after 8 months of treatment [Kraj 2000, 2004]. Pamidronate 90mg IV monthly significantly decreased pain score from baseline but was only significantly different to placebo at one time point over 9 months in a double blind randomised placebo controlled trial of 392 patients [Berenson 1996]. Analgesic use increased with placebo but not with pamidronate (p “significant” but unreported).

See under breast cancer for comparison with zoledronic acid.

Prostate Cancer

A dose finding study in 58 patients reported a significant reduction in bone pain within 12 weeks of approx. 2-3 in a 9 point composite score for pamidronate 90mg monthly and 30mg fortnightly but not 60mg monthly (p ns) [Lipton 1994]. In a double blind randomised placebo controlled study of 350 patients, both 90mg pamidronate IV 3 weekly and placebo did not significantly affect pain measured by the BPI after 9 or 27 weeks (baseline 4.3 and 4.5 respectively on 10 point scale). Oral morphine equivalent increased similarly in both groups [Small 2003].

Thyroid Cancer

In 10 patients given monthly IV 90mg Pamidronate a significant decrease in bone pain after 3 months was reported (54 to 37 on 100 point VAS, $p = 0.0052$) [Vitale 2001].

Bone metastases of any origin

Open label studies of IV pamidronate report significant reductions in pain of approximately 15-33% using various pain scales [Cascinu 1996, 1998, Koeberle 1999, Purohit 1994]. Dose comparative studies suggest that 60 mg and 90mg are of equal efficacy [Koeberle 1999] but it has been reported that a significant response is seen faster with 90mg than 60mg (6 weeks vs. 9 weeks) [Cascinu 1998].

A double blind placebo controlled trial of 120mg in 48 patients reported a 15% difference in pain score between the 2 groups 4 weeks after a single treatment (amalgamated score of pain, performance status and analgesic use, $p = 0.03$). 23% responded after 1 treatment of bisphosphonate and 43% after 2 (>20% improvement for 2 consecutive assessments) [Vinholes 1997 Ann Onc]

A comparative trial randomised 43 patients to receive oral clodronate 1600mg alone, IV clodronate 1500mg stat then oral clodronate as above or IV pamidronate 90mg monthly [Jagdev 2001]. No difference was found between the clodronate groups and they were combined for analysis with pamidronate. Mean amalgamated score of pain, analgesia and performance status, out of 15, worsened from baseline in the clodronate groups from 7 by approx. 1 – 2.5 but improved in the pamidronate group from 8 by approx. 0.8, significantly different at 3 months ($p < 0.01$) and last value ($p < 0.05$). 22% of patients responded to clodronate vs. 56% for pamidronate (an improvement in score at 2 consecutive time points).

ZOLEDRONIC ACID

Summary

In a randomised placebo controlled trial of patients with breast cancer, zoledronic acid was effective in the management of bone pain but difference to placebo unreported. In randomised placebo controlled studies of patients with prostate cancer, 4mg zoledronic acid proved no better than placebo at 15 months but was significantly better for bone pain at 24 months. The 15 month phase was then reanalysed and showed a significant clinical benefit in managing bone pain. In a variety of other tumours there were no differences in bone pain following treatment with zoledronic acid compared with placebo.

Comparative studies suggest equal efficacy on bone pain score of 4mg IV zoledronic acid with 90mg IV pamidronate. The magnitude of effect is approximately 7-17% on heterogenous pain scales in these studies.

Breast cancer

A double blind randomised, placebo controlled trial of 228 patients compared monthly 4mg zoledronic acid IV over 12 months with placebo [Kohno 2005]. Throughout the study the placebo group showed either no change or an increase from baseline in their mean pain score (BPI composite pain scores, 0-10), whereas the zoledronic acid group had a statistically significant decrease from baseline at every point throughout the study, except for week 2 ($p < 0.05$). Significance between placebo and treatment unreported.

In an uncontrolled open label study of 4mg zoledronic acid every 3-4 weeks for 12 infusions in 312 patients, mean pain score (0-10) decreased from 3.3 ± 2.2 at baseline to 2.6 ± 2.3 at the end of treatment, p value unreported [Carteni 2006]. Of the 247 patients with pain at baseline 58% had a decrease in pain score, 19% had no change from baseline and 23% had an increase in pain.

A randomised, double blind, dose response study of 280 breast and myeloma patients treated with either 0.4mg/2mg/4mg zoledronic acid or 90mg pamidronate over 10 months showed that among the 232 patients with pain at study entry, a decrease in pain score was reported for a greater proportion of patients in the 4mg zoledronic acid group (67%) than in the 0.4mg and 2mg zoledronic acid groups and the pamidronate group (51%, 48% and 50% respectively, not statistically significant) [Berenson, Cancer 2001]. The mean change from baseline on a 0-10 scale was -0.3/-0.6/-0.7/-0.1 for the 0.4mg/2mg/4mg zoledronic acid/90mg pamidronate groups (p unreported).

A randomised, double blind study compared 4mg zoledronic acid with 90mg pamidronate given every 3-4 weeks for 12 months in 1648 patients with breast cancer (69%) or myeloma with bone metastases [Rosen 2001, Cancer Journal]. Among patients with pain scores > 0 at baseline (scale 0-10), 53-69% experienced a reduction in pain but no significant difference was found between the two treatment groups. Pain decreased in the first 3 months and remained stable at approx. 0.5 below baseline (mean baseline score 3, p value unreported).

Multiple Myeloma

See under breast cancer for comparison with pamidronate.

Prostate cancer

The effect of zoledronic acid 4mg or 8mg given 3 weekly was assessed in a randomised, placebo controlled trial over 15 months in 208 patients. [Saad 2002]. The 8mg dose was subsequently discontinued due to concerns over renal safety. Mean pain scores (0-10) increased from baseline (approximately 2 ± 2) in both groups at every 3 month interval except at 3 months, where the 4mg zoledronic acid group had a slight reduction from baseline. The mean increase from baseline in pain score at 15 months was 0.88 for placebo vs. 0.58 zoledronic acid ($p=0.134$). 186 patients entered into an additional 9 month extension phase which 122 patients completed. There was a significant difference in change in mean pain from scores from baseline in favour of zoledronic acid compared with placebo at 21 (0.56 vs. 1.07, $p=0.014$) and 24 (0.58 vs. 1.05, $p=0.024$) months. [Saad 2004].

A reanalysis of the above 15 month study was performed following a recommendation in the Cochrane Review of Bisphosphonates for the Relief of Pain against the use of mean pain scores and advocating using the proportion of patients with pain relief [Weinfurt 2006]. At all 11 assessment points, patients randomised to zoledronic acid had a 33% chance of having a favourable response (defined as a decrease of ≥ 2 on a 10 point scale), compared with a 25% chance for placebo ($p=0.036$).

In a case series of 24 patients treated with 4mg zoledronic acid over a 3 month period, 18 were considered responders (VAS reduced to <4) [Fulfaro 2005]. Mean baseline VAS was 7.8 ($SE \pm 0.29$) reduced to 3.6 ($SE \pm 0.3$, $p=0.0005$) after 1 month, and 3.1 ($SE \pm 0.4$, $p=0.0005$) after 3 months.

Bone metastases of any origin

In a placebo controlled trial of 773 patients with bone metastases from lung and other solid tumours, excluding breast and prostate, bone pain scores and analgesic use increased from baseline to month 9 in both placebo and zoledronic acid groups [Rosen 2003, J Clin Oncol].

An open label study of 4mg zoledronic acid given every 3-4 weeks for 6 treatments to 638 patients with myeloma, breast and prostate cancer reported a statistically significant reduction in mean pain scores (0-100) compared with baseline (33.3 baseline vs. 27.2 after 6 doses, $p<0.05$) [Vogel 2004]. Patients with myeloma and breast cancer experienced a significant reduction in pain scores from baseline in at least 4 out of 6 visits, whereas patients with prostate cancer experienced a significant reduction at visit 2 only.

Community vs. hospital infusion of 4mg zoledronic acid in 101 patients with a variety of different tumours was compared in a 9 month crossover study [Wardley 2005]. There were no differences in renal or other toxicity between the 2 settings but patients were significantly more satisfied when the infusion was given in the community. Over the 10 months observation period, treatment with zoledronic acid resulted in a non significant improvement in composite BPI score compared with baseline (mean -0.5, $p=0.077$). However, there were significant reductions in worst pain ($p=0.008$), average pain in the last 7 days ($p=0.039$) and interference with general activity ($p=0.001$).

SUMMARY OF EVIDENCE FOR PAIN BY TUMOUR TYPE

Comparison of bisphosphonates across studies is difficult because of differences in patient populations and the methods used for assessing bone pain and analgesic use.

Open label studies of most bisphosphonates report a significant reduction in pain.

The trials included below are randomised placebo controlled trials and Cochrane Reviews of such evidence.

BREAST CANCER

Bone pain in breast cancer is significantly reduced by intravenous zoledronic acid (4mg), pamidronate (90mg), ibandronic acid (6mg) and oral ibandronic acid (50mg) and pamidronate (300mg). There is conflicting evidence for the use of oral clodronate. A small study of low dose intravenous clodronate reported no difference in pain but an improvement in analgesia of an unspecified amount.

Comparative studies suggest that intravenous zoledronic acid and pamidronate are of equal efficacy.

MULTIPLE MYELOMA

The Cochrane Review of bisphosphonates in multiple myeloma published in 2002 but including articles up to 2001 demonstrated a beneficial effect of bisphosphonates on amelioration of pain (OR 0.59 95% CI 0.46-0.76, $p=0.00005$) with a NNT of 11 (95% CI 7-28) [Djubegovic 2002].

Both oral clodronate and 2mg intravenous ibandronic acid (note low dose) are no better than placebo. For intravenous pamidronate 90mg pain scores are no different to placebo but analgesic requirements decreased by an unspecified amount.

Comparative studies suggest that intravenous zoledronic acid and pamidronate are of equal efficacy.

PROSTATE CANCER

The Cochrane Review of bisphosphonates for advanced prostate cancer calculated a pain response rate of 27.9% and 21.1% for the treatment group and control group respectively [Yuen 2006]. The OR for pain response was 1.54 (95% CI 0.97 to 2.44, $p=0.07$) showing a trend of improved pain relief in the bisphosphonate group, although this was not statistically significant.

Oral clodronate and intravenous clodronate and pamidronate (90mg) are no better than placebo in improving pain scores. Zoledronic acid (4mg) was significantly better than placebo at 24 months, though not at 15 months. In post hoc analysis zoledronic acid confers an 8% higher chance of improvement on a pain scale of at least 2 out of 10 compared to placebo.

BONE METASTASES OF ANY ORIGIN

120mg intravenous pamidronate significantly improves pain by 15%. There is conflicting evidence for the efficacy of oral and intravenous clodronate. Zoledronic acid is no better than placebo.

Comparative studies suggest that pamidronate 90mg is better than intravenous clodronate followed by oral maintenance.

CONCLUSIONS

- The Cochrane Review of bisphosphonates for the relief of pain secondary to bone metastases, published in 2002 and including articles up to 2000, concluded benefits for the treatment group. They found a NNT at 4 weeks of 11 (95% CI 6-36) and at 12 weeks of 7 (95% CI 5-12) [Wong 2002]. The NNH was 16 (95% CI 12-27) for discontinuation of therapy. The authors stated that there was insufficient evidence to recommend bisphosphonates for immediate effect, as first line therapy, or to define the most effective bisphosphonate overall and for different primary neoplasms. They concluded that bisphosphonates should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases.
- We also conclude that there is little evidence to suggest the use of one bisphosphonate over another with regards to efficacy although a small study suggests clodronate to be less effective than pamidronate. Beyond this the choice of bisphosphonate should be governed by local cost in terms of both drug and time / service provision.
- The underlying type of malignancy should not affect the type of bisphosphonate used if for pain alone.
- Studies should not be compared due to the use of heterogeneous pain scales. In individual studies however the magnitude of pain response is small e.g. in breast cancer; 0.3 on 5 point scale (oral ibandronic acid), 0.5 on 5 point scale (6mg intravenous ibandronic acid), 1.2 on 9 point scale (90mg intravenous pamidronate).
- More than a single treatment may be required to improve pain in some patients [Vinhols 1997 Ann Oncol]
- Lack of response to 2 treatments may be an indication to discontinue [Mannix 2000].

RENAL IMPAIRMENT

Zoledronic acid, clodronate and pamidronate have all been shown to be associated with renal impairment but with differing mechanisms of action. Incidence varies between drugs and studies.

Risks factors for developing renal impairment during bisphosphonate treatment

The nephrotoxic potential of bisphosphonates is reduced by longer infusion times. In early studies of zoledronic acid, 4mg was initially infused over 5 minutes in 50ml. The infusion times were later increased to 15 minutes, and infusion volume to 100ml because of concerns over renal safety [Rosen 2001].

Many palliative care patients have pre-existing renal impairment and/or are taking nephrotoxic drugs. Other risk factors would appear to be increasing age, increasing number of bisphosphonate infusions, hypercalcaemia, prior exposure to bisphosphonates and a diagnosis of multiple myeloma. In cases of pre existing renal impairment the dose of bisphosphonate should be modified according to the drug SPC which contain clear guidance and are summarised on the next page.

Onset of renal impairment

Renal impairment can occur at any time during the course of treatment. Studies of zoledronic acid report a median onset of 2 months following first infusion (range 1-242 days). In 25% of cases this occurred after a single infusion [Chang 2003].

CONCLUSIONS

- Renal impairment has been associated with bisphosphonates.
- Clodronate, pamidronate and zoledronic acid appear to be associated with greatest risk of renal toxicity. Studies have so far shown ibandronic acid to have a renal safety profile comparable to placebo.
- Risk factors include coexisting renal impairment, concomitant use of nephrotoxic drugs, shorter infusion time, increasing age, increasing number of bisphosphonate infusions, hypercalcaemia, prior exposure to bisphosphonates and patients with multiple myeloma.
- The SPC's for all bisphosphonates recommend that renal function is monitored periodically throughout treatment. For Aredia® and zoledronic acid this is specified as prior to each infusion. As the dose prescribed and infusion time of each drug should be modified according to the degree of renal impairment, we recommend that renal function is checked prior to each infusion for every bisphosphonate.

SUMMARY OF RECOMMENDED DOSE ADJUSTMENTS IN RENAL IMPAIRMENT

SKELETAL RELATED EVENTS*

Drug	Creatinine clearance (ml/min)					
	< 10	10 - 30	30 - 39	40 - 49	50 - 60	> 60
Zoledronic acid**	Not recommended		3.0mg	3.3mg	3.5mg	4.0mg
Clodronate Po	Contra indicated	50% of normal dose	Normal dose			
Pamidronate	Aredia®; not recommended		Aredia®; normal dose, max. infusion rate of 20mg/hr.			
	Generic pamidronate; normal dose, max. infusion rate of 20mg/hr for all levels of renal impairment.					
Ibandronic acid IV	2mg in 500ml over 1 hr		6mg in 500ml over 1 hr		6mg in 100ml over 15 min	
Ibandronic acid po	50mg once weekly		50mg od			

* taken from individual drug SPC

** Following initiation of zoledronic acid in clinical trials, if serum creatinine increased by >44 from a baseline of <124µmol/l, or >88 from a baseline of >124µmol/l then treatment was withheld and only recommenced when the creatinine level returned to within 10% of baseline.

HYPERCALCAEMIA*

Drug	Creatinine clearance (ml/min)	
	< 10	10 - 80
Zoledronic acid**	No dose adjustment if creatinine <400µmol (please see below).	
Pamidronate	Ca >4, 60mg Ca <4, 30mg ***	Max. infusion rate 20mg / hr (Aredia® not recommended <30ml/min) Ca < 3.0, 15 – 30mg Ca 3.0 to 3.5, 30 – 60mg Ca 3.5 to 4.0, 60 – 90mg Ca > 4.0, 90mg
Ibandronic acid	Ca >3, 4mg; Ca <3, 2mg	

* taken from individual drug SPC

** Zoledronic acid treatment for hypercalcaemia in patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 µmol/l were excluded. The SPC states that no dose adjustment is necessary in hypercalcaemic patients with serum creatinine < 400 µmol/l. However, in clinical practice the use of a potentially less nephrotoxic bisphosphonate is recommended (e.g. pamidronate or ibandronic acid).

*** taken from Renal Drug Handbook guidance

HYPOCALCAEMIA

Hypocalcaemia can occur during treatment with any bisphosphonate [Johnson 1998, Champallou 2003, Carteni 2006, Body 2004]. The incidence of asymptomatic hypocalcaemia varies between bisphosphonates and studies but may be as frequent as >1/10. Symptomatic hypocalcaemia (paraesthesia, tetany, seizures) is very rare. The risk of hypocalcaemia appears to be greater with more potent bisphosphonates e.g. zoledronic acid. The SPCs for all bisphosphonates recommend that calcium levels are monitored but are not specific with regards to timing and frequency. It is also recommended that phosphate and magnesium levels are monitored during zoledronic acid and ibandronic acid treatment.

Risk factors for developing hypocalcaemia

A greater risk of developing hypocalcaemia during bisphosphonate treatment is associated with [Peter 2004];

Conditions which impair the normal compensatory mechanism of parathyroid hormone:

- Hypoparathyroidism (e.g. thyroid or parathyroid surgery, radiotherapy to the neck)
- Vitamin D deficiency (renal impairment, bowel surgery, phenytoin, lack of sunlight exposure, malabsorption, dietary factors)
- Hypomagnesaemia

Concomitant use of:

- Aminoglycosides
- Loop diuretics
- IFN- α

Onset of hypocalcaemia

Hypocalcaemia can occur at any time, from a few days after first treatment to several months after repeated infusions but may occur earlier with more potent bisphosphonates. In reported cases of symptomatic hypocalcaemia, median time to onset was 6 days for zoledronic acid and 9 days for pamidronate [Maalouf 2006].

Monitoring

Patients receiving bisphosphonates should be informed of the symptoms of hypocalcaemia, although early symptoms such as lethargy and low mood may also be manifestations of the underlying disease. It is recommended that calcium levels are monitored intermittently during treatment, therefore levels could be checked prior to each infusion at the same time as renal function. An additional nadir calcium level 4-11 days post infusion (dependant on drug, see hypercalcaemia section) could be checked in patients who describe possible symptoms of hypocalcaemia.

Calcium / vitamin D supplementation

Supplementation with oral calcium 500mg and 400 IU of vitamin D daily (Calcichew D3 Forte 1 tablet) is a requirement for all patients prescribed zoledronic acid and

recommended for those at high risk of hypocalcaemia prescribed pamidronate or ibandronic acid.

Patients should be reminded that for maximal absorption supplements should be taken more than 1 hour after eating or consuming a milky drink, and separately from other medications.

There are no guidelines regarding the level at which to commence supplementation in asymptomatic hypocalcaemia. It would seem sensible to consider supplements for those patients with any level of hypocalcaemia prior to bisphosphonate infusion, although tablet burden should be taken into account. There are also no clear guidelines regarding the level of hypocalcaemia that warrants withholding bisphosphonate therapy. However, communication with a local Endocrinologist with a special interest in calcium metabolism suggests that bisphosphonates should be withheld when serum calcium falls below 2.0mmol/l.

CONCLUSIONS

- Asymptomatic hypocalcaemia during treatment with bisphosphonates is common but symptomatic hypocalcaemia is rare.
- Risk factors include hypoparathyroidism, vitamin D deficiency, hypomagnesemia and concomitant use of certain drugs.
- Calcium and Vitamin D supplements should be prescribed for all patients prescribed zoledronic acid and should be considered for any patient with risk factors for developing hypocalcaemia during treatment with bisphosphonates.
- Monitoring of serum calcium is suggested during treatment with bisphosphonates (e.g. prior to infusion when renal function is already being monitored). Bisphosphonate treatment should be withheld if serum calcium is below 2.0mmol/l. For asymptomatic patients with a serum calcium <2.2 but >2mmol/l treatment should continue but calcium supplements should be considered. Patients should be warned of the symptoms of hypocalcaemia and if any concern a nadir calcium level could be checked 4-11 days after infusion (dependant on drug, see hypercalcaemia section).

OSTEONECROSIS OF THE JAW

Background

Osteonecrosis of the jaw (ONJ) is an uncommon but potentially serious complication of bisphosphonates defined as the persistence of exposed bone in the oral cavity after adequate treatment for 6 weeks, in the absence of metastatic disease and without previous radiation therapy to the affected area. Incidence in cancer patients treated with bisphosphonates varies according to the specific bisphosphonate, dose, duration of treatment and dental history; however a recent systematic review reported an incidence of 6-10% [Woo 2006].

Pathophysiology

The mechanisms and pathophysiology of ONJ remain unclear, although a number of theories have been proposed [Migliorati 2006]. Bisphosphonates inhibit osteoclast-mediated resorption of bone. After administration approximately half the drug is deposited on the bone surface and half is excreted in the urine without undergoing metabolism. The deposited drug is internalised by osteoclasts, which results in the suppression of bone remodelling and increased mineralisation of bone.

While this mechanism may have some benefits, the suppression of bone remodelling prevents the normal restorative processes that occur when microfractures in bone are present. Such microfractures occur commonly in the jaw during daily activity. Since osteoclastic activity is inhibited by bisphosphonates, no bone resorption takes place after the formation of microfractures, leading to accumulation of non-vital bone (that is usually absorbed by osteoclasts). It has also been suggested that in patients receiving chemotherapy, immunosuppression and oral infection may exacerbate this process. Also, given the possibility of an antiangiogenic effect of bisphosphonates, changes in intraosseous blood supply and blood flow could also contribute to the development of osteonecrosis.

Risk factors

The most important predisposing factors for the development of ONJ is the type and total dose of bisphosphonate, and history of trauma, dental surgery or dental infection. In a recent systematic review of 368 cases of ONJ, 60% occurred after a tooth extraction or other dentoalveolar surgery and the remaining cases occurred spontaneously [Woo 2006]. 94% were treated with intravenous bisphosphonates (primarily pamidronate and zoledronic acid), and most patients (85%) had multiple myeloma or metastatic breast cancer. The remaining patients were taking oral bisphosphonates for osteoporosis or Paget's disease. The risk of ONJ increases over time, probably because of the long half life of these drugs. The same systematic review by Woo states that although oral lesions may develop after as few as 4 months, median duration of drug use ranged from 22-39 months (mean 9-14 months). The cumulative hazard was 1% within the first year and 21% at 3 years of treatment with zoledronic acid. In contrast, it was 0% for the first year and 4% in the third year for patients receiving pamidronate.

Other possible risk factors of ONJ include concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co morbid conditions such as anaemia, coagulopathies, infection and pre-existing oral disease [Migliorati 2005].

Clinical features

The typical presentation is a painful, non healing ulcer or areas of yellow-white, hard bone with smooth or ragged borders. Radiographic examination may be negative in early cases. Advanced cases show a moth-eaten, poorly defined radiolucency. 65% cases involve the mandible alone, 26% maxilla alone and 9% both [Woo 2006]. Cultures of exposed bone may identify *Actinomyces* species, however these organisms are a common component of dental plaque.

Management

No effective treatments have been established in prospective studies. The best approach to bisphosphonate-associated ONJ is prevention. All cancer patients should receive a comprehensive dental examination and appropriate preventative dentistry before bisphosphonate therapy. Active oral infections should be treated, and sites at high risk for infection should be eliminated. If the patient requires invasive dental procedures such as tooth removals, commencement of bisphosphonate therapy should be delayed to allow sufficient time for recovery and healing [Marx 2005]. While on therapy, patients should maintain excellent oral hygiene with regular dental reviews but avoid invasive dental procedures if possible.

Prompt referral to a dentist trained in oral medicine, or a maxillofacial surgeon is recommended for patients with symptoms of ONJ. Conservative management includes culture of any lesions, prescribing antibiotics as appropriate, and recommending an antiseptic oral rinse that contains chlorhexidine. Extensive resection has not consistently resulted in wound closure and may lead to worsening or progression of disease [Migliorati 2005].

Currently there is no evidence to support or oppose discontinuation of bisphosphonate therapy once ONJ develops or before required surgery. Because of the long half life of bisphosphonates, recovery of osteoclast function and bone turnover after drug withdrawal may be too gradual for this measure to have any clinical significance. However the removal of any antiangiogenic effects of the drug may play a role in healing and therefore stopping the drug is recommended [Van den Wyngaert 2007].

CONCLUSIONS

- ONJ is a rare condition but has a potentially high impact on quality of life for patients.
- The risk for developing ONJ increases with dose and duration of treatment with bisphosphonates.
- Zoledronic acid appears to be associated with a higher incidence than any of the other IV bisphosphonates, and IV use is more of a risk than oral use.

- Local trauma, including tooth extraction and infection are important predisposing factors. Therefore it is recommended that before initiating non urgent therapy patients should be referred for dental review to optimise oral hygiene. Patients receiving bisphosphonates should be informed of the need to maintain good oral hygiene during treatment, including regular dental check ups.
- Prompt referral to a dentist trained in oral medicine, or a maxillofacial surgeon is recommended for any patient with symptoms suggestive of ONJ.
- There is a lack of prospective, randomised outcome studies once ONJ develops. Antimicrobial rinses, antibiotics, analgesia and surgical debridement are possible treatment options. Once ONJ is established it is advisable to discontinue bisphosphonates until the lesions resolve, even though doing so may not actually promote healing of the lesions. Bisphosphonates should only be reinstituted only if clinically indicated and after careful consideration of risks and benefits.

PRACTICAL CONSIDERATIONS

COST

The widespread use of bisphosphonates will have a major impact on pharmaceutical expenses. Costs will vary depending on the duration of use, the specific bisphosphonate used, and mode of delivery (IV vs. oral).

Pamidronate's longer infusion time compared with zoledronic acid and intravenous ibandronic acid is associated with increased time cost to both patient and provider. However in many centres the absolute cost of zoledronic acid or ibandronic acid may outweigh the potential time benefits.

COMMENCING AND STOPPING TREATMENT

There are few criteria for when bisphosphonate treatment should start and stop.

The ASCO 2003 guidelines for the role of bisphosphonates in breast cancer state that the presence or absence of bone pain should not be a factor in initiating bisphosphonates [Hillner 2003]. They suggest that once initiated, bisphosphonates should be continued until evidence of substantial decline in a patient's performance status. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.

ASCO guidelines for the role of bisphosphonates in multiple myeloma recommend pamidronate or zoledronic acid for any patient with evidence of lytic destruction of bone or compression fracture of the spine from osteopenia [Kyle 2007]. They state clodronate to be an alternative although this is not currently available in the United States. Bisphosphonate treatment should continue for a period of 2 years. At 2 years, physicians should seriously consider discontinuing bisphosphonates in patients with responsive or stable disease as they state there are no trials to demonstrate a benefit of bisphosphonates in myeloma after a 2 year period. Further use is at the discretion of the treating team. For those in whom the drug is withdrawn, the drug should be resumed on relapse with a new SRE.

Longer duration of treatment appears to be a risk factor for developing adverse events such as hypocalcaemia, renal impairment and osteonecrosis of the jaw.

In the future using bone markers may help to individualize and optimize treatment.

ROUTE

Optimal route should be determined on an individual basis and depending on underlying disease. Intravenously administered bisphosphonates are currently the first choice of treatment, as their clinical benefits are well known. Patients receiving IV chemotherapy can be given an IV bisphosphonate at the same time. However for other patients, monthly infusions may reduce QOL as they require frequent hospital visits, regular IV access and blood tests and have lengthy administration times. Oral bisphosphonates may be an alternative in patients with breast cancer or myeloma.

SIDE EFFECTS

Side effect profiles of orally and intravenously administered bisphosphonates are different. Gastrointestinal side effects are a particular issue for orally administered drugs and they are required to be taken on an empty stomach. Following intravenous administration, side effects are usually self limiting flu like reactions (30-55%) and include low grade fever, arthralgia/myalgia, nausea, and increased bone pain. Symptoms occur within 24 hours of first infusion, persist for less than 48 hours and usually diminish or disappear by the second or third infusion. These symptoms may be less common with ibandronic acid [Olson 2007]. Management includes paracetamol, fluids and antiemetics [Wu 2007].

MONITORING

Monitoring of renal function and electrolytes is a requirement during treatment with all bisphosphonates. The SPC states that for zoledronic acid renal function is monitored prior to each infusion. However as the dose prescribed and infusion time of each drug should be modified according to the degree of renal impairment, we recommend that renal function is checked prior to each infusion of bisphosphonate. While checking renal function it would seem relatively straightforward to check serum calcium. Regular monitoring may avoid unnecessary supplementation with Calcium/Vitamin D. (See page 36).

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APPENDIX 1 - ABBREVIATIONS

ASCO	American Society of Clinical Oncology
BNF	British National Formulary
CrCl	Creatinine clearance
CSC	Corrected serum calcium
DEDM	Dose equivalent of daily morphine
HCM	Hypercalcaemia of malignancy
LTHT	Leeds Teaching Hospitals' Trust
ns	not significant
NSAIDS	Non steroidal anti-inflammatory drugs
ONJ	Osteonecrosis of the jaw
PTHrP	Parathyroid hormone related protein
QOL	Quality of life
RCT	Randomised controlled trial
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SMPR	Skeletal morbidity period rate
SMR	Skeletal morbidity rate
SPC	Summary of product characteristics
SRE	Skeletal related events

APPENDIX 2 - GRADING OF EVIDENCE

Evidence identified as relevant to this review was graded according to published criteria developed for the purpose of creating clinical guidelines. A summary of these criteria is included below.

<u>Level</u>	<u>Criteria</u>
1++	High-quality meta-analyses, systematic reviews of RCTs, <u>OR</u> RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, <u>OR</u> RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, <u>OR</u> RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies <u>OR</u> high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Nonanalytic studies, e.g. case reports, case series
4	Expert opinion

From: Keeley PW. Clinical guidelines. *Palliat Med* 2003; **17**: 368-74

BISPHOSPHONATES FOR BONE PAIN / SKELETAL RELATED EVENTS

ADMINISTRATION RECORD

Name:
D.O.B:
Hospital/NHS No:
Address:

Allergies	
Initials	Date

Diagnosis

Indication for Bisphosphonate: Bone Pain ☐ Prevention of skeletal related events ☐

Bisphosphonate initiated by: Oncologist ☐ Palliative Medicine ☐

Is the patient taking calcium supplements? Y / N (See flow chart overleaf for guidance)

Does the patient need a dental review before bisphosphonate treatment? Y / N

Information leaflet offered to patient? Y / N

				PRESCRIPTION					ADMINISTRATION								
Date of blood test	Corrected Serum Calcium	Serum Creatinine	GFR	SEE BACK OF CHART FOR PRESCRIBING ADVICE	Date	Diluent	Volume	Drug	Dose	Duration	Route	Doctor's signature	Fluid Batch and expiry	Drug Batch and expiry	Start time	Set up by: 2 RN to sign	Stop time

BISPHOSPHONATES FOR BONE PAIN & SKELETAL RELATED EVENTS

- The use of bisphosphonates can be complicated by **hypocalcaemia** and **renal impairment**, which can occur at any time following the commencement of treatment. As such **renal function and serum calcium should be tested before** administration and the dose and duration of bisphosphonate should be adjusted accordingly.

NORMAL RENAL FUNCTION

Drug	Dose	Duration of infusion	Frequency	Hypocalcaemia nadir
Zoledronic acid	4mg in 100ml 0.9% Saline	At least 15 min	3-4 weekly	Approximately day 6-11
Pamidronate	90mg in 0.9% Saline (Concentration should not exceed 60mg/250ml)	Maximum infusion rate 1mg/min (Note ASCO guidelines recommend ≥ 2 hours)	3-4 weekly	Approximately day 7
Ibandronic acid	6mg in 100ml 0.9% Saline	At least 15 min	3-4 weekly	Day 5

RENAL IMPAIRMENT

Prescribing should be modified according to creatinine clearance as calculated by the Cockcroft Gault Equation:

$$\text{Estimated GFR (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{wt (kg)} \times [0.85 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/litre)} \times 0.814}$$

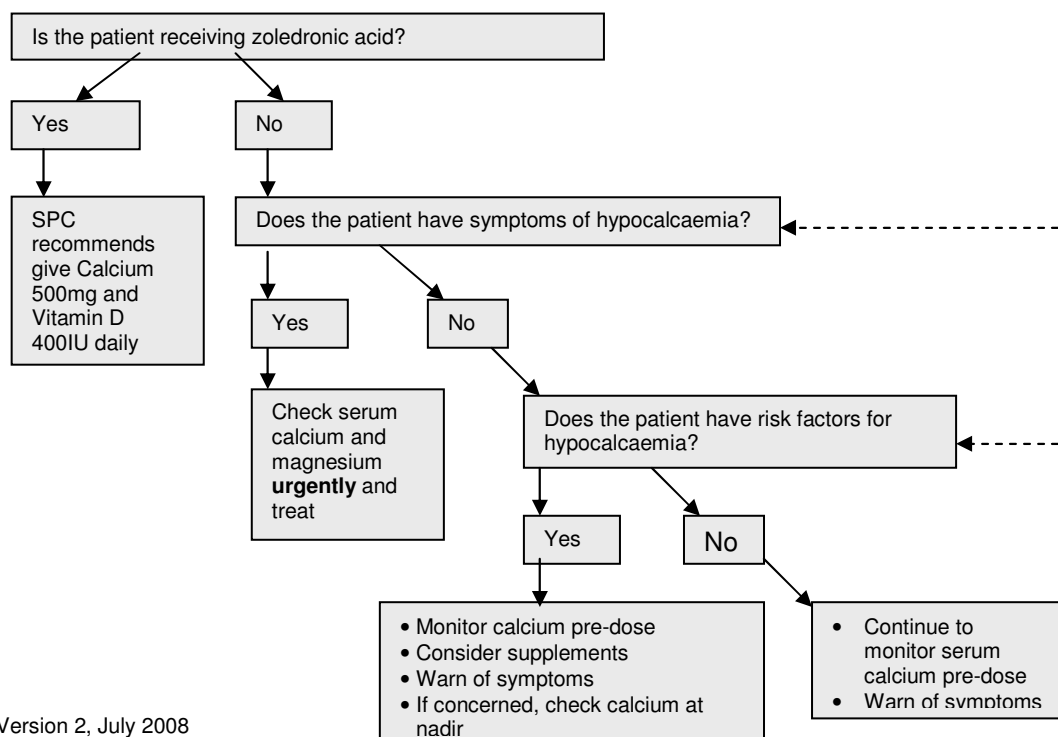
Drug	Creatinine clearance (ml/min)					
	<10	10 -30	30-39	40-49	50-60	>60
Zoledronic acid*	Not recommended		3.0	3.3	3.5	4.0
Pamidronate	Aredia not recommended		Aredia: normal dose, max. infusion rate 20mg / hr			
	Generic pamidronate: normal dose, max. infusion rate of 20mg/hr for all levels of renal impairment					
Ibandronic acid	2mg in 500ml over 1 hour		6mg in 500ml over 1 hour		6mg in 100ml over 15 min	

- In trials a creatinine increase >44 from <124 or >88 from >124 $\mu\text{mol/l}$ led to treatment cessation until returned to within 10% of baseline

HYPOCALCAEMIA

- Bisphosphonate treatment should be withheld if corrected serum calcium is below 2.0mmol/l.
- For asymptomatic patients with a corrected serum calcium <2.2 but >2mmol/l treatment should continue but calcium supplements should be considered. Patients should be warned of the symptoms of hypocalcaemia and if any concern a nadir calcium level checked post infusion (see above table).

- Should my patient be taking calcium and vitamin D supplements?**



SYMPTOMS OF HYPOCALCAEMIA:

- Digital / perioral paraesthesia
- Cramps, carpopedal spasm, tetany, seizures
- Irritability, confusion, depression, lethargy, personality changes
- Symptoms of heart failure

RISK FACTORS FOR HYPOCALCAEMIA:

- Concomitant use of:
 - Aminoglycosides
 - Loop diuretics
 - IFN- α
- Hypomagnesaemia
- Hypoparathyroidism due to:
 - Thyroid surgery
 - Parathyroid surgery
 - Neck radiotherapy
- Vitamin D deficiency
- Renal impairment
- Bowel surgery
- Phenytoin
- Malabsorption
- Dietary deficiency
- Lack of sunlight

BISPHOSPHONATES FOR HYPERCALCAEMIA OF MALIGNANCY

ADMINISTRATION RECORD

Name:
D.O.B:
Hospital/NHS No:
Address:

Allergies

Initials

Date

Diagnosis

Bone Metastases? Y / N

Date of blood test	Corrected Serum Calcium	Serum Creatinine	GFR	SEE BACK OF CHART FOR PRESCRIBING ADVICE	PRESCRIPTION								ADMINISTRATION				
					Date	Diluent	Volume	Drug	Dose	Duration	Route	Doctor's signature	Fluid Batch and expiry	Drug Batch and expiry	Start time	Set up by: 2 RN to sign	Stop time

BISPHOSPHONATES FOR HYPERCALCAEMIA OF MALIGNANCY (HCM)

- The use of bisphosphonates can be complicated by **renal impairment**, which can occur at any time following the commencement of treatment. As such, **renal function should be checked before administration** and the dose and duration of bisphosphonate should be adjusted accordingly.
- Many studies of these drugs **prehydrate** patients with at least 2 litres of fluid before treatment and this practice may improve outcomes. Rehydration itself lowers calcium levels and treats the dehydration associated with hypercalcaemia, as well as reducing the risk of nephrotoxicity associated with bisphosphonates. Therefore prehydration with at least 2 litres of fluid prior to bisphosphonate treatment of HCM is recommended.
- By day 4, 76% of patients will be normocalcaemic with ibandronic acid, 33-50% with pamidronate and 45% with zoledronic acid. Approximately another 40% will be normocalcaemic by day 10 with pamidronate or zoledronic acid. When rechecking corrected serum calcium in patients who remain symptomatic these figures and time of nadir in the table below should be considered.

BISPHOSPHONATE DOSE AND DURATION ACCORDING TO RENAL FUNCTION

Prescribing should be modified according to creatinine clearance as calculated by the Cockcroft Gault Equation:

<p>Estimated GFR = $\frac{[140 - \text{age (years)}] \times \text{wt (kg)} \times [0.85 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/litre)} \times 0.814}$</p> <p>(ml/min)</p>

Drug	Dose		Duration of infusion	Hypocalcaemia nadir
	Normal renal function	Impaired renal function		
Zoledronic acid	4mg in 100ml 0.9% Saline	No dose adjustment if creatinine <400 µmol/l (SPC). NB: other bisphosphonates potentially less nephrotoxic*	At least 15 min	Approximately day 6-11
Pamidronate**	Ca <3.0, 15-30mg Ca 3-3.5, 30-60mg Ca 3.5-4.0, 60-90mg Ca >4.0, 90mg In 0.9% Saline Concentration should not exceed 60mg/250ml	Creatinine clearance <10ml/min: Ca >4, 60mg Ca <4, 30mg (RDH)*** Creatinine clearance >10ml/min: dose as per normal renal function Aredia not recommended if Cr Cl < 30ml/min	Maximum infusion rate 1mg/min (reduce to max. 20mg/hr in renal impairment)	Approximately day 7
Ibandronic acid	Ca > 3, 4mg Ca < 3, 2mg In 500ml 0.9% Saline	No information re dose adjustments for renal impairment in treatment of HCM	2 hours	Day 5

* Zoledronic acid treatment for hypercalcaemia in patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 µmol/l were excluded. The SPC states that no dose adjustment is necessary in hypercalcaemic patients with serum creatinine < 400 µmol/l. However, in clinical practice the use of a potentially less nephrotoxic bisphosphonate is recommended (e.g. pamidronate or ibandronic acid).

** The SPC recommends a dose of pamidronate dependant on the uncorrected serum calcium. Several comparative studies use pamidronate 90mg to treat HCM in all patients regardless of level of hypercalcaemia and without significant adverse effects (renal or symptomatic hypocalcaemia). Pamidronate 90mg is also standard treatment for prevention of skeletal related events (when calcium levels prior to treatment are likely to be within the normal range). Using pamidronate 90mg for any level of hypercalcaemia in patients with cancer is likely to increase the response rate and duration of response. This practice is supported by a recent systematic review of bisphosphonates in the treatment of HCM [Saunders 2004].

*** Renal Drug Handbook