REGIONAL DRUG AND THERAPEUTICS CENTRE

THE USE OF IBANDRONIC ACID IN THE MANAGEMENT OF HYPERCALCAEMIA OF MALIGNANCY, BONE PAIN AND THE PREVENTION OF SKELETAL EVENTS ASSOCIATED WITH SKELETAL METASTASES

Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH

August 2005

REGIONAL DRUG AND THERAPEUTICS CENTRE

THE USE OF IBANDRONIC ACID IN THE MANAGEMENT OF HYPERCALCAEMIA OF MALIGNANCY, BONE PAIN AND THE PREVENTION OF SKELETAL EVENTS ASSOCIATED WITH SKELETAL METASTASES

Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH

August 2005

CONTENTS

SUMMARY

- **Ibandronic acid is a new bisphosphonate. The intravenous (IV) preparation is licensed for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. It is also licensed for the treatment of tumour-induced hypercalcaemia with or without metastases. The oral preparation is indicated for the prevention of skeletal events in patients with breast cancer and bone metastases only.**
- **Hypercalcaemia of malignancy (HCM) is a life-threatening metabolic disorder encountered in patients with metastatic cancer or multiple myeloma. For this condition, ibandronic acid has only been compared with one other bisphosphonate. Current evidence suggests that IV ibandronic acid is as effective as IV pamidronate for the treatment of hypercalcaemia of malignancy.**
- **In patients with multiple myeloma, a monthly dose of 90 mg pamidronate IV was more effective than 4 mg ibandronic acid IV in reducing osteoclast activity and bone resorption. It is therefore not possible to define a role for ibandronic acid in the treatment of multiple myeloma using evidence currently available.**
- **In patients with breast cancer, IV ibandronic acid significantly decreased the number of Skeletal Related Events (SRE) compared with placebo. In two published studies, oral ibandronic acid has been shown to decrease SRE in breast cancer patients. However, one unpublished study highlighted no differences between placebo and ibandronic acid for SRE.**
- **To observe an effect on skeletal morbidity outcomes bisphosphonates need to be given for at least 6 months. They should be started when bone metastases are diagnosed and continued until no longer clinically relevant**
- **There is no evidence currently available to suggest that either oral or intravenous ibandronic acid is significantly better at producing a reduction in SRE in patients with breast cancer than treatments currently available (pamidronate and zoledronic acid).**
- **There is currently no evidence to support the use of ibandronic acid to prevent SRE in patients with other malignancies, such as prostate cancer.**
- **For bone pain secondary to bone metastases, there is insufficient evidence to support the use of ibandronic acid in patients with multiple myeloma and prostate cancer. There is currently conflicting evidence that ibandronic acid reduces bone pain for breast cancer patients.**
- **Adverse events with the oral preparation are mostly due to upper GI symptoms, such as abdominal pain 2.1%, dyspepsia 7%, nausea 3.5%, oesophagitis 2.1%, and hypocalcaemia 9.4%. After IV administration, acute phase reaction/flu-like syndrome 5.3%, diarrhoea 5.3%, myalgia 5.3%, headache 5.9% and hypocalcaemia 7.9% have been reported. Oesophagitis has not been observed after IV administration. Renal toxicity is of concern with some members of this class of drug, but has not been highlighted with**

ibandronic acid. However, patient numbers are small and the trials have been short-term.

- **Oral administration may have advantages over parenteral routes as it will decrease patient time at cancer centres. However, there are no studies comparing oral ibandronic acid with other bisphosphonates. A full assessment of capacity issues needs to be made given the limited evidence. Decisions to use oral ibandronate in particular will require the support of primary care commissioners due to the shift in funding for bisphosphonates from secondary to primary care.**
- **In the Northern and Yorkshire Region in 2001, 4500 patients were diagnosed with breast cancer, 393 with multiple myeloma and 3462 with prostate cancer. More than 50% of these patients will eventually develop bone metastases and require treatment with a bisphosphonate.**
- **The scientific committee of the European Medicines Agency has issued a positive opinion recommending approval of once monthly ibandronic acid 150 mg film-coated tablets for the treatment of osteoporosis. Roche and Glaxo are also seeking U.S. approval for an intravenous form of ibandronic acid to be given once every three months.**

`

BACKGROUND

Hypercalcaemia of malignancy (HCM) is the most common life-threatening metabolic disorder encountered in patients with cancer and occurs in 40-50% of multiple myeloma and breast cancer patients.[1] Clinical symptoms include polyuria, polydipsia, nausea, dehydration and drowsiness. HCM primarily occurs due to increased release of calcium from the bone resulting from increased osteoclast activity.[2] The current mainstay of treatment comprises rehydration and administration of agents, such as bisphosphonates, that inhibit bone resorption.[2]

While almost every malignancy can cause bone metastases, breast, lung and prostate cancers account for more than 80% of cases.[3] Over 50% of these patients with lung, breast or prostate cancer will eventually develop bone metastases. Metastatic bone disease causes substantial morbidity among cancer patients; complications include pathological fractures, hypercalcaemia, nerve root compression, spinal cord compression, bone marrow infiltration, pain and reduced mobility.[4]

Breast cancer is the most common cause of cancer among women and is also the primary cause of cancer death among women globally.[5] Bone is the most common site of metastatic involvement, affecting more than half of women during the course of their disease.[6] Of those patients with recurrent disease, 30% will develop their first metastases in bone and skeletal disease will be present in approximately 80% at death.[7] The incidence of new breast cancer cases in the UK in 2000 was 69.4 per 100,000 population. In the former Northern and Yorkshire Region, there were 4500 new patients diagnosed with breast cancer in 2001; this equates to a crude incidence rate of 68.9 per 100,000 population.[8,9]

Multiple myeloma is associated with abnormal bone remodelling due to increased osteoclast bone resorption and inhibition of osteoblastic bone formation.[10] This results in pronounced bone loss and osteolytic lesions predisposing to pathological fractures. Widespread bone destruction may lead to hypercalcaemia, resulting in a vicious cycle of dehydration, worsening hypercalcaemia, and renal failure. The incidence of multiple myeloma in the UK was 6.4 per 100,000 in 2000. In the former Northern and Yorkshire region, there were 393 reported cases in 2001; this equates to an incidence rate of 6 per 100,000.[8,9,10] It is extremely rare in people aged under 40 years but incidence increases to over 30 per 100,000 in those aged over 80 years.[9] The median age at diagnosis is 69 years with a slight male predominance. Most experts believe multiple myeloma to be incurable with current treatment; measures to reduce morbidity from skeletal involvement are therefore important for optimising quality of life.[11]

Prostate cancer is the sixth most common cancer in the world and the third most common cancer in men.[12] In 2000, an estimated 27,149 new cases of prostate cancer were diagnosed in the UK (46 per 100,000 population).[9] In the former Northern &Yorkshire region, there were 3462 new cases of prostate cancer in 2001 (52 per 100,000 population).[8] Prostate cancer is uncommon under the age of 50 years. About 85% of men with prostate cancer are diagnosed after the age of 65 years.[12]

Until relatively recently, the management of symptomatic bone disease depended on analgesics, radiotherapy, endocrine therapy and chemotherapy.[6] Despite these frequently effective treatments, progressive skeletal destruction often leads to ongoing symptoms and deterioration in quality of life.[6] Bisphosphonates are synthetic analogues of naturally occurring pyrophosphate compounds that inhibit osteoclastic bone resorption.[6] They have been useful in treating many disorders, such as metabolic bone disease, Paget's disease, osteoporosis and metastatic bone disease, and in patients with malignancy they have become standard treatment for tumour-induced hypercalcaemia.[6] Ibandronic acid is a third generation bisphosphonate which is available as an intravenous (IV) and oral preparation. Both the IV and oral preparations are licensed for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.[13, 14] Ibandronic acid IV is also licensed for the treatment of tumour-induced hypercalcaemia with or without metastases.[13]

The purpose of this report is to review the evidence that supports the use of ibandronic acid to treat hypercalcaemia of malignancy and for the treatment of bone pain and prevention of skeletal events associated with skeletal metastases.

EFFICACY

Hypercalcaemia of malignancy (HCM)

Three clinical trials have examined the efficacy of IV ibandronic acid in the treatment of HCM.[15,16,2] The first was a dose-finding phase II trial (n=174) that compared 3 different doses of IV ibandronic acid.[15] This study was an open, randomised trial that included patients with neoplastic disease and a corrected serum calcium level greater than 2.7 mmol/L. Patients were initially treated with rehydration therapy and if hypercalcaemia persisted after fluid repletion, were randomly assigned to treatment with a single infusion of 0.6 mg (n= 50), 1.1 mg (n= 46) or 2.0 mg (n=55) ibandronic acid. The primary outcome was restoration of normocalcaemia (serum calcium <2.7 mmol/L). Of the 151 patients assessable, 83 were classified as responders to ibandronic acid: 0.6 mg (n=22), 1.1 mg (n=24) and 2 mg (n=37). Significantly more patients in the 2mg than the 0.6mg group responded (p= 0.0276). The median times to relapse of hypercalcaemia were 11 days (0.6 mg), 17 days (1.1 mg) and 12 days (2 mg).

A multicentre, double-blind, randomised trial compared higher doses of IV ibandronic acid in patients with cancer-associated hypercalcaemia.[16] One hundred and thirty one patients were randomised to receive single dose ibandronic acid 2 mg (n=45), 4 mg (n=44) or 6 mg (n=42). The primary efficacy evaluation was a decrease in serum calcium to $\leq$2.7 mmol/L after treatment. Secondary outcomes measured were the time in the normal range and the time to relapse, defined as an increase of albumin-corrected serum calcium to $\geq$3.0 mmol/L in patients who had an initial response. Eight patients were excluded from analysis after ibandronic acid administration because of protocol violations, leaving a total of 125 patients evaluable for response. Serum calcium levels fell progressively in each group from day 2, reaching a nadir at day 5. The proportions of patients who achieved serum calcium values below 2.7 mmol/L were: 50% in the 2 mg group, 75.6% in the 4 mg group and 77.5% in the 6

mg group (p<0.05; 2 mg vs others). The median time in the normal range was 12 days for the 2 and 4 mg doses and 11 days for the 6 mg dose. The median time to relapse was 18 days in the 4 mg group and 26 days in the 6 mg group. The duration of response was not significantly different between the three treatment groups.

A third, small, open-label study (n=67) randomised patients with HCM to receive either a single dose of IV ibandronic acid (2 or 4 mg) or pamidronate infusion (15, 30, 60 or 90 mg).[2] Thirty-four patients received ibandronic acid and thirty-three received pamidronate. The dose administered was dependent on the baseline-corrected serum calcium level (CSC). The primary efficacy variable was the change in CSC from baseline to day 4. The mean change in CSC from day 0 to day 4 was 0.73 $\pm$ 0.48 mmol/L for ibandronic acid and 0.57 $\pm$ 0.33 mmol/L for pamidronate. The mean difference between the decreases in the ibandronic acid and pamidronate groups was 0.09 mmol/L, suggesting that the hypocalcaemic effect of ibandronic acid was not inferior to that of pamidronate. The numbers responding to the first doses of ibandronic acid and pamidronate were similar (76.5% and 75.8%, respectively). The mean duration of response was 14 days in patients treated with ibandronic acid and 4 days in those receiving pamidronate (p=0.03).

Prevention of skeletal events associated with skeletal metastases

Four published clinical trials have assessed the efficacy of IV and oral ibandronic acid for the prevention of skeletal related events associated with skeletal metastases.[17,18,20,21] Two of these trials were in patients with breast cancer[17,18] and two in multiple myeloma patients[20,21]. A fifth trial in breast cancer patients remains unpublished.[7]

Breast cancer

A phase III (n=466), randomised, placebo-controlled, parallel-group, multi-centre study compared the efficacy of IV ibandronic acid 6 mg by infusion (n=154) or a 2 mg bolus (n=154) with placebo IV bolus or infusion (n=158) given every 3-4 weeks in women with metastatic bone disease due to breast cancer for a maximum of 96 weeks.[17] The study was blinded with respect to placebo or ibandronic acid treatment but dosing was open-label due to differences in the mode of delivery. The primary outcome measure was the number of 12-week periods with new skeletal complications (bone events), allowing for the time the patient spent on the study. This was expressed as the skeletal morbidity period rate (SMPR) calculated as the number of periods with new bone complications divided by the total observation time in periods. Bone events were defined as any of: vertebral fractures, pathological non-vertebral fractures, radiotherapy for bone complications (uncontrolled bone pain or impending fractures) or surgery for bone complications (fractures or impending fractures). It was stated that the SMPR was used rather than the number of events divided by time in the study since skeletal complications occurring close together are often likely to be related, rather than distinct, events. The secondary outcomes measured included assessment of bone pain, analgesic consumption, patient survival and markers of bone turnover. The primary and secondary outcomes were conducted on the intention to treat population. Patients receiving ibandronic acid 6 mg had a 20% reduction in SMPR compared with placebo (1.19 vs 1.48 periods with

events per patient year; p= 0.004). More patients in the ibandronic acid 6 mg group experienced no new bone events compared with the placebo group (49% vs 38%; p=0.052). This result was not, however, statistically significant, but indicates that nine patients would need to be treated for up to 96 weeks with IV ibandronic acid to prevent one additional patient developing a new bone event. Among the individual components of the primary endpoint, the SMPR for vertebral fractures and events requiring radiotherapy were both significantly lower in the 2 mg and 6 mg ibandronic acid treatment groups compared with placebo (global p value = 0.023 for vertebral fractures and 0.012 for events requiring radiotherapy). Only 43% of the ibandronic acid 6 mg group, 47% of the 2 mg group and 31% of the placebo patients completed 96 weeks of the study. Adverse clinical events, death and refusal of treatment were the main reasons for withdrawal. The majority of adverse clinical events were related to the underlying disease.

Two phase III trials assessing the efficacy of oral ibandronic acid for the treatment of metastatic bone disease in breast cancer patients have been conducted, only one of which has been fully published. [7,18] Both trials were similar in design and measured the same primary outcomes.

In the published study, 435 patients were randomised to receive placebo (n=143) or oral ibandronic acid 20 mg (n=144) or 50 mg (n=148) for up to 96 weeks.[18] The primary efficacy measure was the number of 12 week periods with new skeletal complications (SMPR). The SMPR was significantly reduced with oral ibandronic acid (placebo 1.20, 20 mg group 0.97 (p=0.024), 50 mg group 0.98 (p=0.037)). Ibandronic acid 50 mg significantly reduced the need for radiotherapy (p=0.005 vs placebo). The relative risk of skeletal events was reduced by 38% (20 mg dose) and 39% (50 mg dose) (p=0.009 and p=0.005, respectively, vs placebo).

In the unpublished study, 411 patients were randomised to receive placebo (n=134), ibandronic acid 20 mg (n=138) or 50 mg (n=139) for up to 96 weeks.[7] The primary efficacy endpoint was again the number of 12 week periods with new bone complications (SMPR). Efficacy was not demonstrated in either the 20 mg or 50 mg groups. The reason for the lack of a statistically significant treatment effect on the primary efficacy endpoint was possibly because the baseline characteristics of the patients were different. In particular, a greater proportion of the patients in the active treatment groups had a WHO performance status of '2', were currently receiving cytotoxic drugs, had pre-existing fractures and exhibited anaemia. The drop-out rates in both of these studies were high (58-60%).[7] However, such a high drop-out rate is to be expected in a study population with metastatic breast cancer over a period of 96 weeks (median survival of about 2 years).[7]

Body et al published a pooled analysis of these two phase III trials (n=546).[19] The results from the 50 mg group vs placebo only are reported in this study. The primary composite endpoint was the SMPR; however, this study was not powered to detect differences in the components of the composite endpoints. Results were reported using intention-to-treat analyses. Oral ibandronic acid 50 mg significantly reduced the mean SMPR compared with placebo (0.95 vs 1.18, respectively; p=0.004). There was a significant reduction in the mean number of events requiring radiotherapy (0.73 vs. 0.98; p<0.001) and events requiring surgery (0.47 vs 0.53; p=0.037). There was no significant difference between the number of skeletal fractures with ibandronic acid and placebo (p=0.19). Only 42% and 38% of patients in the

ibandronic acid and placebo groups, respectively, completed the 96-week treatment period. The most frequent reasons for withdrawal were malignancy progression (12% in the ibandronic acid group and 19% in the placebo group), death (15% vs 12%) and other adverse events (10% vs 12%).

Multiple myeloma

Two published trials have assessed the efficacy of ibandronic acid in multiple myeloma patients for SRE.

A double-blind, multi-centre, placebo-controlled study assessed the efficacy of ibandronic acid for preventing skeletal related events (SRE) in 198 patients with multiple myeloma.[20] Patients were randomised to receive either ibandronic acid 2 mg (n=99) as an IV bolus or placebo (n=99) monthly for between 12 and 24 months. The primary endpoint was defined as the number of 3-month periods with new bone complications, such as peripheral pathological fracture, significant vertebral reduction ($\geq$25%), hypercalcaemic event (albumin-corrected serum calcium concentration of >2.8 mmol/L), severe bone pain (necessitating opiate treatment), radiation therapy, or surgery to bone. This primary endpoint was categorised into four classes (no event, one period with event, two periods with event and three or more periods with event). Secondary endpoints for drug efficacy were the proportion of patients with new osteolytic sites, progression of osteolytic lesions, progressive pre-existing fractures and bone pain score. The authors do not state whether the trial was powered to detect differences between the secondary endpoints.

The analysis was on an intention-to-treat basis for both primary and secondary outcomes. A total of 173 patients (85 placebo and 88 ibandronic acid) received chemotherapy, interferon therapy, or both. There was no difference between the treatment groups regarding quality and intensity of chemotherapy administered. Ninety-one patients (46%) completed the study; 49 received ibandronic acid and 42 placebo. One hundred and seven patients dropped out, primarily due to severe adverse events (40 placebo and 42 ibandronic acid). The authors did not state whether this was attributable to disease progression or treatment.

The number of 3-month periods with new bone complications were similar in placebo and ibandronic acid-treated patients. No significant difference in SRE per patient year was observed between the ibandronic acid and placebo groups (2.13 and 2.05, respectively).

A small, randomised, non-blinded clinical study (n=44) compared the efficacy of IV pamidronate and IV ibandronic acid on bone turnover and disease activity in multiple myeloma patients.[21] Forty-five healthy individuals with no evidence of bone disease were used as a control group. Patients with stage II/III multiple myeloma received either IV pamidronate 90 mg (n=23) or IV ibandronic acid 4 mg (n=21) infusion monthly in addition to conventional chemotherapy. Primary and secondary outcomes and power calculations were not stated for this study.

This trial compared the effects of pamidronate and ibandronic acid on biochemical bone markers of bone resorption (*N*-terminal cross-linking telopeptide of type I collagen (NTX) and tartrate-resistant acid phosphatase type 5b (TRACP-5b)), bone

formation markers (bone alkaline phosphatase and osteocalcin), markers for disease activity (paraprotein, CRP, β_2-microglobulin) and interleukin-6 (IL-6).

In both groups, the combination of chemotherapy with either pamidronate or ibandronic acid produced a significant reduction of TRACP-5b (compared with baseline) from the second month of treatment for patients on pamidronate (p=0.03) and from the sixth month of treatment for patients on ibandronic acid (p=0.04). There was a greater reduction of NTX and IL-6 in the pamidronate group than in the ibandronic acid group starting at the second month of treatment (p=0.002 and p=0.001, respectively). There was no difference in skeletal events throughout the 10-month follow-up period. The results from this trial are difficult to interpret because no specific primary outcome was stated and the trial was small.

Bone pain

Four of the trials discussed above assessed bone pain and analgesic consumption as secondary endpoints.[7,17,18,19]

Oral ibandronic acid

In the first trial, 435 patients were randomised to receive either placebo or oral ibandronic acid 20 mg or 50 mg once daily for up to 96 weeks.[18] Bone pain was assessed at each 4-weekly visit and patients were asked to assess their bone pain on a scale from 0 (none) to 4 (intolerable). Analgesic use was scored on a scale from 0 (none) to 6 (opiates $\geq$100 mg morphine or equivalent daily). Drop-out rates in this trial were high and Last-Observation-Carried-Forward scores were used. From baseline to study endpoint, bone pain scores increased in both the placebo and the oral ibandronic acid 50 mg groups (+0.21 and +0.03, respectively; p=0.021). The mean analgesic scores for 50 mg ibandronic acid and placebo were not significantly different (p=0.074).

A pooled analysis of the results of the above trial and a second unpublished trial (n=564) assessed the efficacy and safety of oral ibandronic acid 50 mg in the treatment of women with breast cancer and bone metastases.[19] The mean bone pain scores increased in the placebo group (0.20) and decreased in the ibandronic acid 50 mg group (-0.10; p=0.0001).[7] Analgesic use increased in both the placebo and ibandronic acid groups (0.85 and 0.60, respectively; p=0.019). The reduction in bone pain was not achieved through increased use of analgesia in the ibandronate group.[7]

IV ibandronic acid

An open randomised trial looked at the efficacy of IV ibandronic acid (2 mg and 6 mg) compared with placebo for up to 96 weeks in patients with breast cancer and bone metastases.[17] Bone pain, analgesic consumption and quality of life were examined as secondary efficacy outcomes. The results for these secondary endpoints were published separately.[22] Quality of life was assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Scale - Core 30 questionnaire (QLQ - C30). Bone pain was assessed on a 5-point scale (from 0=none to 4=intolerable).

Compared with baseline measurements, the bone pain score was increased at the last assessment in both the placebo and 2 mg groups, but was significantly reduced in patients receiving 6 mg ibandronic acid (-0.28±1.11; p<0.001 compared with placebo). Analgesic requirements increased throughout the study in all treatment groups. The analgesic requirements of the ibandronic acid groups were not significantly different from those of the placebo group. The effect of treatment on quality of life was determined by calculating the mean change in global quality of life score from baseline to last study visit and the mean change in the five individual functional domains, global health status and symptom scores. A significant improvement in quality of life was demonstrated for patients receiving ibandronic acid (p<0.05) for all global health status. Overall, at the last assessment, the 6 mg ibandronic acid group showed significantly better functioning compared with placebo (p=0.004), and had significantly better scores for physical, emotional and social functioning and global health status (p<0.05).

A further study assessed bone pain, quality of life and analgesic consumption as secondary endpoints in multiple myeloma patients (n=198).[20] These patients were treated with either IV bolus ibandronic acid 2 mg, or IV placebo. Bone pain scores were assessed using a bone pain score scale where the range was 0=none to 4=intolerable. Quality of Life was measured using the EORTC scale. There were no significant differences between the groups with respect to bone pain and analgesic consumption or quality of life.

Two small open studies have assessed bone pain as the primary focus.

In the first open study (n=25), patients with symptomatic skeletal metastases from prostate cancer were treated with IV ibandronic acid 6 mg.[23] The primary study endpoint was pain reduction assessed with an 11-point visual analogue scale (VAS) from 0=no pain to 10=severe pain. Patients were initially started with an IV saturation dose of 6 mg ibandronic acid daily for 3 days and then the same dose administered every 4 weeks.

All patients were allowed to continue their analgesic medication and to adjust the dosage over a 14-day period to achieve optimal pain control. A significant reduction in pain score from 6.5 to 2.0 (p<0.001) was achieved in 23 patients, 9 patients were completely pain free and 14 patients experienced a significant decrease of their daily analgesic consumption. The results do not state how long the patients took part in the study. It is difficult to interpret these results as all patients were allowed to continue their analgesic medication until day 14 to achieve optimal pain control and the trial did not have a control group.

A second, open-label, pilot study assessed the efficacy and safety of ibandronic acid in the treatment of opioid-resistant bone pain associated with metastatic bone disease.[24] Eighteen patients with advanced tumours, metastatic bone disease and opioid-resistant bone pain received 4 mg IV ibandronic acid daily for 4 days.

Baseline opioid analgesic use was equivalent to 400 mg/day morphine and patients were assessed for 6 weeks or until death. At baseline, all the patients in the study were experiencing moderate to severe bone pain (VAS pain score of 5-6). The results for this study state that ibandronate significantly reduced pain scores within 7 days (p<0.001) compared with baseline. No comparator was used in this study and the value for the change in baseline pain scores is not given.

ADVERSE EFFECTS

GENERAL

Pooled data from two studies (n=564) assessed the efficacy and safety of 50 mg oral ibandronic acid in breast cancer patients with metastatic bone disease.[19] The incidence of drug-related adverse effects was higher with ibandronic acid (26.6%) than with placebo (17.7%). These were mostly upper GI effects, such as dyspepsia (7%), nausea (3.5%), abdominal pain (2.1%) and oesophagitis (2.1%), and hypocalcaemia (9.4%).

In a trial comparing IV ibandronic acid 2 mg and 6 mg with placebo, the treatment-related adverse events attributed to ibandronic acid 6 mg were hypocalcaemia (7.9%), headache (5.9%), acute-phase reaction/flu-like syndrome (5.3%), diarrhoea (5.3%) and myalgia (5.3%).[7] A transient increase in bone pain and transient proteinuria were also reported. Oesophagitis was not observed after IV administration of ibandronic acid.[7]

RENAL

In one phase III study (n=466), there was no evidence of renal toxicity associated with ibandronic acid treatment.[17] The percentages of patients with increased serum creatinine levels (300 mM) were low and similar among treatment groups (2.6% ibandronic acid 6 mg, 0.7% ibandronic acid 2 mg, 1.3% placebo). In the pooled analysis of patients taking oral ibandronic acid, there was a slightly higher incidence of renal adverse effects compared with placebo (5.2% vs 4.7%, respectively).[19]

In the oral studies, the numbers of patients with renal adverse events in the three treatment groups were similar.[7] There were more cases of renal failure in the two active treatment groups (20 mg 6 patients; 50 mg 5 patients) than in the placebo group (3 cases). However, there were more reports of increased serum creatinine levels in the placebo group (6 patients) than either the 20 mg (2 patients) or 50 mg (4 patients) treatment groups. Therefore, the overall numbers of events indicative of impaired renal function in all three groups were similar (8, 9 and 9 individuals, respectively, who were reported to have either increased creatinine levels or kidney failure in the three study arms).

One small short-term study examining the effect of intravenous ibandronic acid on renal function in breast cancer patients with metastatic bone disease has been published.[25] Patients (n=74) were randomised to double-blind (but not dose-blind) treatment with bolus injections of ibandronic acid 2 mg, 1-hour infusions of ibandronic acid 6 mg or placebo injections or infusions (n=23, n=23, n=28, respectively). Patients received either three injections or three infusions over a three-month period.

The outcomes measured were urinary excretion of total protein, albumin, alpha-1-microglobulin, N-acetyl–β–D-glucosaminidase, serum creatinine and frequency of haematuria. Levels were assessed at days 1, 2, 5 and 10 after each dose of placebo or ibandronic acid. No statistically significant changes in pre- and post-treatment levels were observed in any group. However, this was a very short term study.

DOSAGE, ADMINISTRATION AND COST

The recommended doses of ibandronic acid depend on the indication:

- For the prevention of skeletal events in patients with breast cancer and bone metastases, the recommended IV dose is 6 mg added to 500ml normal saline or 500ml dextrose 5% infused over 1 hour every 3-4 weeks.[13]
- For the treatment of tumour-induced hypercalcaemia, IV doses of 2 mg (moderate hypercalcaemia) or 4 mg (severe hypercalcaemia) are used.[13]

The oral preparation is only indicated for the prevention of skeletal events in patients with breast cancer and bone metastases.[14] The recommended daily dose is 50 mg daily, which should be taken after an overnight fast (at least 6 hours), swallowed with a full glass of water and before the first food or drink of the day. Fasting should be continued for at least 30 minutes after taking the tablet and patients should not lie down for 60 minutes after taking the tablet.

Current costs for 6 months of licensed treatments are summarised below. Costs are calculated assuming one dose of IV treatment is required each month.

Treatment	Dose	6 month cost (+VAT)*
IV ibandronic acid	6 mg every 3-4 weeks	£1,170.00
Oral ibandronic acid	50 mg daily	£1,253.57
IV pamidronate (generic)	90 mg every 3-4 weeks	£ 990.00
IV pamidronate (Aredia®)	90 mg every 3-4 weeks	£1,022.70
IV zoledronic acid	4 mg every 3-4 weeks	£1,170.00

*NHS basic price before any discounts; does not include cost of reconstitution or associated administration costs, such as nursing time. Generic prices are likely to decrease.

A recent Health Technology Assessment undertook an economic review of the cost-effectiveness of bisphosphonates (ibandronic acid was not included) in the treatment of hypercalcaemia and prevention of skeletal morbidity.[26] The economic evidence reviewed was of limited quality; therefore, the findings based on this need to be interpreted with caution.[26] For hypercalcaemia, the HTA concluded that zoledronic acid was the most cost-effective treatment (approximately £22,900 per life year gained). For skeletal morbidity, the overall cost of bisphosphonate therapy to prevent one SRE was estimated at £250 and £1500 per event for patients with breast cancer and multiple myeloma, respectively. The model used suggested that bisphosphonate treatment was sometimes cost saving in breast cancer patients in whom fractures are prevented. The models were sensitive to the probability of averting an SRE, the unit cost of an SRE and the prices of the bisphosphonates.[26]

There are no published cost-effectiveness data available on the use of ibandronic acid for the treatment of hypercalcaemia of malignancy or the prevention of skeletal events associated with skeletal metastases.

PLACE IN TREATMENT

- **Hypercalcaemia**

Bisphosphonates are now the drugs of choice for the treatment of acute HCM with over 70% of patients reaching normocalcaemia (mean time to normocalcaemia ranges from 2 to 6 days when treated with any bisphosphonate).[26] Ibandronic acid has been directly compared with only one other bisphosphonate, pamidronate; it has not been compared with zoledronic acid. One small open study (n=67) suggests that IV ibandronic acid is as effective as IV pamidronate for lowering serum calcium levels in patients with HCM.[2]

- **Prevention of skeletal events associated with skeletal metastases**

Multiple Myeloma

A review carried out by the American Society of Clinical Oncology (ASCO) concluded that, in multiple myeloma, oral clodronate, IV zoledronic acid and IV pamidronate are superior to placebo in reducing skeletal complications.[11] However, the superiority of one agent cannot be definitively established. They also concluded that IV zoledronic acid is as effective as IV pamidronate. The review recommends the use of IV pamidronate or IV zoledronic acid and which is used will depend upon choosing between the higher cost of zoledronic acid with its shorter infusion time (15 minutes) and the less expensive pamidronate with its longer infusion time (2 hours).[11]

Ibandronic acid is currently not licensed for the treatment of multiple myeloma. Ibandronic acid 2 mg IV was no better than placebo for prevention of SRE.[20] In multiple myeloma patients, pamidronate 90 mg was more effective in reducing osteoclast activity and bone resorption than ibandronic acid 4 mg.[21] It is therefore not possible to define a role for ibandronic acid in the treatment of multiple myeloma based on the evidence currently available.

Breast cancer

The situation for patients with metastatic disease and breast cancer is less clear cut. A recent systematic review of bisphosphonates on skeletal morbidity in metastatic cancer concluded that for patients with metastatic bone disease, bisphosphonates significantly reduced skeletal morbidity (except for spinal cord compression) and increased time to the first skeletal related event.[4] Treatment should start when bone metastases are diagnosed and be continued until no longer clinically relevant. This review did not include ibandronic acid. To observe an effect on skeletal morbidity outcomes bisphosphonates need to be given for at least 6 months. The reviewers also suggest that, at present, most evidence supports the use of IV

bisphosphonates, because the pooled results of trials that used IV bisphosphonates were highly significant.

A second review assessed bisphosphonates in breast cancer patients and concluded that bisphosphonates reduce the incidence and rate of skeletal events in women with advanced breast cancer. IV pamidronate (45 mg, 60 mg or 90 mg) reduces the rate of skeletal events and increases the time to skeletal event, but only high-dose pamidronate (90 mg) significantly reduces the risk of developing a skeletal event.[6] Zoledronic acid 4 mg appears to be equivalent to IV pamidronate 90mg, with regard to risk of skeletal events, skeletal morbidity, time to the first skeletal event, pain and quality of life.

Compared with placebo, IV ibandronic acid 6 mg has shown a 20% reduction in the frequency of 12-week periods with bone events.[27] To prevent one additional patient developing a new bone event nine patients would need to be treated for up to 96 weeks with IV ibandronic acid.

A published pooled analysis[19] of one published and one unpublished phase III trial[7,19] has shown a significant reduction in the mean SMPR with oral ibandronic acid compared with placebo. In the published study, the SMPR was significantly reduced, whereas in the unpublished study, there was no statistically significant difference between the placebo and ibandronic acid groups for the primary endpoint (SMPR).[7]

Oral ibandronate appears to offer a further treatment option for patients with metastatic breast cancer. As the evidence is limited patients should be carefully monitored for adverse events.

Prostate cancer

Currently, there is insufficient evidence to support the use of ibandronic acid to prevent SRE in patients with prostate cancer.

- **Bone pain**

First-line treatment of bone pain is usually radiotherapy if the patient is well enough. With regard to analgesia, a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids will usually be an effective combination for bone pain.[28] The role of bisphosphonates for painful bone metastases has been relatively recently reviewed.[29] The reviewers concluded that although there is some evidence to support the effectiveness of bisphosphonates in providing pain relief for bone metastases, there is insufficient evidence to recommend them as first-line therapy. They should be considered where analgesics and/or radiotherapy are inadequate for the management of painful bone metastases. This review did not include ibandronic acid.

One published phase III trial showed no significant decrease in bone pain scores and mean analgesic consumption when oral ibandronic acid was compared with placebo in breast cancer patients.[18] There was a significant reduction in bone pain scores and a significant improvement in q\uality of life for patients with breast cancer receiving IV ibandronic acid 6 mg.[17]

Infusion times for the bisphosphonates are: zoledronic acid 4 mg, 15 minutes; ibandronic acid, 1 hour and those for pamidronate are: 1.5 to 4.5 hours.[31,13,30,]

In terms of drug costs, generic pamidronate is the cheapest bisphophonate; however, nursing time costs and capacity issues need to be taken into consideration. IV ibandronic acid would appear to have little or no advantage over zoledronic acid as the infusion time for zoledronic acid is 15 minutes compared with 1 hour for ibandronic acid and costs for both drugs are similar.

ARRANGEMENTS FOR PRESCRIBING

Oral administration may have advantages over parenteral routes as it will decrease patient time at cancer centres. However, there are no studies comparing oral ibandronic acid with other bisphosphonates. A full assessment of capacity issues needs to be made given the limited evidence. In particular, decisions to use oral ibandronate will require the support of primary care commissioners due to the shift in funding for bisphosphonates from secondary to primary care.

FUTURE DEVELOPMENTS

The scientific committee of the European Medicines Agency has issued a positive opinion recommending approval of once monthly ibandronic acid 150 mg film-coated tablets for the treatment of osteoporosis. Roche and Glaxo are also seeking U.S. approval for an intravenous form of ibandronic acid to be given once every three months.

Two large-scale trials assessing high-dose IV ibandronic acid 6 mg for 3 consecutive days followed by maintenance treatment in patients with moderate to severe metastatic bone pain are to start shortly.

ACKNOWLEDGEMENTS

We are grateful to the following people for helpful advice and comments in the preparation of this report. The Regional Drug and Therapeutics Centre accepts final responsibility for the content of this document.

Geoff Saunders	Macmillan Cancer Network Pharmacist	Greater Manchester and Cheshire Cancer Network
Dr Mark Verrill	Senior Lecturer in Medical Oncology	Northern Institute for Cancer Research

REFERENCES

1. Falk S and Fallon M. ABC of palliative care: Emergencies. Br Med J 1997; 315:1525-8.
2. Pecherstorfer M, Steinhauer EU, Rizzoli R et al. Efficacy and safety of ibandronate in the treatment of hypercalcaemia of malignancy: a randomised multicentric comparison to pamidronate. Support Care Cancer 2003; 11:539-47.
3. Bone metastases. PDQ Information for Health Care Professionals. Cancer Web http://cancerweb.ncl.ac.uk/cancernet/103857.html (Last accessed: 01/02/2005).
4. Ross JR, Saunders Y, Edmonds PM et al. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. BMJ 2003; 327:469-74.
5. Bray F, McCarron P and Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004; 6:229-39.
6. Pavlakis N, Stockler M. Bisphosphonates for breast cancer (Cochrane review). In The Cochrane library. Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.
7. EMEA. European Public Assessment Report (EPAR) CPMP/253/96 Bondronat® http://www.emea.eu.int/humandocs/Humans/EPAR/bondronat/bondronat.htm (Last accessed 25/01/05).
8. Number of new cases of certain cancers, Former Northern and Yorkshire Region, 2001.
9. CancerStats Incidence-UK Cancer Research UK February 2004 http://www.cancerresearchuk.org/statistics (Last accessed 21/02/2005)
10. Singer CRJ. ABC of clinical haematology: Multiple myeloma and related conditions. Br Med J 1997; 314:960.
11. Berenson JR, Hilner BE, Kyle RA et al. American Society of Clinical Oncology Clinical Practice Guidelines: The Role of Bisphosphonates in Multiple Myeloma. J. Clin. Oncol 2002; 20:3719-36.
12. Wilt T. Prostate cancer: Non metastatic. Clinical evidence http://www.clinicalevidence.com/ceweb/conditions/msh/1804/1804_background.jsp (Last accessed 25/01/05).
13. Bondronat® 2 mg/ml & 6 mg/ml Summary of Product Characteristics. Roche Products Limited, 2005 http://emc.medicines.org.uk/ (Last accessed 25/01/05).
14. Bondronat® 50 mg Summary of Product Characteristics. Roche Pharmaceuticals Limited 2005, http://emc.medicines.org.uk/ (Last accessed 25/01/05).
15. Pecherstorfer M, Herrmann Z, Body JJ et al. Randomised Phase II Trial Comparing Different Doses of the Bisphosphonate Ibandronate in the Treatment of Hypercalcaemia of Malignancy. J Clin Oncol 1996; 14: 268-76.
16. Ralston SH, Thiebaud D, Herrmann Z et al. Dose-response study of ibandronate in the treatment of cancer-associated hypercalcaemia. Br J Cancer 1997; 75:295-300.
17. Body JJ, Diel IJ, Lichinitzer MR et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003; 14:1399-1405.
18. Tripathy D, Lichinitzer M, Lazarev A et al. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomised double blind, placebo controlled trial. Ann Oncol 2004; 15 743-50.
19. Body JJ, Diel IJ, Lichinitzer M et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo controlled phase III studies. Br J Cancer. 2004; 90:1133-7.
20. Menssen HD, Sakalova A, Fontana A et al. Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival and bone resorption markers in patients with advanced multiple myeloma. J Clin Oncol 2002; 20:2353-9.

21. Terpos E, Viniou N, de la Fuente J et al. Pamidronate is superior to ibandronate in decreasing bone resorption, interleukin–6 and beta 2-microglobulin in multiple myeloma. Eur J Haematol 2003; 70:34-42.

22. Diel I, Body JJ, Lichinitser M et al. Improved quality of life after long term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. Eur J Cancer 2004; 40:1704-12.

23. Heidenreich A, Elert A, Hofmann R. Ibandronate in the treatment of prostate cancer associated painful osseous metastases. Prostate Cancer and Prostatic Dis 2002; 5:231-5.

24. Mancini I, Dumon JC and Body JJ et al . Efficacy and safety of ibandronate in the treatment of opioid resistant bone pain associated with metastatic bone disease: A pilot study. J Clin Oncol 2004; 22:3587-92.

25. Lyubimova NV, Kushlinsky NE, Lichinitser MR et al. Renal safety of intravenous ibandronic acid in breast cancer patients with metastatic bone disease. Clin Drug Invest 2003; 23:707-16.

26. Ross JR, Saunders Y, Edmonds PM et al. A systematic review of the role of bisphosphonates in metastatic disease. Health Technol Assess 2004; 8(4). http://www.hta.nhsweb.nhs.uk/fullmono/mon804.pdf (Last accessed 25/01/2005).

27. London New Drugs Group. APC/DTC *Briefing*. Ibandronate (Bondronat®) for the treatment of bone metastases. October 2004. http://www.druginfozone.org/Record%20Viewing/viewRecord.aspx?id=540003 (Last accessed 27/01/2005).

28. Allen M and Taylor R. Issues in pain control in palliative care. Pharm J 1999; 262:620-24

29. Wong R and Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases (Cochrane review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.

30. Novartis Pharmaceuticals UK Ltd Aredia® Summary of Product Characteristics. http://emc.medicines.org.uk/ (Last accessed 25/01/2005).

31. Novartis Pharmaceuticals UK Ltd Zometa® Summary of Product Characteristics http://emc.medicines.org.uk/ (Last accessed 25/01/2005).

APPENDIX 1. SUMMARY OF MAJOR CLINICAL TRIALS OF IBANDRONIC ACID.

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label.

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Pecherstorfer M et al 2003[3]	O, ,R, PG, MC, S.	Ibandronate 2 mg IV (max 2 doses) or Ibandronate 4 mg IV (max 2 doses) Pamidronate 15, 30, 60 or 90 mg (max 2 doses)	37 34	Patients aged >18 years, suffering from malignancy and presenting with albumin-corrected serum calcium >2.7 mmol/L	Non malignant causes of hypercalcaemia, pregnancy, lactation, bisphosphonate treatment within one month, calcitonin treatment within one week, or therapy with investigational drugs 30 days prior to study.	The change in corrected serum calcium (CSC) from baseline to day 4.	The mean change in CSC from day 0 to day 4 was 0.73$\pm$ 0.48 mmol/L for ibandronate and 0.57$\pm$ 0.33 mmol/L for pamidronate.	Adverse events due to ibandronate were: flu-like symptoms (2), hypocalcaemia (2), hypokalaemia (1) respiratory (1) and diarrhoea(1).

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Pecherstorfer 1996[15]	R, O, MC, S.	Ibandronate 0.6 mg Ibandronate 1.1 mg Ibandronate 2.0 mg	50 46 55	Neoplastic disease, serum calcium >2.7 mmol/L, serum creatinine ≤440 mol/L.	Primary hyperparathyroidism, treatment with bisphosphonates within the last 3 months, treatment with mithramycin or calcitonin within the last 4 weeks, cystostatic treatment within the last week before the appearance of hypercalcaemia, start of hormonal treatment within 4 weeks and of corticosteroids within 1 week before study.	Restoration of normocalcaemia (serum calcium <2.7 mmol/L)	A total of 83 (55%) were responders to ibandronate (ibandronate 0.6 mg n = 22, ibandronate 1.1 mg n= 24 and ibandronate 2 mg n = 37)	3 serious (thrombocytopenia, nausea and fever) and 16 non-serious AE attributed to ibandronate (10 cases of fever, 4 hypocalcaemia, 1 oesophagitis, and 1 increase in liver enzymes).

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Ralston SH et al 1997[16]	MC, DB, R, S	Ibandronate 2 mg	45	Malignant disease, albumin corrected serum calcium values ≥3.0 mmol/l after a minimum of 24 hours rehydration and urine output ≥2 litres/day	Serum creatinine ≥265µmol/L or other causes for the hypercalcaemia. Treatment with bisphosphonates during the preceding 3 months or plicamycin during the preceding 4 weeks and cytostatic drugs or calcitonin during the preceding week of the study.	Serum calcium level of ≤2.7mmol/l after treatment.	50% of patients in the 2 mg group, 75.6% in the 4 mg group and 77.5% in the 6 mg group achieved serum calcium level <2.7 mmol/l ($p<0.05$; 2 mg vs others).	12.9% of patients reported fever caused by ibandronate. Asymptomatic hypocalcaemia was observed in 6 patients.
		Ibandronate 4 mg	44					
		Ibandronate 6 mg	42					

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Body JJ et al 2003[17]	R, DB, PC, MC, PG (open label with respect to dose)	Ibandronate 2mg IV bolus every 3-4 weeks (max 96 weeks) Ibandronate 6 mg infusion every 3-4 weeks (max 96 weeks) Placebo IV bolus or infusion every 3-4 (max 96 weeks)	154 154 158	Women aged >18 with breast cancer and bone metastases, WHO status of ≤2.	Life expectancy of <60 weeks, pregnant patients or received bisphosphonates or gallium nitrate within the last 6 months, any investigational drug or an aminoglycoside within the last 30 days, or previous high dose chemotherapy, hypercalcaemia, hypocalcaemia, serum creatinine >3 mg /dl, Paget's disease of the bone, primary hyperparathyroidism, aspirin-sensitive asthma, or known liver or brain metastases.	SMPR defined as the number of 12-week periods with new skeletal complications, divided by the total observation time. Skeletal complications included vertebral fractures, non vertebral fractures, radiotherapy for bone complications or surgery for bone complications.	Patients receiving ibandronate 6 mg had a 20% relative reduction in the SMPR compared with placebo (1.19 vs 1.48 periods with events per patient year; p = 0.004). The SMPR for vertebral fractures and events requiring radiotherapy were both significantly lower in the Ibandronate 2-mg and 6-mg groups (global p=0.23 for vertebral fractures and p=0.012 for events requiring radiotherapy).	63% of patients in placebo group had a least 1 adverse event, 53% in 6-mg group and 58% in 2 mg group, mainly due to disease progression. Three patients experienced serious adverse events related to treatment. One in the ibandronate 2-mg group (asthenia & hydronephrosis) and 2 in the ibandronate 6-mg (one with bone pain and one with lung oedema).

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Tripathy et al 2004[18]	R, PG, DB, PC, MC.	Ibandronate 20 mg PO daily for 96 weeks. Ibandronate 50 mg PO daily for 96 weeks Placebo daily for 96 weeks	144 148 143	Breast cancer with bone metastases, WHO status: 0, 1 or 2, >18 years.	Previous treatment with bisphosphonates or gallium nitrate within the last 6 months, life expectancy <60 weeks, hypercalcaemia, hypocalcaemia, severely impaired renal function, Paget's disease of bone, primary hyperparathyroidism, known liver/brain metastases, treatment with aminoglycoside antibiotics within 4 weeks prior to the start of the study medication.	Skeletal morbidity period rate (SMPR) defined as the number of 12-week periods with new skeletal complications divided by the total observation time. Skeletal complications included vertebral fractures, non-vertebral fractures, radiotherapy for bone complications, and surgery for bone complications.	SMPR for all new bone events was significantly reduced with oral ibandronate 50 mg and 20 mg compared with placebo (global p=0.044). Significant reductions in bone events requiring radiotherapy (p <0.005) with ibandronate 50 mg.	Drug related AEs were: ibandronate 20 mg 26.4%, ibandronate 50 mg 27.9% and placebo 21.7%. Higher incidence of dyspepsia, nausea and oesophagitis in the ibandronate group.

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Body JJ et al 2004[19]	PA, DB, PC, R, MC, PG.	Placebo PO daily for 96 weeks Ibandronate 50 mg PO daily for 96 weeks	277 287	Breast cancer, radiologically confirmed bone metastases, WHO status: 0, 1 or 2, >18 years.	Previous treatment with bisphosphonates or gallium nitrate within the last 6 months, life expectancy <60 weeks, hypercalcaemia, hypocalcaemia, severely impaired renal function, Paget's disease of bone, primary hyperparathyroidism, known liver/brain metastases, receiving high-dose chemotherapy, history of aspirin-sensitive asthma or receiving treatment with aminoglycosides within 4 weeks.	Mean SMPR defined as the number of 12-week periods with new skeletal complications, divided by the total observation time. Skeletal complications included vertebral fractures, non-vertebral fractures, radiotherapy for bone complications, and surgery for bone complications.	SMPR for all new bone events was significantly reduced with oral ibandronate 50 mg compared with placebo (p=0.004).	Most frequent AE: malignancy progression: ibandronic acid 67.5% and placebo 70.8%. Drug related AEs: ibandronate 26.6%, placebo 17.7%. Higher incidence of dyspepsia, nausea and oesophagitis in the ibandronate group. Renal AEs: ibandronate; 5.2% and placebo; 4.7%

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Menssen et al. 2002[20]	R, DB, PC, PG, MC.	Ibandronate 2mg IV bolus for 12-24 months Placebo for 12-24 months	99 99	Adults with stage II/III multiple myeloma, life expectancy >12 months, ≥1 osteolytic lesion.	Serum creatinine >265.2 mol/L, corrected calcium >2.7mmol/L, treatment with fluorides or bisphosphonates during the last 6 months and 3 months, respectively, treatment with calcitonin during the last month, active metabolic bone disease, bedridden, pregnant or lactating, history of other concomitant cancer, aspirin-sensitive asthma, treatment with aminoglycosides in the last 3 months, participation in another clinical trial during the last 4 weeks.	Number of 3-month periods with new bone complications, (peripheral pathological fracture, significant vertebral reduction (>25%), hypercalcaemia, severe bone pain, radiation therapy.	The number of 3-month periods with new bone complications was similar in placebo and ibandronate groups. No significant difference in SREs per patient year was observed between the ibandronate and placebo group.	86% of patients experienced at least one AE. Ninety-one patients completed the study (49 ibandronate, 42 placebo). 107 patients dropped out prematurely (50 ibandronate, 57 placebo). The primary reason for drop outs was AEs (40 placebo, 42 ibandronate).

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Terpos E et al 2003[21]	R, O, MC.	Pamidronate 90 mg IV infusion monthly Ibandronate 4 mg IV infusion monthly	23 21	Confirmed multiple myeloma stage II/III, paraprotein detectable in blood or urine, and skeletal radiographs showing definite osteolytic lesions or diffuse osteoporosis.	Serum creatinine >4 mg/dL, ascites, total bilirubin >2.5mg/dL, abnormal electrocardiogram, bisphosphonate, calcitonin, or corticosteroid treatment within 2 months of enrolment.	None stated. Bone resorption markers (*N*-terminal cross-linking telopeptide of type I collagen (NTX) and tartrate-resistant acid phosphatase type 5b (TRACP-5b)), bone formation markers (bone alkaline phosphatase and bone osteocalcin) and markers of disease activity (paraprotein, CRP, β2-microglobulin) and interleukin (IL-6)) were measured.	Greater reduction of NTX, IL-6 and β2-microglobulin in group I than in group II, starting at the second month of treatment. (p=0.002, 0.001 and 0.004, respectively) and of TRACP-5b, starting at the fourth month (p=0.014), There were no differences in skeletal events during this period.	One patient in the pamidronate group and 2 patients in the ibandronate group had febrile episodes after the first infusion. Two patients in the ibandronate group had an episode of hypocalcaemia (after the eight and ninth cycle) and one of them had to discontinue treatment because of severe hypocalcaemia that needed hospitalisation.

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Deil et al 2004[22]	R, O, PC, PG, MC.	Ibandronate 2 mg IV bolus 3-4 weeks for 96 weeks	154	Breast cancer, radiologically confirmed bone metastases, WHO status: 0, 1 or 2, >18 years.	Previous treatment with bisphosphonates or gallium nitrate within the last 6 months, life expectancy <60 weeks, hypercalcaemia, hypocalcaemia, severely impaired renal function, previous high-dose chemotherapy, Paget's disease of bone, primary hyperparathyroidism, known liver/brain metastases, receiving high-dose chemotherapy, history of aspirin-sensitive asthma or receiving treatment with aminoglycosides within 4 weeks, pregnant, lactating, receiving investigational drugs or aminoglycoside in last 30 days.	Secondary outcome: bone pain (using scale from 0-4), analgesic consumption and quality of life(EORTC)	Mean change in bone pain score was significantly different ($p<0.001$) between ibandronate 6 mg and placebo. Analgesic requirements increased in all groups. No statistically significant differences among groups. Significant improvement in quality of life for patients treated with ibandronate ($p<0.05$) for all global health. Ibandronate 6 mg: significantly better functioning compared with placebo ($p= 0.004$)	Flu-like syndrome and arthralgia occurred slightly more frequently in the ibandronate groups than in the placebo group. Flu-like syndrome: placebo 1.9%, ibandronate 2mg 6.5%, ibandronate 6mg 6.6%. Arthralgia:placebo 7.6%, ibandronate 2mg 13.1%, ibandronate 6mg 11.2%
		Ibandronate 6 mg IV infusion every 3-4 weeks for 96 weeks	154					
		Placebo IV every 3-4 weeks	158					

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Heidenreich et al 2002[23]	O.	Ibandronate 6 mg IV for 3 days, then ibandronate 6 mg every 4 weeks.	25	Symptomatic skeletal metastases from hormone refractory prostate cancer (HRPCA) ,life expectancy of >3 months, capable of completing pain scales and diary of analgesic consumption.	Serum creatinine > 2.5 mg/dL, use of bisphosphonates during the last 3 months or cytotoxic drugs during the last 4 weeks.	Pain reduction documented by the use of 10-point VAS, daily analgesic requirements.	Significant reduction in pain score from 6.5 (5-10) to 2.0 (0-4) achieved in 23 patients ($p<0.001$). Nine patients were completely pain free without further need for analgesic medication. Fourteen patients experienced a significant reduction in consumption of analgesic drugs.	4 patients experienced febrile episode after infusion.

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Mancini et al 2004 [24]	O.	Ibandronate 4 mg IV daily for 4 days	18	Any malignant tumour, history of moderate to severe, opioid resistant, metastatic bone pain.	Received bone radiotherapy in previous 4 weeks, received bisphosphonates in last 2 months, hypercalcaemia, impaired renal function, a change to systemic hormonal treatment or chemotherapy during the last 4 weeks, delirium or confusion.	Not stated.	Significant reduction in pain scores (using VAS) from baseline with ibandronate within 7 days ($p<0.001$).	One patient experienced fever, myalgia, malaise. One patient experienced transient increase in bone pain lasting 2-3 hours post treatment.

Key: R-randomised controlled trial; DB-double blinded; PC-placebo-controlled; PG-Parallel-group; MC-multi-centre; PA-Pooled analysis; PO-oral; IV-intravenous; CI-confidence interval; AE-adverse effect; SMPR-skeletal morbidity period rate; WHO-World Health Organisation; EORTC-European Organisation for the Research and Treatment of Cancer; VAS-Visual Analogue Scale, S-Stratified, O - Open-label,

Reference	Design	Intervention	Patient Nos	Inclusion criteria	Exclusion criteria	Primary Outcome	Results	Adverse Effects
Lyubimova et al 2003[25].	O, R, PC.	Ibandronate 2 mg IV bolus every 4 weeks for 3 months	23	Breast cancer with bone metastases, (WHO grade 0-2), normal serum calcium, serum creatinine <265 μmol/L, life expectancy of >60 weeks.	Liver or brain metastases, high-dose chemotherapy	Measurements of urinary excretion of total protein, albumin, alpha 1 microglobulin, N acetyl-β-D-glucosaminidase, frequency of haematuria, serum creatinine.	Assessments of proteinuria, haematuria, enzymuria and serum creatinine indicated that there were no statistically significant changes between pre- and post-treatment levels in patients receiving ibandronic acid 2 or 6 mg or between patients receiving ibandronic acid or placebo.	No adverse effects stated.
		Ibandronate 6 mg, IV infusion every 4 weeks for 3 months	28					
		Placebo IV infusion every 4 weeks for 3 months	23					