Cost-Effectiveness of Oral Ibandronate Versus IV Zoledronic Acid or IV Pamidronate for Bone Metastases in Patients Receiving Oral Hormonal Therapy for Breast Cancer in the United Kingdom

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ABSTRACT

Background: Oral ibandronate is a single-nitrogen bisphosphonate whose efficacy is similar to that of IV ibandronate for the treatment of bone metastases.

Objective: The aim of this study was to compare the cost-effectiveness of oral ibandronate with zoledronic acid and generic pamidronate (both administered by IV) for the treatment of bone metastases in patients with breast cancer receiving oral hormonal therapy in the United Kingdom.

Methods: A global economic model was adapted to the UK National Health Service. Patients were assumed to receive oral hormonal therapy for 50% of their projected 14.3-month survival. The primary outcome was incremental cost per quality-adjusted life-year (QALY). Bisphosphonate efficacy data for relative risk reduction of skeletal-related events (SREs) were obtained from clinical trials. Resource use data and costs associated with IV bisphosphonate infusions were derived from published studies and a unit cost database; monthly drug acquisition costs were obtained from the British National Formulary. Utility scores were applied to time with or without an SRE to adjust survival for quality of life. Therefore, differences in QALYs were driven by utility weights rather than survival time. Model design and inputs were validated through expert UK clinician review. The absence of comparative efficacy and safety data from clinical trials for the different bisphosphonates was a model limitation that we addressed by supporting our assumptions with UK expert clinician opinion and with expert clinician opinion outside of the United Kingdom, and by conducting sensitivity analyses.

Results: The projected total cost per patient was £307 less with oral ibandronate compared with zoledronic acid, and £158 less compared with the use of generic pamidronate (due to a reduction in staff time for infusions, avoidance of renal safety monitoring visits, and, in the case of IV generic pamidronate, a reduction in the number of SREs). Oral ibandronate was estimated to lead to a gain of 0.02 QALY, making it the economically dominant treatment option.

Conclusions: In this study, we found that oral ibandronate was cost-effective for the management of bone metastases from breast cancer among patients receiving oral hormonal therapy in the United Kingdom. Oral ibandronate provided effective SRE and bone-pain management while avoiding resource use and costs associated with regular IV bisphosphonate infusions. Due to uncertainty surrounding the model assumptions, it would be valuable to repeat the analyses using data from comparative bisphosphonate trials, once they become available. (*Clin Ther.* 2005; 27:1295–1310) Copyright © 2005 Excerpta Medica, Inc.

Key words: cost-effectiveness, ibandronate, oral, bisphosphonate, bone metastases, skeletal-related events, zoledronic acid.

Accepted for publication June 1, 2005.
doi:10.1016/j.clinthera.2005.08.006
0149-2918/05/$19.00

INTRODUCTION

Advanced malignant disease frequently metastasizes to the bone, particularly in multiple myeloma, lung cancer, prostate cancer, and breast cancer.[1,2] Approximately 80% of breast cancer patients progressing to metastatic disease will develop bone lesions.[3] Each year, an estimated 25% to 40% of these patients will need radiotherapy for bone pain, 5% to 30% will develop hypercalcemia, and 17% to 50% will experience vertebral fractures.[4] Consequently, bone metastases from breast cancer are linked to poor quality of life (QoL), disability, and distress.[5] Because both the incidence of breast cancer and the number of patients surviving the disease are increasing worldwide,[6] the burden of associated bone disease can be expected to grow in the future.

Treatment goals in metastatic bone disease include the reduction of skeletal morbidity, alleviation of metastatic bone pain, and improvement in QoL and mobility. Used as adjuncts to conventional anticancer therapies, current management options may include radiotherapy, surgery, analgesics, and bisphosphonates.[7] Bisphosphonates reduce the incidence of new bone events by inhibiting pathological osteoclast-mediated bone resorption and have become incorporated into standard therapy for malignancy-related bone disease.[7] These agents can also offer pain relief, which appears to be independent of the primary tumor type or the nature of bone lesions (ie, lytic or sclerotic).[8–11]

As well as having clinical consequences, breast-cancer bone metastases have an enormous impact on health care systems. In 2002, the typical lifetime treatment cost for advanced breast cancer (ie, stage IV) was estimated at more than £12,500 per patient in the United Kingdom.[12] Much of the financial burden of malignancy-related bone disease arises from hospital management of complications, rather than antineoplastic therapy.[4] A 2004 study conducted in the United States found that mean total costs for managing breast cancer and bone metastases were US $52,099 greater per patient among those with skeletal-related events (SREs) compared with those who did not have SREs, and the costs directly attributable to bone complications were US $14,580 per patient.[13]

By reducing the rate of SREs and relieving symptoms, bisphosphonates have the potential to reduce hospital stays and the need for bone surgery, radiotherapy, or analgesics. Another substantial cost driver is the health care resources required for IV administration, including drug acquisition, pharmacy and nurse time for preparing and administering infusions, patient renal safety monitoring, and the use of other hospital equipment.[4,14] At present, it is difficult to compare the cost-effectiveness of individual bisphosphonates (due to interstudy variations in patient populations) and in clinical outcomes and measurements,[4,6] as well as differences in drug pricing between countries. With its shorter infusion time (15 minutes vs 90 minutes), it might be expected that zoledronic acid would be more cost-effective than pamidronate. In a 2001 microcosting analysis of these 2 bisphosphonates, although zoledronic acid 4 mg increased the availability of infusion chairs compared with pamidronate 90 mg, health care costs per patient remained similar (US $728 and US $776, respectively).[14]

In patients no longer receiving IV infusions of chemotherapy, oral bisphosphonates are expected to be cost-effective, eliminating the use of infusion supplies as well as hospital visits solely to administer IV bisphosphonates.[15] To date, few economic analyses of oral bisphosphonates have been conducted (as confirmed by MEDLINE search using terms *cost* or *economic*, and *oral*, and *bisphosphonate* or *ibandronate* or *ibandronic* or *clodronate*; all years; all languages). One study reported that clodronate might be cost saving in patients with breast cancer and bone metastases if hospital costs for skeletal complications were reduced by ≥20%.[16] A 1997 retrospective analysis of resource consumption for a 1-year, placebo-controlled, randomized trial found that clodronate reduced hospitalizations by 19%, shortened the duration of hospital stay by ~7 days, and lowered expenditures for radiotherapy. By increasing the rate of SRE-free survival by 9% and delaying the occurrence of bone events by 64 days, clodronate was projected to cost 7976 francs (approximately €9000 [year-2005 conversion rate]) for preventing 1 patient from having an SRE in 1 year.[17] Both studies were limited in their analysis of SREs only; neither took QoL end points, such as bone pain, into account.

Ibandronate is a single-nitrogen bisphosphonate that has been approved in more than 40 countries since 2003 for the management of bone metastases due to breast cancer. Ibandronate is available in IV and oral formulations with apparently similar efficacy against SREs and metastatic bone pain.[4,18–20] Economic models have been developed to compare the cost-effectiveness of oral ibandronate with other bisphosphonates in patients with breast cancer and bone metastases in the

United Kingdom. Among patients receiving IV chemotherapy in the United Kingdom, oral ibandronate was found to be cost-effective compared with zoledronic acid and generic pamidronate.[21] The current analysis is the first to compare the cost-effectiveness of oral ibandronate with that of these IV bisphosphonates for the treatment of bone metastases in breast cancer patients receiving oral hormonal therapy.

PATIENTS AND METHODS

Model Scope and Perspective

The model estimated per-patient costs and benefits for expected mean survival following an intent-to-treat approach and produced a cost-utility analysis with incremental cost per quality-adjusted life-year (QALY) as the primary outcome. The model was adapted to the perspective of the UK National Health Service (NHS). Only direct health care costs were considered, assuming a single funding source for all costs at the hospital level.

Mean Survival

Due to the absence of direct comparative survival data, a mean survival of 14.3 months was assumed, as was used in a previous cost-effectiveness model of IV pamidronate versus placebo.[22–24] This mean survival was assumed to be equivalent for all of the bisphosphonates in the model, because a Phase III comparative trial failed to show a statistically significant survival advantage for zoledronic acid compared with pamidronate in patients with established bone metastases.[25] The comparative survival benefits of ibandronate versus other bisphosphonates are yet to be investigated in this patient population. However, the effect of a longer survival period on cost-effectiveness was tested using sensitivity analysis.

Patient Population

The analysis was undertaken for a sample of women with breast cancer and metastatic bone disease who were assumed to be receiving oral hormonal therapy. Population characteristics (ie, age, disease progression, performance status) were aligned with those of Phase III trials of oral ibandronate in metastatic bone disease from breast cancer.[18] Patients in these trials had a median age of 57 years (range, 27–92 years), and had received a diagnosis of bone metastases ~6 months earlier (median time since initial breast cancer diagnosis was 3 years, 7 months). Most patients (84%) had a World Health Organization performance status of 0 or 1, and 70% to 80% of patients had received oral hormonal therapy (F. Hoffmann-La Roche Ltd., Basel, Switzerland, oral ibandronate clinical study report, 2002).[18]

Key Assumptions

The model incorporated several key assumptions for treatment practices and costs that were based on review by 2 clinician experts in the United Kingdom and 1 in Belgium. According to these assumptions, ~50% of patients starting hormonal therapy are positive for both estrogen and progesterone receptors and receive hormonal therapy for about 65% of their metastatic life. The other ~50% are assumed to be positive for only 1 type of receptor and receive hormonal therapy for ~40% of their metastatic life. Therefore, we assumed that the typical patients would remain on hormonal therapy for ~7.5 months (just over half of the mean survival time).

Other assumptions included that once hormonal therapy had failed, patients would be switched to a 4-month chemotherapy cycle. IV bisphosphonates would be administered once per month regardless of whether patients were on or off chemotherapy (while on chemotherapy, IV bisphosphonates would be administered on the day of chemotherapy infusion). Oral ibandronate would require monitoring once every 3 months during routine oncologic assessment. Monitoring for IV bisphosphonates would be undertaken at every infusion and an extra biochemistry test would be done every second month (ie, when there was no routine oncologic assessment). Moreover, patients could discontinue treatment for drug-related adverse events (assumed at 1 month) or for noncompliance (assumed at 6 months). No health care–professional costs would be specifically associated with administering an oral bisphosphonate, except patient monitoring costs. Costs for chemotherapy would be similar between patients receiving different bisphosphonates and are therefore excluded from the analysis.

Other key assumptions are described below, as part of the model inputs.

Model Inputs

SREs

The key effectiveness driver in the model was the mean number of SREs while receiving each bisphosphonate (**Table I**).[22,26,27] These were not directly comparable across published studies because of interstudy

Table I. Model inputs: skeletal-related events (SREs).

Drug	SRE Relative Risk Reduction, %	Expected Number of SREs	Months per Patient With/Without SRE*
Placebo	NA	3.23[22]	NA
Oral ibandronate	38[26]	2.00	2.00/12.30
IV zoledronic acid	38†	2.00	2.00/12.30
IV pamidronate	35[27]	2.10	2.10/12.20

NA = not applicable.
*Over 14.3 months' survival.
†Assuming same SRE efficacy as oral ibandronate, based on clinical experts.

differences in patient populations, time horizons, and efficacy measures.[4,24–30] Therefore, a baseline (ie, placebo) level of 3.23 months with an SRE per patient was assumed, as used in a previous cost-effectiveness analysis,[22] and each drug's relative risk reduction for SREs was applied to this placebo value. The risk reduction rates for oral ibandronate 50 mg and IV pamidronate 90 mg were taken from published placebo-controlled trials.[18,26,27] At the time of model development, there were no published results from a placebo-controlled trial of zoledronic acid in metastatic bone disease from breast cancer (confirmed by MEDLINE search using the following terms: *IV* or *intravenous* and *zoledronic* or *zoledronate*, and *placebo*, and *breast*, and *metastatic* or *metastases*; all years; all languages), so we conservatively assumed the same SRE relative risk reduction as for oral ibandronate (**Table I**).

The duration of a single SRE was assumed to be 1 month, as in a previous cost-effectiveness analysis (pamidronate vs placebo).[22] The number of months spent with or without an SRE over 14.3 months of survival was calculated for each treatment and the associated costs and QoL weights were applied.

Bone Pain Management

The assumed proportion of patients on placebo receiving each type of medication and dosing/duration over a 1-year period was provided by our 3 clinician experts. A monthly cost was applied to the survival time to yield the expected total cost of analgesic use for patients not receiving bisphosphonates.

For oral ibandronate, we assumed that a 7% reduction in analgesics score versus placebo would reflect the reduction in analgesic use associated with this treatment.[18–20] We assumed a 3% reduction in analgesic use with both zoledronic acid and pamidronate because no comparable placebo-controlled data on reduction in analgesics score, nor clear evidence of a statistically significant reduction in bone pain below baseline levels was available from clinical trials.[9,25,27,31] A reduction of 7% in analgesic use for all bisphosphonates was explored in a sensitivity analysis.

Utilities

To reflect the benefit that bisphosphonates might have on reducing bone pain in general, we used the QALY as the primary outcome measure. QALYs are estimated by summing the years of survival, weighted by QoL.[32]

Bisphosphonates have incremental benefits that might be reflected in maintained or even improved QoL by avoiding SREs and/or reduction in bone pain.[10,20] The time with or without SREs was adjusted for QoL using the utility estimates presented in **Table II.** One published study in patients with metastatic bone disease reported a 0.4 baseline utility for placebo,[33] which we used as the rate for a month without an SRE. For 1 month with an SRE, we reduced the baseline utility by 30%, regardless of which bisphosphonate the patient would receive.[22] We assumed a 5% increase in baseline utility per month without an SRE due to bone pain relief with oral ibandronate, which was shown to be significantly reduced below baseline for 2 years in Phase III trials (at end point, –0.1 vs 0.2; $P = 0.001$).[19,20] We considered this to be a conservative estimate, given the overall impact of pain on QoL in these patients.[1,34]

Although pamidronate and zoledronic acid reduced bone pain below baseline for 1 year in a comparative

Table II. Model inputs: utilities.

Parameter	Value	Reference
Baseline utility for patient with metastatic bone disease	0.4	van den Hout et al[33]
Reduction in baseline utility due to SRE, %	30	Hillner et al[22]
Utility for a month with an SRE	0.28	Calculated*
Increase in baseline utility when using oral ibandronate	0.02	Estimate†
Utility for an SRE-free month when receiving oral ibandronate	0.42	Calculated‡
Utility for an SRE-free month when receiving IV pamidronate or IV zoledronic acid	0.40	van den Hout et al[33]

SRE = skeletal-related event.
*Calculated as 0.4 × 70%.
†Based on an assumption of 5% increase in baseline utility (0.40 × 0.05 = 0.02).
‡Calculated as 0.40 + 0.02.

Phase III trial of patients with metastatic breast cancer or multiple myeloma,[25] these reductions were not shown to be statistically significant and they were not reported in the 2-year results of the same study.[28] Bone pain levels increased from baseline in other pamidronate trials over time.[27] For the base case, we therefore assumed no improved utility due to bone pain relief with these bisphosphonates. No improved utility with oral ibandronate was explored in the sensitivity analysis.

Discontinuation Due to Adverse Events and Failed Compliance

Discontinuation can occur because of a drug-related adverse event or noncompliance. A discontinuation rate of 3.1% (9 out of 286 reported adverse events) for oral ibandronate was taken from Phase III trials.[35] Approximately 6% to 7% of patients participating in IV zoledronic acid trials discontinued treatment due to treatment-related adverse events,[36] but based on the opinions of our 3 expert clinicians, this was lowered to 4.0%. In the absence of published data, the discontinuation rate for IV pamidronate was assumed to be 2.0%, as reported for IV ibandronate.[37] The probabilities for treatment discontinuation used in the base-case cost-effectiveness analysis are shown in Table III.

Base-case values for failed compliance were obtained from expert clinician opinion. We assumed that after 4 months of IV bisphosphonates, 25% of patients would decline further IV treatment because of the inconvenience of monthly hospital visits. An estimated 50% of these patients would then switch to oral ibandronate, with the rest (ie, 12.5% of the overall sample) stopping all bisphosphonate treatment. The SRE risk reduction rates, derived from trials and from the published literature, were applied to patients either continuing treatment or discontinuing treatment due to adverse events. Therefore, these data do not take into account those who might discontinue due to failed compliance. As a result, we conservatively assumed that the overall SRE risk reduction rates would continue to apply to patients who discontinued IV bisphosphonates due to failed compliance (ie, the treatment effect would extend beyond the treatment period). For the 12.5% of patients projected to switch to oral ibandronate, we assumed that the expected number of SREs over survival would be weighted for the time on IV bisphosphonate versus oral ibandronate, thus transferring some of the SRE reduction benefit from oral ibandronate to the IV bisphosphonate arms. We also weighted analgesic use and QoL (ie, utility) for the time on each treatment, assuming no time lag in these outcomes.

Drug Safety

The model took into account the potential impact of drug-related renal impairment on treatment costs. This affected 8.8% to 15.2% of patients receiving zoledronic acid in Phase III trials of patients with breast cancer, multiple myeloma, prostate cancer, or other solid tumors.[38] Because there were no safety results available from placebo-controlled trials of zole-

Table III. Probabilities of treatment continuation used in base-case cost-effectiveness analysis.

Variable	Probability of Continuation: Oral Ibandronate, %	Probability of Continuation: IV Zoledronic Acid, %	Probability of Continuation: IV Pamidronate, %	Time Point
Patient continued	96.9	71.0	73.0	14.3 months' survival
Switch to oral ibandronate after failed compliance	0.0	12.5	12.5	At 6 months
Discontinuation after adverse events	3.1	4.0	2.0	At 1 month
Discontinuation after failed compliance	0.0	12.5	12.5	At 6 months
Total	100	100	100	

dronic acid in breast cancer patients only, we applied the 9% risk of renal impairment over 1 year of treatment from a breast cancer and multiple myeloma trial[25] to the placebo rate of renal impairment from the IV and oral ibandronate breast cancer trials (4%).[39] This resulted in a conservative 5% incidence rate for zoledronic acid. The same definition of renal impairment was used in each study (serum creatinine increase of 0.5 mg/dL from baseline, if baseline serum creatinine was <1.4 mg/dL; 1.0 mg/dL from baseline, if baseline serum creatinine was >1.4 mg/dL, or twice the baseline value). The model also included a probability of renal failure (0.015%) with zoledronic acid[40] to assess its impact on treatment-related costs.

Based on Phase III trial data (risk comparable to placebo) and the absence of published reports of renal toxicity in clinical practice, no drug-related renal impairment was assumed for oral ibandronate.[35]

The incidence of renal impairment with IV pamidronate was 8% in the trial of zoledronic acid and pamidronate for patients with bone metastases from breast cancer or multiple myeloma.[25] However, the prescribing information for IV pamidronate only reports a risk of renal deterioration in patients with multiple myeloma, rather than breast cancer (the target population of the model),[41] and no renal events were reported in placebo-controlled trials.[26] Therefore, the model conservatively assumed no additional risk of renal toxicity with IV pamidronate, as with ibandronate. This was supported by expert clinician opinion.

Resource Use

Staff time and supplies for bisphosphonate infusions were obtained from a US microcosting study[14] and were validated by a UK clinician for the UK setting. Although recommended infusion times differ between bisphosphonates (15 minutes for zoledronic acid vs 90 minutes for pamidronate), it was assumed that nurses can treat multiple patients at the same time and are free to carry out other tasks once IV lines have been inserted. The choice of 22 minutes and 30 seconds was based on an infusion time for pamidronate of 90 minutes and expert opinion suggesting that nurses administering lengthy infusions can treat up to 4 patients in a clinic suite at any given time.

Unit Costs

Table IV shows the unit costs of UK health care resources included in the model.[42–48] Unit costs were applied to SRE management, IV bisphosphonate administration (ie, personnel time and supplies), laboratory tests, renal impairment or failure, pain management, and drug acquisition.

Clinical trials of ibandronate, zoledronic acid, and pamidronate defined SREs as pathological fracture, spinal cord compression, radiation therapy, and surgery to bone. For the model, we estimated a total cost for SRE management from 2003 NHS mean costs for pathological fractures due to malignancy of bone and connective tissue (with or without complications, codes H53 and H54).[43] These codes include all medi-

Table IV. Unit costs used in the model.

Type of Care	Unit Cost, Year-2003 £	Source
Bisphosphonates		
Oral ibandronate 50 mg/d	195	BNF 46[42]
IV zoledronic acid 4 mg (q3–4 weeks)	195	BNF 46[42]
IV generic pamidronate 90 mg (q3–4 weeks)	165	BNF 46[42]
SRE management		
Pathological fracture and radiotherapy	2351	NHS Reference Costs 2003[43]
IV administration costs		
Personnel per hour		
Physician	90	PSSRU[44]
Pharmacy technician	11	PlanetRecruit[45]
Nurse	18	PSSRU[44]
Auxiliary nurse	10	PSSRU[44]
Infusion supplies	11.27	Medisave,[46]* BNF 46,[42]† UK hospital‡
Laboratory tests		
Biochemistry plus hemogram test	25.66	MEDTAP[47]
Renal failure		
Home dialysis, per session	128	NICE Appraisal Guidance[48]
Hospital dialysis, per session	146	NICE Appraisal Guidance[48]
Renal impairment, per week§	11	BNF 46[42]
Pain management, per month‖	19	BNF 46[42]

BNF 46 = British National Formulary 46; SRE = skeletal-related event; NHS = UK National Health Service; PSSRU = Personal Social Services Resource Unit; NICE = National Institute for Health and Clinical Excellence.
*Needle, gauze, swab, syringe, set of gloves, medical tape, and sample tubes.
†250 mL 5% dextrose solution.
‡Disposable IV set.
§Including recombinant human erythropoietin and angiotensin-converting enzyme inhibitors.
‖Including morphine, oxycodone, acetaminophen, and ibuprofen.

cal services given to patients in these 2 diagnostic groups (ie, fracture management with surgery and radiotherapy, elective [nonemergency] and nonelective [emergency] treatment). The radiotherapy cost excluded transport to the radiotherapy department.

Sensitivity Analyses

One-Way Sensitivity Analyses

We checked the robustness of the base-case results by conducting a series of 1-way sensitivity analyses, varying key assumptions that might reduce the cost-effectiveness advantage of oral ibandronate over the IV bisphosphonates. The following scenarios were included: prolonged survival of 24 months (base case, 14.3 months); no QoL advantage for ibandronate (base case assumed a 5% increase in baseline utility for a month without an SRE and no advantage for the comparators); 7% reduction in analgesic usage for all bisphosphonates (base case, 7% for oral ibandronate vs 3% for zoledronic acid and pamidronate); 100% compliance/no discontinuation (base case assumes that some patients will stop IV bisphosphonates due to drug-related adverse events or noncompliance); 2% discontinuation rate due to treatment-related adverse events for all bisphosphonates, and no renal impairment for zoledronic acid; nursing cost directly correlated to length of infusion (ie, 15 minutes for zoledronic acid vs 90 minutes for pamidronate, rather

than 22 minutes and 30 seconds for all options); no SRE efficacy advantage for oral ibandronate over pamidronate (38% risk reduction for oral ibandronate, compared with 35% for pamidronate); and 50% decrease in SRE treatment cost.

Probabilistic Analysis

A probabilistic sensitivity analysis was performed to account for uncertainty in the model parameters. This method handles uncertainty in the cost-effectiveness results by assigning a distribution to selected parameters and undertaking repeated Monte Carlo simulations of the cost-effectiveness analysis.[49] Five thousand simulations were undertaken and, for each threshold value of a QALY gained (£0 to £100,000), the probability of the results being cost-effective was calculated.

RESULTS

Base-Case Analysis

With an expected survival of 14.3 months for patients with breast cancer and bone metastases receiving oral hormonal therapy, the model projected that the total cost of treatment (including drug acquisition), renal impairment and failure, SREs, and pain management would be £307 less per patient with oral ibandronate than with zoledronic acid and £158 less per patient than with IV generic pamidronate (**Table V**).

Table V. Base-case cost-effectiveness results for oral ibandronate compared with IV zoledronic acid and IV pamidronate.

	Oral Ibandronate	IV Zoledronic Acid	IV Pamidronate
Cost per patient, £			
Bisphosphonate treatment continuation	2737	2496	2213
Bisphosphonate treatment switch to oral ibandronate	0	377	360
Bisphosphonate discontinuation	6	133	111
Renal toxicity*	0	34	0
SREs	4708	4708	4915
Pain management	249	259	259
Total	7700	8008	7858
Savings per patient, £			
Versus zoledronic acid	307		
Versus pamidronate	158		
SREs, mo			
Per patient with an SRE	2.00	2.00	2.09
Per patient without an SRE	12.30	12.30	12.21
Additional SRE-free time versus zoledronic acid	0.00		
Additional SRE-free time versus pamidronate	0.09		
Quality-adjusted end points			
QALYs with SREs, mo	0.56	0.56	0.59
QALYs without SREs, mo	5.16	4.94	4.91
Total quality-adjusted life-months	5.73	5.51	5.49
Total QALYs	0.477	0.459	0.458
Additional QALYs versus zoledronic acid	0.018†		
Additional QALYs versus pamidronate	0.019‡		

SRE = skeletal-related event; QALYs = quality-adjusted life-years.
*Impairment and failure.
†6.7 Days.
‡7.1 Days.

Differences in QALYs were driven by utility weights rather than survival time. Taking a fixed reduction in utility for the time with SREs into account, as well as a 5% increase in baseline utility with oral ibandronate per month with an SRE, oral ibandronate led to a gain of 0.018 and 0.019 QALYs compared with IV zoledronic acid and IV pamidronate, respectively. This corresponded to an additional 6.7 and 7.1 quality-adjusted life-days. The reduction in cost and increase in outcome results in oral ibandronate being the dominant treatment option.

Sensitivity Analyses

One-Way Analysis

Table VI summarizes the results of the one-way sensitivity analyses.

A 24-month survival would increase the time in which a patient was not undergoing chemotherapy; therefore, because of additional IV infusions, the incremental cost advantage of oral ibandronate over zoledronic acid rose from £307 per patient in the base case to £428, with incremental outcomes increasing as well. Similarly, a reduction in survival time would proportionately decrease both costs and outcomes. The base-case incremental costs were unchanged when no QoL advantage was assumed for oral ibandronate; therefore, oral ibandronate remained cost-saving versus both IV bisphosphonates.

A 7% reduction in analgesic use for all options would slightly reduce cost savings with oral ibandronate. With a 2% rate of discontinuation due to treatment-related adverse events and no renal toxicity for all bisphosphonates, the incremental cost advantage of oral ibandronate would increase very slightly versus zoledronic acid, and would decrease versus pamidronate, without substantially affecting incremental outcome. With 100% compliance/no discontinuation, the dominance of oral ibandronate would increase because patients who discontinued zoledronic acid and IV pamidronate in the base case would now be kept on treatment, thus accumulating drug costs.

If the nurse were assumed to stay with the patient throughout the whole infusion, staff cost would increase with IV generic pamidronate, making oral ibandronate more dominant. A zoledronic acid infusion time of 15 minutes would reduce staff costs, resulting in oral ibandronate becoming less dominant. If there were no SRE efficacy benefit over IV pamidronate, then oral ibandronate would be slightly more costly. Assuming a 50% decrease in SRE treatment cost, the incremental cost advantage of oral ibandronate would decrease considerably versus generic pamidronate, without affecting the outcome benefit.

All 1-way sensitivity analyses showed a positive incremental net benefit, implying that oral ibandronate consistently remained cost-effective versus both IV bisphosphonates, given a cost-effectiveness threshold of £30,000 per QALY.

Probabilistic Analysis

By means of pairwise comparisons, the cost-effectiveness acceptability curves showed that at a cost per QALY of £30,000 and above, oral ibandronate was the cost-effective strategy in ≥82% of simulations versus IV zoledronic acid and ≥79% of simulations versus IV pamidronate (**Figures 1** and **2**). The likelihood of oral ibandronate being cost-effective would increase with rising thresholds, because the incremental outcomes associated with oral ibandronate (QALYs as a result of higher utility weights) were valued at a higher amount.

DISCUSSION

The model predicted that oral ibandronate is cost-effective compared with IV bisphosphonates, due to its efficacy in reducing SREs and bone pain, favorable tolerability profile, and avoidance of monthly bisphosphonate infusions. The model was unavoidably limited by its reliance on data from noncomparative trials of different bisphosphonates, leading to subjectivity in the assessment of drug efficacy and safety, as well as in the choice of assumptions. To overcome this, we applied the risk reduction of SREs with each bisphosphonate to the same placebo rate of SREs in patients with bone metastases due to breast cancer, as reported in 1 randomized trial.[22] This was supported by expert clinician opinion. At the time of model development, there were no published results from a placebo-controlled trial of zoledronic acid in metastatic bone disease from breast cancer, so we conservatively assumed the same SRE relative risk reduction as for oral ibandronate (ie, 38%). Recently, trial results for zoledronic acid in Japanese breast cancer patients with bone metastases have been published, showing a 39% risk reduction in SREs versus placebo.[50]

Table VI. Sensitivity analyses of oral ibandronate compared with IV zoledronic acid and IV pamidronate.

Variable	Oral Ibandronate Versus IV Zoledronic Acid	Oral Ibandronate Versus IV Pamidronate
Base case		
Incremental net benefit, £	859	737
Cost savings, £	307	158
Additional QALYs	0.018	0.019
Prolonged survival of 24 months		
Incremental net benefit, £	1335	1151
Cost savings, £	428	197
Additional QALYs	0.030	0.032
No QoL advantage for oral ibandronate: 0% increase in utility		
Incremental net benefit, £	307	184
Cost savings, £	307	158
Additional QALYs	0.000	0.001
7% Reduction in analgesics usage		
Incremental net benefit, £	850	729
Cost savings, £	299	149
Additional QALYs	0.018	0.019
2% Adverse event discontinuation rate and no renal toxicity		
Incremental net benefit, £	861	707
Cost savings, £	308	128
Additional QALYs	0.018	0.019
100% Compliance/no discontinuation due to failed compliance		
Incremental net benefit, £	1349	1088
Cost savings, £	734	444
Additional QALYs	0.020	0.021
Nursing cost as a function of infusion time*		
Incremental net benefit, £	833	969
Cost savings, £	282	390
Additional QALYs	0.018	0.019
No SRE efficacy advantage: 38% risk reduction for all		
Incremental net benefit, £	859	503
Cost savings, £	307	−50
Additional QALYs	0.018	0.018
50% Decrease in SRE treatment cost		
Incremental net benefit, £	859	634
Cost savings, £	307	54
Additional QALYs	0.018	0.019

QALYs = quality-adjusted life-years; QoL = quality of life; SRE = skeletal-related event.
*1.5 Hours for pamidronate and 15 minutes for zoledronic acid.

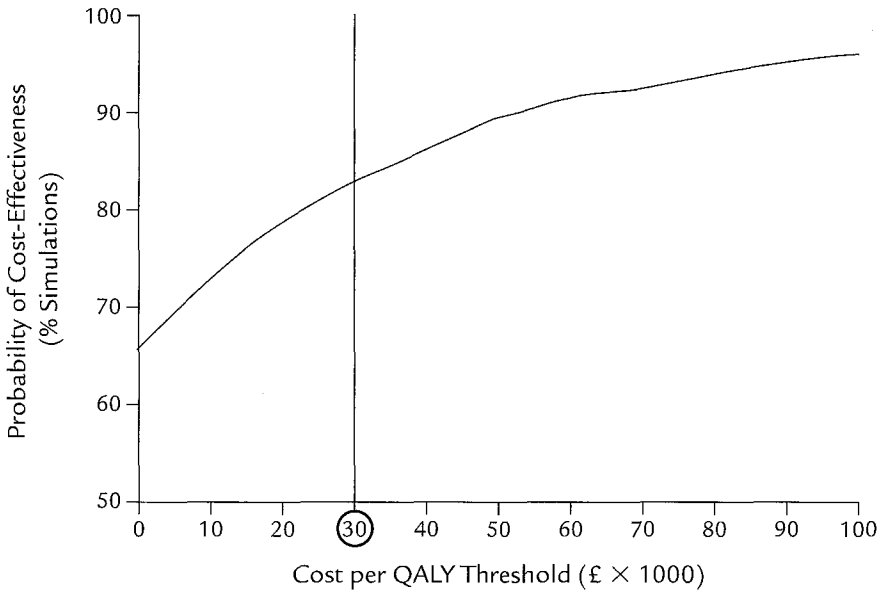

Figure 1. Cost-effectiveness acceptability curve of oral ibandronate versus IV generic pamidronate and IV zoledronic acid. QALY = quality-adjusted life-year.

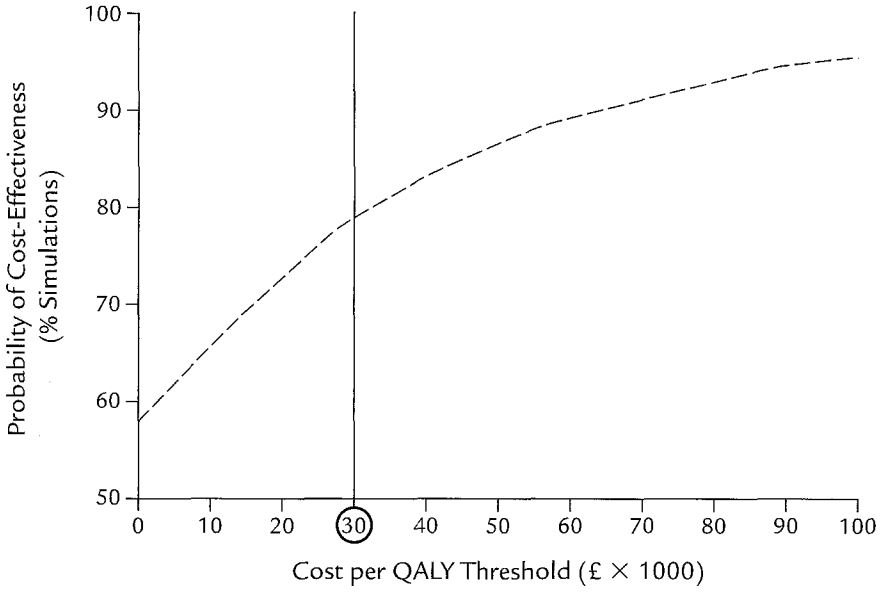

Figure 2. Cost-effectiveness acceptability curve for oral ibandronate versus IV generic pamidronate. QALY = quality-adjusted life-year.

A Phase III trial is currently underway to assess the comparative efficacy of oral ibandronate and zoledronic acid in patients with breast cancer and bone metastases. Preliminary results suggest that oral ibandronate is not inferior to zoledronic acid for reducing the bone resorption marker cross-linked C-terminal telopeptide of type I collagen in serum.[51] This and other bone turnover markers are considered to act as surrogates for bisphosphonate clinical efficacy. Once further head-to-head efficacy data become available for oral ibandronate and zoledronic acid, we plan to repeat the model analysis.

We assumed that the expected number of SREs over survival time for zoledronic acid and pamidronate would be weighted for the time on IV bisphosphonate compared with time on oral ibandronate. The discontinuation rate for IV bisphosphonates was based on our discussions with clinician experts because there are no comparative published data on failed compliance. Assuming that 12.5% of patients discontinued zoledronic acid and pamidronate (see "Patients and Methods"), lower mean drug costs would be expected for the IV bisphosphonates. In addition, we would expect that if a patient were to discontinue, the SRE risk reduction might decrease over time. However, in the absence of data for the loss of SRE efficacy with discontinuation, we conservatively assumed the same SRE risk reduction for all patients, regardless of continuing or discontinuing treatment. We also conducted a sensitivity analysis in which the compliance rate for IV bisphosphonates was assumed to be 100%. The dominance of oral ibandronate over IV bisphosphonates actually increased in our model, due to higher drug costs for zoledronic acid and pamidronate. The model did not assume noncompliance for oral ibandronate based on clinician opinion and the absence of patients withdrawing from Phase III clinical trials due to difficulty with taking their medication.[16]

For bone pain reduction, we applied an estimated increase in utility with oral ibandronate to a baseline utility value in patients with metastatic bone disease,[32] but we assumed there would be no corresponding increase in utility with IV bisphosphonates due to the absence of statistically significant reductions in bone pain from baseline in Phase III clinical trials.[25,27] However, since the model analysis was conducted, such reductions in bone pain have been reported with zoledronic acid in the trial of Japanese patients with breast cancer and bone metastases.[50] Assuming a similar 5% increase in utility for zoledronic acid as for oral ibandronate, the QALY advantage of ibandronate would be reduced, but there would be no effect on costs (ie, ibandronate would remain cost saving).

The absence of comparative data also meant that the chosen model assumptions for drug safety were the best estimates from interstudy comparisons and published clinical reports. The model assumed that zoledronic acid had a 5% risk of renal impairment, with extra costs for patient safety monitoring (ie, serum creatinine) and managing adverse events. It is possible that the rate for zoledronic acid was overestimated because it was calculated using the results of a trial including patients with multiple myeloma (for whom the risk of renal impairment is relatively high) and applied to a placebo rate from an IV ibandronate trial using the same methodology. However, myeloma patients comprised 31% of the study population in the zoledronic acid trial[25] and a higher incidence of renal toxicity has been reported in other trials,[38] as well as in clinical practice.[52,53] The risk of renal failure for zoledronic acid was extremely low, at 0.015% (from a published report based on clinical experience),[40] and had little impact on overall costs (£4 per patient, part of the £34 renal toxicity cost noted in **Figure 1**). The efficacy and safety data from Phase III trials used in the model were obtained from patients receiving oral hormonal therapy and oral chemotherapy for breast cancer, even though the patient population for this model was assumed to be receiving hormonal therapy for much of their survival time. Given the limited clinical experience with oral ibandronate in the United Kingdom, it was not possible to incorporate accurate information on typical national treatment patterns. Although patients receiving oral hormonal therapy might be more likely to receive oral ibandronate than IV bisphosphonates in clinical practice due to the ease of combining these ambulatory regimens, using data from chemotherapy patients remained relevant. The reason for this is that the model assumed that patients failing on hormonal therapy would be switched to a 4-month IV chemotherapy cycle.

To simplify the model, only renal toxicity (an adverse event with potentially considerable management costs) was included. Other adverse events for oral or IV bisphosphonates were not considered because there is no published evidence for significant differences of other adverse events between these agents. The most frequent mild upper gastrointestinal adverse events reported with oral ibandronate in the Phase III trials of breast cancer patients were dyspepsia (7.0% vs 4.7% with placebo), nausea (3.5% vs 1.4% with placebo), esophagitis (2.1% vs 0.7% with placebo), and abdominal pain (2.1% vs 0.7% with placebo), but their incidence was only slightly higher than that seen with placebo.[18]

A key cost driver in the model was SRE management (£2351 per patient), calculated from NHS reference costs for pathologic fractures.[43] To allow for all treatment possibilities, the pathologic fracture cost

included both nonelective and elective treatment. The inclusion of nonemergency fracture cases (which are less common) could have inflated the SRE management cost. Because the reference cost includes all malignancies of bone and connective tissue, it may not be accurate for the typical patient with breast cancer and bone metastases. However, breast cancer (along with prostate cancer) is the most common cause of SREs.[34] Therefore, costs for breast cancer patients would have been the main driver for generating the mean NHS cost of treating SREs. To account for the reference cost limitation, a worst-case reduction of SRE management cost by 50% was explored in a sensitivity analysis. Even though this reduced the overall cost advantage of oral ibandronate versus IV pamidronate (no change vs zoledronic acid because the SRE risk reduction was assumed to be the same), oral ibandronate remained cost saving.

The drug acquisition costs for all bisphosphonates in the model were obtained from the British National Formulary. The cost of pamidronate in the United Kingdom may be reduced in the future, given the growing availability of generics. Using the current model assumptions, the cost of pamidronate would need to be reduced below £152 for oral ibandronate to have similar costs in the given population of patients with breast cancer and bone metastases receiving oral hormonal therapy, and below £101 to have no incremental net benefit and therefore make oral ibandronate cost-ineffective (calculations not shown). However, no allowance has been made for the possibility that bisphosphonate drug costs might be reduced below national formulary levels due to local contracts and bulk purchases by the NHS.

One of the main influences on resource use in the model was the chosen infusion time for zoledronic acid and IV pamidronate of 22 minutes and 30 seconds, based on the assumption that nurses typically attend to a number of patients (eg, 4) in a treatment suite at any given time. Using recommended infusion times in the model would obviously increase the amount of time spent with patients receiving pamidronate (90 minutes) compared with zoledronic acid (15 minutes), increasing the cost-effectiveness of oral ibandronate versus pamidronate and slightly reducing the cost-effectiveness of oral ibandronate versus zoledronic acid (as shown by the sensitivity analysis of infusion time). However, a previous microcosting study of medical resource use suggested that the time nurses spend with patients receiving zoledronic acid and pamidronate is closer to 1 and 2 hours, respectively.[14]

It might be expected that the dominance of oral ibandronate would be increased if indirect costs were included in the model. By reducing the incidence of SREs and providing long-term bone pain relief, oral ibandronate could reduce patient disability and subsequently improve work productivity for patients and caregivers by reducing the number of working days lost. Expenses for travel to and from the hospital for monthly infusions would also be avoided.

It would be valuable to repeat this cost-effectiveness analysis using comparative efficacy and safety data for ibandronate versus other bisphosphonates. These are awaited from randomized controlled trials. It would also be interesting to repeat this analysis for other health care systems, to compare the results with those for the UK NHS. The economic impact of varying drug-pricing structures and practices for the management of primary tumors and bone metastases could then also be evaluated.

CONCLUSIONS

From the perspective of the UK NHS, this model analysis found that oral ibandronate was cost-effective compared with zoledronic acid and pamidronate for the treatment of bone metastases in breast cancer patients who were concurrently undergoing oral hormonal therapy. With oral ibandronate, the resource use and cost implications of regular IV bisphosphonate infusions (ie, hospital staff time and supplies) and patient safety monitoring were avoided. Compared with pamidronate, but not zoledronic acid, lower SRE costs were also expected. The model found that oral ibandronate remained cost saving in the absence of a utility benefit.

Due to the limitations surrounding the model assumptions, it would be valuable to perform additional analyses when efficacy and safety data become available from comparative, randomized trials of oral ibandronate versus other bisphosphonates for patients with bone metastases.

ACKNOWLEDGMENTS

Dr. Body has received honoraria and grant support from Hoffmann-La Roche Inc.; Dr. Canney has received honoraria, grants, or consultancy fees from Astra Zeneca Pharmaceuticals, Pfizer Corporation,

Schering-Plough Corporation, Novartis Pharmaceuticals Corporation, Hoffmann-La Roche Inc., Aventis Pharmaceuticals, Bioenvision, Amgen, Inc., and Eli Lilly, Inc. Dr. Barrett-Lee has acted as an advisory board member for Roche Pharmaceuticals UK with personal honoraria amounting to less than £10,000. His clinical-trials institution in Wales has received funding (in partnership with the Cancer Research UK organization) to run a large, randomized trial of zoledronic acid versus oral ibandronic acid.

The authors would like to thank Thomson Gardiner-Caldwell US for their assistance in preparing this manuscript.

REFERENCES

1. Diel IJ, Solomayer EF, Bastert G. Treatment of metastatic bone disease in breast cancer: Bisphosphonates. *Clin Breast Cancer.* 2000;1:43–51.
2. Domchek SM, Younger J, Finkelstein DM, Seiden MV. Predictors of skeletal complications in patients with metastatic breast carcinoma. *Cancer.* 2000;89:363–368.
3. Scheid V, Buzdar AU, Smith TL, Hortobagyi GN. Clinical course of breast cancer patients with osseous metastasis treated with combination chemotherapy. *Cancer.* 1986;58: 2589–2593.
4. Body JJ. Effectiveness and cost of bisphosphonate therapy in tumor bone disease. *Cancer.* 2003;97(Suppl 3):859–865.
5. Janjan N. Bone metastases: Approaches to management. *Semin Oncol.* 2001;28(Suppl 11):28–34.
6. Liberato NL, Marchetti M, Barosi G. Clinical and economic issues in the treatment of advanced breast cancer with bisphosphonates. *Drugs Aging.* 2003;20:631–642.
7. Hillner BE, Ingle JN, Chlebowski RT, et al, for the American Society of Clinical Oncology. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer [published correction appears in *J Clin Oncol.* 2004;22:1351]. *J Clin Oncol.* 2003;21:4042–4057.
8. Brown JE, Neville-Webbe H, Coleman RE. The role of bisphosphonates in breast and prostate cancers. *Endocr Relat Cancer.* 2004;11:207–224.
9. Fulfaro F, Casuccio A, Ticozzi C, Ripamonti C. The role of bisphosphonates in the treatment of painful metastatic bone disease: A review of phase III trials. *Pain.* 1998;78: 157–169.
10. Mancini I, Dumon JC, Body JJ. 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;22:3587–3592.
11. Ohlmann C, Heidenreich A. Efficacy of ibandronate in the management of painful osseous metastases due to hormone refractory prostate cancer. *Support Care Cancer.* 2003;11:396.
12. Remak E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *Br J Cancer.* 2004;91:77–83.
13. Delea T, McKiernan J, Liss M, et al. Effects of skeletal complications on total medical care costs in women with bone metastases of breast cancer. *Bone.* 2004;34:S86.
14. DesHarnais Castel L, Bajwa K, Markle JP, et al. A microcosting analysis of zoledronic acid and pamidronate therapy in patients with metastatic bone disease. *Support Care Cancer.* 2001;9:545–551.
15. Maxwell C, Swift R, Goode M, et al. Advances in supportive care of patients with cancer and bone metastases: Nursing implications of zoledronic acid. *Clin J Oncol Nurs.* 2003;7:403–408.
16. Biermann WA, Cantor RI, Fellin FM, et al. An evaluation of the potential cost reductions resulting from the use of clodronate in the treatment of metastatic carcinoma of the breast to bone. *Bone.* 1991;12(Suppl 1):S37–S42.
17. Guignard E, Dardenne J, Pelc A. Economic assessment of clodronate in the preventive treatment of bone resorption in patients with metastatic breast cancer. *Eur J Cancer.* 1997;33(Suppl 9):S25. Abstract PP30.
18. 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;90:1133–1137.
19. Body J-J, Tripathy D, Pecherstorfer M, Bergstrom B. Intravenous and oral ibandronate reduces the risk of skeletal related events in metastatic bone disease from breast cancer. *Breast Cancer Res Treat.* 2003;82(Suppl 1): S133. Abstract.
20. Body JJ, Diel IJ, Bell R, et al. Oral ibandronate improves bone pain and preserves quality of life in patients with skeletal metastases due to breast cancer. *Pain.* 2004;111:306–312.
21. De Cock E, Hutton J, Barrett-Lee P, et al. Cost-effectiveness of oral ibandronic acid versus intravenous (iv) zoledronic acid and iv pamidronate in the treatment of metastatic bone disease in breast cancer. *Ann Oncol.* 2004;15:iii50.
22. Hillner BE, Weeks JC, Desch CE, Smith TJ. Pamidronate in prevention of bone complications in metastatic breast cancer: A cost-effectiveness analysis. *J Clin Oncol.* 2000; 18:72–79.
23. Hortobagyi GN, Theriault RL, Porter L, et al, for the Protocol 19 Aredia Breast Cancer Study Group. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. *N Engl J Med.* 1996;335:1785–1791.
24. Hortobagyi GN, Theriault RL, Lipton A, et al, for the Protocol 19 Aredia Breast Cancer Study Group. Long-term prevention of skeletal complications of metastatic

breast cancer with pamidronate. *J Clin Oncol*. 1998;16:2038–2044.
25. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: A phase III, double-blind, comparative trial. *Cancer J*. 2001;7:377–387.
26. Body JJ, Kanis J, Diel I, Bergstrom B. Risk reductions in metastatic breast cancer: Multivariate Poisson regression analyses of oral and iv ibandronate. *Proc Am Soc Clin Oncol*. 2003;22:46.
27. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: Long term follow-up of two randomized, placebo-controlled trials. *Cancer*. 2000;88:1082–1090.
28. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: A randomized, double-blind, multicenter, comparative trial. *Cancer*. 2003;98:1735–1744.
29. Rosen LS, Gordon D, Tchekmedyian S, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: A phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol*. 2003;21: 3150–3157.
30. Saad F. Zoledronic acid significantly reduces pathologic fractures in patients with advanced-stage prostate cancer metastatic to bone. *Clin Prostate Cancer*. 2002;1:145–152.
31. Berenson JR. Zoledronic acid in cancer patients with bone metastases: Results of phase I and II trials. *Semin Oncol*. 2001;28(Suppl 6):25–34.
32. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Quality-adjusted-life-years (QALY). In: *Methods for the Economic Evaluation of Health Care Programmes*. 2nd ed. Oxford, UK: Oxford University Press; 1997:165–183.
33. van den Hout WB, van der Linden YM, Steenland E, et al. Single-versus multiple-fraction radiotherapy in patients with painful bone metastases: Cost-utility analysis based on a randomized trial. *J Natl Cancer Inst*. 2003;95:222–229.
34. Coleman RE. Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev*. 2001;27:165–176.
35. Diel I, Bell R, Tripathy D, et al. Renal safety of oral and intravenous ibandronate in metastatic bone disease: Phase III clinical trial results. *Support Care Cancer*. 2003;11:415.
36. Li EC, Davis LE. Zoledronic acid: A new parenteral bisphosphonate. *Clin Ther*. 2003;25:2669–2708.
37. Body JJ, Diel IJ, Lichinitser MR, et al, for the MF 4265 Study Group. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol*. 2003;14:1399–1405.
38. Ibrahim A, Scher N, Williams G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. *Clin Cancer Res*. 2003;9: 2394–2399.
39. Body J, Diel I, Bergström B. Intravenous ibandronate does not affect time to renal function deterioration in patients with metastatic bone disease from breast cancer. *Support Care Cancer*. 2004;12:405.
40. Chang JT, Green L, Beitz J. Renal failure with the use of zoledronic acid. *N Engl J Med*. 2003;349:1676–1679.
41. Aredia [product summary]. Basel, Switzerland: Novartis AG; 2002.
42. British National Formulary 46. London, UK: British Medical Association; 2004.
43. NHS Reference Costs 2003 and National Tariff 2004. Appendix 4—National Schedule of Reference Costs: NHS Trusts and Primary Care Trusts Combined. Available at: http://www.dh.gov.uk/. Accessed February 2004.
44. Personal Social Services Resource Unit. *Unit Costs of Health and Social Care 2003*. Canterbury, UK: University of Kent at Canterbury; 2003.
45. PlanetRecruit Web site. Available at: http://www.yahoo.workthing.com. Accessed February 2004.
46. Medisave Web site. Available at: http://www.medisave.co.uk. Accessed February 2004.
47. MEDTAP Unit Cost Database. London, UK: MEDTAP International; 2003.
48. NICE Appraisal Guidance 48. Available at: http://www.nice.org.uk/page.aspx?o=36747. Accessed February 2004.
49. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ*. 1994;3:309–319.
50. Kohno N, Aogi K, Minami H, et al. Zoledronic acid reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer. *Breast Cancer Res Treat*. 2004;88: S133.
51. Body JJ, Lichinitser M, Tjulandin SA, et al. Comparative reductions in bone turnover markers with oral ibandronate and intravenous (iv) zoledronic acid in patients with bone metastases from breast cancer: Phase III trial results. Presented at: Skeletal Complications of Malignancy IV Congress; Bethesda, Md; April 28–30, 2005.
52. Johnson KB, Gable P, Kaime EM, et al. Significant deterioration in renal function with the new bisphosphonate, zoledronic acid. *Proc ASCO*. 2003;22:738.

53. Mazj S, Lichtman SM. Renal dysfunction associated with bisphosphonate use: Retrospective analysis of 293 patients with respect to age and other clinical characteristics. *Proc Am Soc Clin Oncol.* 2004;23:735.

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