Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The technology studied was pamidronate (a bisphosphonate or anti-bone dissolution agent) provided monthly at a dose of 90 mg to women with metastatic breast cancer for the prevention of bone complications.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised women with metastatic breast cancer, one or more osteolytic lesions at least 1 cm in diameter and an expected survival of at least 9 months. Patients were receiving either hormonal therapy or chemotherapy.

Setting
This study was set in secondary care. The economic study was carried out in the United States.

Dates to which data relate
The effectiveness data related to the period 1996 to 1999. The resource use and cost data related to 1998 and possibly later as some data were derived from websites.

Source of effectiveness data
The effectiveness data were based on a synthesis of two previous trials and on opinion.

Modelling
A model was used to project the costs and disutilities of adverse events over 24 months. The authors opted not to use a Markov model on the basis that good effectiveness data were available from two trials.

Outcomes assessed in the review
The outcomes assessed were survival, the incidence of skeletal-related events (SRE) including surgery for pathological fracture, radiation for fracture or pain control, conservatively treated pathological fracture, spinal cord compression and hypercalcaemia.
Study designs and other criteria for inclusion in the review
The two trials used were international, multicentre, randomised and double-blind. They included women with metastatic breast cancer with one or more osteolytic lesions at least 1cm in diameter.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
The authors used the two trials to gain approval for pamidronate from the United States Food and Drug Administration.

Methods used to judge relevance and validity, and for extracting data
See previous comment.

Number of primary studies included
Two primary studies were included.

Methods of combining primary studies
The trials used were parallel studies differentiated by whether the patient received hormonal therapy or chemotherapy as their systemic treatment. These studies were not combined but were analysed separately.

Investigation of differences between primary studies
As part of the sensitivity analyses, the results were pooled. This was justified with reference to the results of a study that found no significant difference in the odds ratio of having a SRE between recipients of hormonal therapy or chemotherapy. The authors acknowledged that the number need to treat to prevent an SRE did differ between the two studies and that this weakened the case for pooling the data in a cost-effectiveness study.

Results of the review
The median survival for chemotherapy patients was 14.8 months on pamidronate versus 14.0 months on placebo; for hormonal patients the corresponding results were 23.2 months and 23.5 months.

The total number of SREs (presumably over a 24 month period) in the chemotherapy trial was 387 for patients on pamidronate versus 630 for patients on placebo. The corresponding numbers for hormonal patients were 475 and 627. This includes a high percentage of fractures not requiring surgery.

In the chemotherapy trial there were 251 fractures among patients on pamidronate versus 349 for patients on placebo. In the hormonal trial, the corresponding numbers were 331 versus 403.

In the chemotherapy trial, 105 courses of radiotherapy were given in the pamidronate group versus 207 courses in the placebo group. In the hormonal trial 114 versus 192 courses were given.

Methods used to derive estimates of effectiveness
The authors made various assumptions to complete their model, some of which were relaxed or changed using sensitivity analysis.

Estimates of effectiveness and key assumptions
The assumptions included:
pamidronate had no impact on survival;
the monthly death rate was constant (3% in the hormonal group and 4.9% in the chemotherapy group)
and the cost and quality-of-life impact for each SRE lasted for one month only.
Furthermore, patients could only have 1 SRE per month.

**Measure of benefits used in the economic analysis**
The benefits were measured in SREs avoided and in quality-adjusted life years (QALYs). Quality of life values were
assigned on the basis of expert opinion.

**Direct costs**
The authors estimated a marginal cost for each category of SRE and for pamidronate therapy. The derivation of these
costs was described and for some resource use details were included. For example, the radiation cost was based on a
two-week course of 30 Gy over 10 fractions. For pamidronate and radiation, the costs were estimated by converting the
charges from a hospital database. For the other SREs, the costs were estimated by the authors and were informed by a
national source of inpatient charges (Agency for Health Care Policy and Research website). Most data relate to 1998;
no date was given for the AHCPR data. The costs for systemic therapy (chemotherapy or hormonal) were assumed to
be unaffected by pamidronate treatment and were excluded. Discounting was not relevant as the timeframe of the study
was limited to 24 months. The costs included were relevant to a hospital setting.

**Statistical analysis of costs**
The authors provided ranges for the costs but treated the data deterministically.

**Indirect Costs**
The authors assume that patient out-of-pocket costs and lost wages would not be affected by the use of pamidronate and
therefore they excluded these indirect costs from the analysis. They did, however, include in the cost of radiation
treatment a cost for work lost by the person accompanying the patient to the hospital. This cost was estimated to be 14
half-days at $50 per half-day where the unit cost projections were found in another study dated 1998 (see the reference
below).

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors conducted one-way sensitivity analyses to test the robustness of some of their assumptions and the effect of
varying the price of pamidronate. Since the authors knew that some fractures sustained by patients were asymptomatic,
they re-estimated the cost-effectiveness ratios including only those SREs requiring active therapy. They also excluded
the SRE of hypercalcaemia for which pamidronate was already the standard of care for treatment. In addition, the
authors investigated the impact of an SRE lasting for 2 months, and of reducing the utility associated with an SRE to
zero (the value usually assigned to death).

**Estimated benefits used in the economic analysis**
The average number of SRE-free months increased by 1.13 (from 11.07) in the chemotherapy group and by 0.82 in the
hormonal treatment group. Pamidronate was associated with a gain of 0.037 QALYs in the chemotherapy group and
0.026 QALYs in the hormonal group.
Cost results
The total per patient cost for pamidronate was $17,906 in the chemotherapy group and $20,319 in the hormonal group. These compare with the placebo costs of $13,938 and $12,634 respectively. Thus the net incremental cost of pamidronate treatment was $3,936 in the chemotherapy group and $7,685 in the hormonal group over a 24-month period.

Synthesis of costs and benefits
The incremental cost-effectiveness ratios per QALY gained were $108,200 with chemotherapy and $305,300 with hormonal treatment. These results were found to be sensitive to the costs of providing pamidronate and the costs of asymptomatic or conservatively treated fractures. Using the often-quoted $50,000 per QALY threshold, the cost of pamidronate would need to decrease from $775 to $618 for the treatment to be cost-effective. Even under the most favourable scenario (the utility of an SRE set to zero), the incremental cost-effectiveness ratio was still $60,100 per QALY gained.

Authors' conclusions
Pamidronate is effective at preventing skeletal related events in breast-cancer patients, but the cost is high.

CRD COMMENTARY - Selection of comparators
Since the effectiveness data were derived from clinical trials, placebo was used as the comparator. This must be compared with current practice in your own setting for the prevention of bone complications in metastatic breast cancer.

Validity of estimate of measure of effectiveness
The effectiveness results were based on two studies that appear to have had high internal validity and the data from each study were analysed separately. The patients in these studies appear to have been reasonably representative of the study population but the sample sizes were small. The authors justified their assumptions regarding monthly death rates and cited the need for further research on the duration of symptoms or disutility from SREs. The duration of follow-up was 24 months which is the upper limit of the median survival for women with metastatic breast cancer. Pamidronate was not thought to affect survival.

Validity of estimate of measure of benefit
The authors acknowledged the limitation of using utility values generated by expert opinion. Some of the assumptions, particularly those regarding quality of life estimates, seem to have been arbitrary. For example it was assumed that patients experienced no disutility by having to undergo pamidronate treatment. Despite this, the authors made most of their assumptions in favour of pamidronate and concluded that their analysis still did not reveal it to be cost-effective. However, they also acknowledged that the assumption of the disutility associated with an SRE is limited to one month in duration may bias against pamidronate. The authors attempted to adjust for this in the sensitivity analysis, but cited this variable as one for which further research could reduce uncertainty.

Validity of estimate of costs
The authors provided details of how their direct costs were estimated. Some of these details may be applicable in other health care settings. The authors claimed to have adopted a societal perspective but included an indirect cost component in the radiation cost only. The authors assumed that the use of pamidronate would not result in different out-of-pocket costs or lost wages compared with not using it. The justification for this assumption was not clear in light of the fact that pamidronate does affect quality of life and the incidence of SREs.

Other issues
Although this study was based on multinational trials, the economic analysis was conducted in the USA. It would have
been useful to know if any similar studies exist and whether or not the findings are consistent. A thorough literature search could have enhanced the validity of this study by using pooled results on larger patient numbers.

**Implications of the study**
The authors highlight, as a topic for further research, the duration of symptoms with SREs for the patient population.

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**Other publications of related interest**

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