Recommendations for use of Bisphosphonates

for advanced breast cancer

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A CLINICAL PRACTICE GUIDELINE DEVELOPED BY NATIONAL BREAST AND OVARIAN CANCER CENTRE (NBOCC)*

This document supplements guideline recommendation 27 on the use of bisphosphonates as supportive treatment (page 10) and guideline recommendation 47 on bisphosphonates as analgesics for cancer pain (page 12) contained in the National Breast Cancer Centre (NBCC)* *Clinical practice guidelines for the management of advanced breast cancer*, 2001.[1]

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* In February 2008, National Breast Cancer Centre (NBCC), incorporating the Ovarian Cancer Program, changed its name to National Breast and Ovarian Cancer Centre (NBOCC). In July 2011, NBOCC amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

Purpose

This guideline includes statements and recommendations based on available, high-level evidence about the use of bisphosphonates for *advanced breast cancer*. The guideline provides health professionals with information designed to help them make management recommendations for improved patient outcomes. NBOCC* also develops information specifically for consumers about the diagnosis and treatment of advanced breast cancer.

Endorsed by:

MOGA
MEDICAL ONCOLOGY GROUP OF AUSTRALIA

The Royal Australian and New Zealand College of Radiologists
The Faculty of Radiation Oncology

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Background

The NBOCC* *Clinical practice guidelines for the management of advanced breast cancer*[1] define *advanced breast cancer* as both locally advanced and *metastatic breast cancer* (cancer that has spread to other parts of the body). This topic-specific clinical practice guideline on the use of bisphosphonates for advanced breast cancer is based on evidence for women with advanced breast cancer who have bone metastases and women with *locally advanced breast cancer* without bone metastases.

Treatment for women with advanced breast cancer includes the use of supportive drug treatments to reduce disease-related symptoms and slow progression of disease, thereby enhancing the woman's quality of life. Bone metastases are common in advanced breast cancer and the cancer deposits can cause bone resorption, causing bone pain, fractures, hypercalcaemia and spinal cord compression.

Bisphosphonates act to reduce the activity of bone-absorbing cells and are the standard supportive drug treatment for women with bone metastases. In women with at least one *bone metastasis*, bisphosphonates can be used to reduce skeletal events (defined as new bone metastases, pathological fractures, spinal cord compression, irradiation of or surgery on bone, or the development or progression of bone pain).[2]

There are two classes of bisphosphonates:

- nitrogenous (alendronate, ibandronate,[^] neridronate, olapadronate, pamidronate, risedronate and zoledronic acid[^^]) and
- non-nitrogenous (clodronate, etidronate and tiludronate).

Bisphosphonates are administered orally or intravenously depending on the drug.

[^]Ibandronate is also called ibandronic acid.

[^^]Zoledronic acid is also called zoledronate or zolendronate.

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Clinical practice recommendations

The recommendations are based on the statements of evidence for use of bisphosphonates for *advanced breast cancer*.

Recommendations to individuals should be based on their circumstances, the absolute benefits and harms of treatment, and their personal preferences. These factors should be discussed with the woman.[4]

Clinicians should conduct a dental examination and be aware of baseline tests (biochemistry including creatinine, serum calcium and vitamin D) and contraindications[a] prior to prescribing bisphosphonates. Women taking bisphosphonates should be reviewed regularly and monitored for adverse events by clinicians familiar with bisphosphonates.

RECOMMENDATIONS	LEVEL OF EVIDENCE[5]	REFERENCE
In women with advanced breast cancer and clinically evident bone metastases (who may or may not be having systemic therapy):		
Bone health		
Bisphosphonates should be considered to reduce: • risk of developing a skeletal event • risk of hypercalcaemia • rate (frequency) of skeletal events	I	Cochrane[2]
Bisphosphonates should be considered to delay time to a skeletal event	I	Cochrane[2]
Bone pain		
Bisphosphonates should be considered to reduce bone pain	I	Cochrane[2]
Type of bisphosphonate and mode of administration		
The type of bisphosphonate and mode of administration should be tailored to the individual's situation with regard to disease, treatment and patient factors and individual patient benefit: *Disease* • number and location of bone metastases • presence of bone pain • hypercalcaemia *Treatment* • long-term effects of bisphosphonates • toxicities and their management • frequency and mode of administration of other anticancer therapies *Patient*		

RECOMMENDATIONS	LEVEL OF EVIDENCE[5]	REFERENCE
• patient performance status and overall prognosis • patient preference • renal function • accessibility of services		
Schedule and duration of administration		
Effective doses and schedule are: • Intravenous ibandronate: 6mg every 4 weeks • Intravenous pamidronate: 90mg every 3–4 weeks • Intravenous zoledronic acid: 4mg every 3–4 weeks • Oral clodronate: 1600mg daily • Oral ibandronate: 50mg daily		Pharmaceutical Benefits Scheme[5]
In the absence of unacceptable toxicities, bisphosphonate use beyond 2–3 years should be considered on a case by case basis by the clinician and patient after assessing clinical benefit and potential risks		
Adverse events[b]		
Dental assessment measures should be considered for patients: i. baseline mouth assessment with a dental visit to detect potential dental conditions and dental care if required ii. ongoing good dental hygiene and dental checks	III-3	Ripamonti[7]
Women taking bisphosphonates should be routinely informed of the need for good dental health, and dental health and oral cavity should be monitored for osteonecrosis of the jaw		Khosla[8]
Women taking zoledronic acid should be monitored for renal toxicity	II	Rosen[9]

[a] Contraindications and baseline tests for bisphosphonates mentioned in this guideline are available in the product information (PI) on the *Pharmaceutical Benefits Scheme* website at www.pbs.gov.au

[b] Precautionary information for bisphosphonates mentioned in this guideline is available in the product information (PI) on the Pharmaceutical Benefits Scheme website at www.pbs.gov.au

Statements of evidence

Below are the statements of evidence on which the recommendations are based.

STATEMENTS	LEVEL OF EVIDENCE[5]	REFERENCE
In women with *advanced breast cancer* **without** clinically evident bone metastases, bisphosphonates do not reduce the incidence of skeletal metastases	I	Cochrane[2]
In women with advanced breast cancer and clinically evident bone metastases (who may or may not be having systemic therapy):		
Bone health		
The following bisphosphonates significantly reduce the risk of developing a skeletal event: • intravenous zoledronic acid • intravenous pamidronate • oral clodronate	I	Cochrane[2]
Bisphosphonates significantly reduce the risk of hypercalcaemia	I	Ross[10]
Bisphosphonates reduce the rate (frequency) of skeletal events	I	Cochrane[2]
The following bisphosphonates significantly delay time to a skeletal event: • intravenous ibandronate • intravenous pamidronate • intravenous zoledronic acid • oral clodronate	I	Cochrane[2]
Bone pain		
The following bisphosphonates significantly reduce bone pain: • intravenous or oral ibandronate • intravenous pamidronate • intravenous zoledronic acid	I	Cochrane[2]
Overall survival		
Treatment with bisphosphonates does not affect overall survival	I	Cochrane,[2] Ha[11]
Oral clodronate does not affect bone metastasis-free survival or non-skeletal metastasis-free survival	I	Ha[11]
Quality of life		
Ibandronate (oral or intravenous) significantly improves quality of life	II	Body[12-13]
There are insufficient data to indicate a significant difference in quality of life with other bisphosphonates		
Type of bisphosphonate and mode of administration		

STATEMENTS	LEVEL OF EVIDENCE[5]	REFERENCE
There is no significant difference between treatment with intravenous zoledronic acid or intravenous pamidronate in: • risk of developing a skeletal event, • time to first skeletal event • skeletal morbidity rate However, for women with osteolytic lesions, zoledronic acid is associated with longer time to first skeletal event and lower skeletal morbidity rate than pamidronate	II	Rosen[9]
There are insufficient data to indicate a significant difference in relation to type of bisphosphonate		
Intravenous and oral bisphosphonates both significantly reduce the risk of developing a skeletal event	I	Cochrane[2]
Schedule and duration of administration		
The clinical studies evaluating bisphosphonates were limited to therapy no greater than 2–3 years However, many women with advanced breast cancer can have disease control with modern bisphosphonates for longer periods of time There are no formal data evaluating the cumulative effect of bisphosphonates or reduced frequency of administration The optimal schedule of bisphosphonates is unknown and there are no studies evaluating long-term bisphosphonate use, or shorter versus longer-term bisphosphonate use		
Adverse events		
Bisphosphonates are associated with mild and infrequent toxicity	I	Cochrane[2]
Mild gastrointestinal toxicity is associated with oral bisphosphonates		Cochrane[2]
Oral ibandronate appears to have fewer side effects than intravenous zoledronic acid	II	Body[14]
Renal toxicity is associated with intravenous zoledronic acid and is related to dose and infusion time		Cochrane[2]
The evidence on *risk factors* predisposing to osteonecrosis of the jaw is weak Some suggested risk factors include intravenous bisphosphonates and duration of exposure to bisphosphonate treatment, tooth extraction and invasive dental work, and pre-existing dental or periodontal disease		Khosla[8]
Dental preventive measures (baseline mouth assessment with a dental visit to detect potential dental conditions and dental care if required) before	III-3	Ripamonti[7]

STATEMENTS	LEVEL OF EVIDENCE[5]	REFERENCE
bisphosphonate therapy significantly lower rates of osteonecrosis of the jaw in patients taking bisphosphonates		
Other new emerging therapies		
Evidence from one large study has indicated greater benefit with denosumab, a new bone agent, compared to zoledronic acid in delaying or preventing skeletal events	II	Stopeck[15]

Summary of evidence

The NBOCC* statements and recommendations about the use of bisphosphonates for women with *advanced breast cancer* are based on a Cochrane review and meta-analysis investigating the use of bisphosphonates for breast cancer (2005 and 2007 update)[2] and an NBOCC* systematic review,[3] which includes available evidence published between January 2007 and April 2010 from randomised trials.

The Cochrane review includes 18 published randomised controlled trials, which examined the effect of bisphosphonates in women with advanced breast cancer. The studies compared the use of any bisphosphonate administered orally or intravenously in any dose and for any duration with placebo, no treatment or another bisphosphonate. The majority (15 studies) included women with advanced breast cancer and clinically evident bone metastases (metastases confirmed with diagnostic imaging). Three studies included women without clinically evident bone metastases with locally advanced or advanced breast cancer.

Eleven studies investigated oral ibandronate, clodronate or pamidronate administered either daily or twice a day. Seven studies investigated intravenous pamidronate, ibandronate, clodronate or zoledronic acid, given every three to four weeks. Most studies administered bisphosphonates for a duration between one and two years.

Bisphosphonates were administered in addition to other systemic therapies, such as *chemotherapy* or hormonal therapy. Since the studies included in the Cochrane review were published between 1983 and 2004, the concurrent systemic therapies used in these studies may differ from the current standard breast cancer treatments (such as *aromatase inhibitors*, *taxanes* and targeted therapies).

The NBOCC* systematic review identified one meta-analysis on the effect of oral clodronate for breast cancer, five full text papers describing randomised trials of bisphosphonates for advanced breast cancer and one additional study reported in abstract only. All studies identified were in women with breast cancer with bone metastases. Various bisphosphonate comparisons were investigated, as well as a comparison with subcutaneous denosumab, a new bone agent.

(See Table 1 – Meta-analysis results of study outcomes from the Cochrane Review)

* In July 2011, National Breast and Ovarian Cancer Centre (NBOCC) amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

Summary of trial or study results

Table 1. Meta-analysis results of study outcomes from the Cochrane Review[2]

Outcome	No. studies	No. participants	Relative risk (95% CI)
Overall risk of skeletal events (including hypercalcaemia)	8	2189	0.83 (0.78, 0.89)
Overall risk of skeletal events (excluding hypercalcaemia)	8	2656	0.85 (0.79, 0.91)
Overall risk of skeletal events by drug route of administration:			
• intravenous (IV)	5	1918	0.83 (0.78, 0.89)
• oral	5	1147	0.84 (0.76, 0.93)
Overall risk of skeletal events by individual drug at recommended dosing:			
• IV zoledronic acid 4mg	1	227	0.59 (0.42, 0.82)
• IV pamidronate 90mg	1	751	0.77 (0.69, 0.87)
• oral clodronate 1600mg	3	422	0.84 (0.72, 0.98)
• IV ibandronate 6mg	1	312	0.82 (0.67, 1.00)
• oral ibandronate 50mg	1	564	0.86 (0.73, 1.02)
Incidence of bone metastases (in women without prior bone metastases)	3	320	0.99 (0.67, 1.47)
Survival	10	2255	0.99 (0.93, 1.05)

Bone health

A Cochrane pooled analysis[2] of eight studies of women with *advanced breast cancer* and clinically evident bone metastases showed that bisphosphonates reduced the risk of developing a skeletal event, including hypercalcaemia, by 17% ($p<0.00001$) compared to no bisphosphonate. A Cochrane meta-analysis[2] of risk of skeletal events by individual drug at recommended dosing showed a statistically significant reduction in risk with intravenous zoledronic acid, intravenous pamidronate and oral clodronate. A reduced risk was reported for oral and intravenous ibandronate; however this was not statistically significant (Table 1).

Twelve studies identified in the Cochrane Review[2] reported lower skeletal event rates with bisphosphonates and ten of these studies reported a statistically significant reduction in skeletal event rate with all bisphosphonates. The definition and measurement of skeletal event rate varied across studies and included skeletal morbidity rate (number of events per year), cumulative events in the follow-up period, cumulative proportion of skeletal events and total events per study group.

Thirteen studies[2] assessed the effect of bisphosphonates on time to skeletal event. Of these, seven studies of intravenous pamidronate, intravenous ibandronate, oral clodronate and intravenous zoledronic acid reported that

bisphosphonates significantly delayed time to skeletal event compared to no bisphosphonates. Studies on oral ibandronate and oral pamidronate reported that bisphosphonates delayed time to skeletal events compared to no bisphosphonates; however this was not statistically significant.

Three studies of bisphosphonates in women without clinically evident bone metastases identified in the Cochrane Review[2] did not show a significant reduction in the incidence of skeletal metastases associated with the use of bisphosphonates (Table 1).

Bone pain

The Cochrane Review[2] identified 11 studies that reported the effect of bisphosphonates on bone pain, compared with no bisphosphonate or placebo. A significant reduction in bone pain was reported in four large studies of ibandronate (intravenous and oral), intravenous pamidronate and intravenous zoledronic acid and two smaller studies (n<150) on oral pamidronate and oral clodronate.

Another Cochrane review[16] on the use of bisphosphonates for bone pain for patients with multiple primary disease sites (including breast) concluded that bisphosphonates provide modest pain relief for patients with painful bone metastases and that bisphosphonates should be considered where analgesics and/or *radiotherapy* are inadequate.

Overall survival

Ten studies identified in a Cochrane Review meta-analysis[2] reported overall survival, with no study reporting a significant difference between women taking bisphosphonates compared with no bisphosphonates or placebo (Table 1). Similarly, a separate meta-analysis[11] showed that oral clodronate did not affect overall survival for women with advanced breast cancer.

The meta-analysis of oral clodronate also reported that bisphosphonates did not significantly affect bone metastasis-free survival and non-skeletal metastasis-free survival.

Quality of life

Patient-rated quality of life data was reported in seven bisphosphonate studies.[2] Of these, two studies on ibandronate showed statistically significant improvements in quality of life for the women taking bisphosphonates. However, the remaining studies reported no significant differences in quality of life with bisphosphonates compared to no bisphosphonates.

Type of bisphosphonate and mode of administration

A randomised study comparing intravenous zoledronic acid with intravenous pamidronate[9] did not show a significant difference between the two bisphosphonates with regard to developing a skeletal event, time to first skeletal event or skeletal morbidity rate.

The efficacy of intravenous and oral bisphosphonates was assessed in two Cochrane pooled analyses[2] of women with advanced breast cancer and clinically evident bone metastases. A pooled analysis of five studies showed that intravenous bisphosphonates significantly reduced the risk of developing a skeletal event by 17% (p<0.00001) and a separate pooled analysis of five studies showed that oral bisphosphonates significantly reduced risk of developing a skeletal event by 16% (p=0.001) (Table 1).

Schedule and duration of administration

Most studies of bisphosphonates in women with advanced breast cancer identified in the Cochrane Review[2] administered bisphosphonates over a period of two to three years. However, the optimal schedule and duration of bisphosphonates is not known.

Adverse events[c]

Seventeen studies identified in the Cochrane Review[2] reported adverse events or toxicity but little serious toxicity was reported. Gastrointestinal toxicity (nausea and vomiting) was the most frequent side effect reported by women in oral clodronate studies, and an oral pamidronate study[17] reported a withdrawal rate of 25% of pamidronate participants due to gastrointestinal toxicity. Serum creatinine, serum calcium and bilirubin levels were identified in most studies to determine patient eligibility or exclusion on the basis of renal function, calcium levels and liver function. In one study[9] comparing intravenous pamidronate with zoledronic acid, renal toxicity was reported more frequently for zoledronic acid participants (4–30% depending on treatment group). In the same study, calcium and vitamin D supplements were given to all participants and there was no reported *hypocalcaemia*. A separate study[18] of intravenous zoledronic acid without calcium and vitamin D supplements showed a higher incidence of *grade* I hypocalcaemia with zoledronic acid than placebo. A literature review[19] on adverse effects associated with bisphosphonates identified renal toxicity with intravenous bisphosphonates, mainly zoledronic acid and to a lesser extent pamidronate. Intravenous ibandronate and oral bisphosphonates were identified as having a safety profile similar to placebo with regard to renal toxicity.

A taskforce of the American Society for Bone and Mineral Research conducted a review of bisphosphonate-associated osteonecrosis of the jaw (BP ONJ) in 2007.[8] While the taskforce recognised that the evidence on *risk factors* predisposing to BP ONJ was weak, some risk factors were suggested, including intravenous bisphosphonates and duration of exposure to bisphosphonate treatment, tooth extraction and invasive dental work, and pre-existing dental or periodontal disease.

Most studies identified in the Cochrane Review[2] pre-dated recognition of BP ONJ as a potential adverse event; therefore the true incidence of BP ONJ in women with advanced breast cancer is unknown. More recent prospective studies in the *adjuvant* breast cancer setting may provide an indication of the incidence of BP ONJ. One systematic review and meta-analysis[20] of 15 randomised controlled trials reported that osteonecrosis of the jaw was a rare event in women with *early breast cancer*, occurring in 13 of the 5,312 patients receiving bisphosphonates (0.2%). All thirteen occurrences were in patients taking zoledronic acid, and the meta-analysis showed a significant increase in osteonecrosis of the jaw with zoledronic acid compared with no bisphosphonates.

Limited information is available evaluating the effect of dental preventive measures and incidence of BP ONJ in cancer patients. A non-randomised study by the National Cancer Institute of Milan[7] found that patients who underwent dental preventive measures (baseline mouth assessment with a dental visit to detect potential dental conditions and dental care if required) before bisphosphonate therapy had significantly lower rates of BP ONJ than patients who did not receive any preventive measures (1.7% vs 7.8% respectively, p=0.016). American expert panels[21-22] have suggested that patients should have a dental examination before beginning therapy with bisphosphonates and that patients should be informed on the importance of maintaining good oral hygiene and having regular dental assessments.

Table 2. Bisphosphonates and their side effects[2-3,6]

Please see the statements of evidence for further evidence on adverse effects of bisphosphonates.

Agent	Characteristic side effects
Clodronate	Gastrointestinal toxicity (diarrhoea), hypocalcaemia (abnormally low calcium levels)
Ibandronate	Gastrointestinal toxicity, *arthralgia* (joint pain)
Pamidronate	Gastrointestinal toxicity, fever, hypocalcaemia (abnormally low calcium levels), *phlebitis* (inflammation of a vein), flu-like symptoms, *hypophosphataemia* (abnormally low phosphate levels)
Zoledronic acid	Anaemia, fever, nausea, fatigue, hypocalcaemia (abnormally low calcium levels), renal toxicity, nervous system disorders, flu-like symptoms, arthralgia (joint pain), *myalgia* (muscle pain), hypophosphataemia (abnormally low phosphate levels)

Other new emerging therapies

Denosumab is a monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL), thereby inhibiting osteoclast function and bone resorption. Evidence from a large study[15] suggests that denosumab may result in improved outcomes in delaying or preventing skeletal-related events compared to zoledronic acid, with similar toxicity. The study identified fewer adverse events potentially associated with renal toxicity (5% vs 9%) for patients taking denosumab.

[c] Precautionary information for bisphosphonates mentioned in this guideline is available in the product information (PI) on the *Pharmaceutical Benefits Scheme* website at www.pbs.gov.au

Strengths and weaknesses of evidence

The overall quality of the evidence included in the guideline was good, including a meta-analysis of randomised controlled trials conducted by Cochrane.[2] Whilst participant numbers in the Cochrane review varied (33–1130), 50% of studies had more than 200 participants.

A major limitation of the evidence is the variation in reporting and assessment of quality of life and adverse events (particularly pain) between trials. While five full text papers and one abstract describing randomised controlled trials investigating bisphosphonates for *advanced breast cancer* have been published since the last update of the Cochrane review in 2007, most were limited by relatively small number of patients and short treatment and follow-up times. Information about optimal timing and duration of bisphosphonate treatment is not yet available and there is limited evidence about the association between bisphosphonates and osteonecrosis of the jaw.

Unanswered questions

Important unanswered questions about the use of bisphosphonates for *advanced breast cancer* are outlined below. Some of these questions may be addressed in ongoing trials.

- What is the optimal schedule and maximum duration for use of bisphosphonates?
- How do bisphosphonates affect overall quality of life?
- What is the impact of bisphosphonates on vitamin D and calcium levels, and what is the potential for use of vitamin D and calcium supplements?
- What baseline tests should be used to determine who could benefit from bisphosphonates?
- How should bisphosphonates be used at the end of life?
- What are the relative harms/benefits of different bisphosphonates?
- What is the relationship between bisphosphonate type and dosage and osteonecrosis of the jaw?
- How do bisphosphonates compare with new bone acting agents?
- How do bisphosphonates interact with newer breast cancer *systemic treatments* (such as targeted therapies)?
- What is the role of biochemical markers to monitor bisphosphonate use?

Ongoing and additional trials or studies

A number of additional randomised controlled trials investigating the use of bisphosphonates for *advanced breast cancer* are ongoing and/or awaiting results:

- two ongoing trials comparing oral ibandronate to intravenous zoledronic acid (SWOG-S0308; ZICE)[23-24]
- four ongoing trials comparing different schedules of zoledronic acid (BISMARK; CALGB-70604; NCT00320710; NCT00375427)[25-28]
- one ongoing trial comparing single dose ibandronate to single dose *radiotherapy* for bone pain (ISRCTN86185157).[29]

References

1. National Breast Cancer Centre. Clinical practice guidelines for the management of *advanced breast cancer*. Canberra: Commonwealth of Australia, 2001.

2. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. *Cochrane database of systematic reviews (Online)* 2005(3):CD003474.

3. National Breast and Ovarian Cancer Centre. Bisphosphonates for advanced breast cancer - a systematic review. Surry Hills: NBOCC, 2010.

4. National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guidelines for the psychosocial care of adults with cancer. Camperdown: National Breast Cancer Centre, 2003.

5. National Health and Medical Research Council. NHMRC additional levels of evidence and *grades* for recommendations for developers of guidelines. Canberra: Commonwealth of Australia, 2009.

6. *Pharmaceutical Benefits Scheme* www.pbs.gov.au Accessed: 30 July 2010.

7. Ripamonti CI, Maniezzo M, Campa T, et al. Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. *Ann Oncol* 2009;20(1):137-45.

8. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007;22(10):1479-91.

9. Rosen LS, Gordon DH, Dugan W, Jr., et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast *carcinoma* patients with at least one osteolytic lesion. *Cancer* 2004;100(1):36-43.

10. Ross JR, Saunders Y, Edmonds PM, et al. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ* 2003;327(7413):469.

11. Ha TC, Li H. Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* 2007;96(12):1796-801.

12. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003;14(9):1399-405.

13. 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(6):1133-7.

14. Body JJ, Lichinitser M, Tjulandin S, et al. Oral ibandronate is as active as intravenous zoledronic acid for reducing bone turnover markers in women with breast cancer and bone metastases. *Ann Oncol* 2007;18(7):1165-71.

15. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010;28(35):5132-9.

16. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane database of systematic reviews (Online)* 2002(2):CD002068.

17. van Holten-Verzantvoort AT, Bijvoet OL, Cleton FJ, et al. Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. *Lancet* 1987;2(8566):983-5.

18. Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol* 2005;23(15):3314-21.

19. Diel IJ, Bergner R, Grotz KA. Adverse effects of bisphosphonates: current issues. *J Support Oncol* 2007;5(10):475-82.

20. Mauri D, Valachis A, Polyzos IP, et al. Osteonecrosis of the jaw and use of bisphosphonates in *adjuvant* breast cancer treatment: a meta-analysis. *Breast Cancer Res Treat* 2009;116(3):433-9.

21. Ruggiero S, Gralow J, Marx RE, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. *J Oncol Pract* 2006;2(1):7-14.

22. Edwards BJ, Hellstein JW, Jacobsen PL, et al. Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: an advisory statement from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc* 2008;139(12):1674-7.

23. National Cancer Institute Clinical Trials (PDQ) SWOG-S0308. http://www.cancer.gov/clinicaltrials/SWOG-S0308 Accessed: September 2010.

24. National Cancer Institute Clinical Trials (PDQ) ZICE. http://www.cancer.gov/clinicaltrials/WCTU-ZICE Accessed: September 2010.

25. National Cancer Institute Clinical Trials (PDQ) NCRI-BISMARK. http://www.cancer.gov/clinicaltrials/NCRI-BISMARK Accessed: September 2010.

26. National Cancer Institute Clinical Trials (PDQ) CALGB-70604. http://www.cancer.gov/clinicaltrials/CALGB-70604 Accessed: September 2010.

27. *Clinical trials*.gov NCT00320710. http://clinicaltrials.gov/ct2/show/NCT00320710 Accessed: September 2010.

28. Clinical trials.gov NCT00375427. http://clinicaltrials.gov/ct2/show/NCT00375427 Accessed: September 2010.

29. Controlled-Trials ISRCTN86185157 http://www.controlled-trials.com/ISRCTN86185157/ Accessed: September 2010.

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Membership of NBOCC* Bisphosphonates Working Group

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Dr Nick Pavlakis	Medical Oncologist (chair)
Ms Denice Bassanelli	Consumer Representative
Ms Sholeh Boyle	Specialist Breast Nurse
Dr Rosyln Drummond	Radiation Oncologist
Dr Belinda Kiely	Medical Oncologist
Ms Marlene Parsons	Consumer Representative
Ms Geraldine Robertson	Consumer Representative
Associate Professor Andrew Spillane	Surgical Oncologist
Dr Bronwyn Stuckey	Endocrinologist

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NBOCC* staff

Ms Sue Sinclair	General Manager
Ms Ornella Care	Program Manager
Ms Emma Lonsdale	Project Officer
Dr Anne Nelson	Evidence Review and Research Leader
Ms Rosemary Wade	Senior Project Officer - Research

External review

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Development process

Priority topic areas for NBOCC* guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary Working Group, including consumers, is established for each topic identified and is involved in all aspects of guideline development.

A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

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Additional information

Pharmaceutical Benefits Scheme listings for drugs mentioned in this guideline for the use of bisphosphonates for *advanced breast cancer* are available at www.pbs.gov.au

Recommendations for use of bisphosphonates for advanced breast cancer was prepared and produced by:

National Breast and Ovarian Cancer Centre*
Level 1 Suite 103/355 Crown Street Surry Hills NSW 2010
Tel: +61 2 9357 9400 Fax: +61 2 9357 9477 Freecall 1800 624 973
Website: www.nbocc.org.au

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