Recommendations for use of Bisphosphonates

in early breast cancer

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A CLINICAL PRACTICE GUIDELINE DEVELOPED BY CANCER AUSTRALIA*

This document supplements information contained in the *Clinical practice guidelines for the management of early breast cancer*, 2nd edition 2001.[1]

Recommendations for use of bisphosphonates for advanced breast cancer[2] are also available from the Cancer Australia website.

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Purpose

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

Endorsed by:

Breast Surgeons of Australia and New Zealand Inc.

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

MOGA

The Royal Australasian College of Surgeons

* 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.

Background

The *Clinical practice guidelines for the management of early breast cancer*[1] define *early breast cancer* as tumours of not more than five centimetres diameter with either impalpable or palpable, but not fixed, *lymph nodes* and with no evidence of distant metastases. This guideline is based on evidence on the use of bisphosphonates in women with early breast cancer.

Treatment for women with early breast cancer includes the use of *adjuvant* therapies, such as chemotherapy and *endocrine therapies*, to reduce the risk of cancer *recurrence* or *metastasis* and improve overall survival. *Chemotherapy* and some endocrine therapies (aromatase inhibitors and ovarian suppression) are associated with *bone mineral density* loss, which may increase risk of *osteoporosis* and fractures.

Bisphosphonates act to reduce the activity of bone-absorbing cells, thus limiting bone mineral density loss, and are standard care in the treatment of osteoporosis.

There are two classes of bisphosphonates, which are administered orally or intravenously depending on the drug:

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

The available evidence about the use of bisphosphonates in early breast cancer is limited, especially as the patient populations and treatment regimens vary across trials and there is limited long-term data.

^Ibandronate is also called ibandronic acid.
^^Zoledronic acid is also called zoledronate or zolendronate.

Clinical Practice Recommendations

The recommendations are based on the statements of current evidence for use of bisphosphonates in women treated for *early 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.[3]

RECOMMENDATIONS	LEVEL OF EVIDENCE[4]	REFERENCE
In women with early breast cancer who are receiving or have received systemic therapy:		
Bone health		
Short-term use of bisphosphonates (up to 4 years) should be considered to reduce loss of *bone mineral density* in lumbar spine, hip and femoral neck associated with treatment for early breast cancer (chemotherapy, endocrine therapy)	II	McCloskey,[5] Saarto,[6] ARIBON,[7] Kristensen,[8] REBBeCa,[9] SABRE,[10] ABCSG-12,[11] Hershman[12]
Schedule and duration of administration		
In postmenopausal women with *osteopenia*, upfront[a] intravenous zoledronic acid (4mg every 6 months) should be considered over delayed[b] treatment to prevent bone mineral density loss associated with *aromatase inhibitor* treatment for breast cancer	II	Z-FAST/ZO-FAST[13]
Adverse events		
A dental check up prior to commencing bisphosphonates should be considered		Edwards,[14] Ruggiero[15]
Women taking bisphosphonates should be routinely informed of the need for good oral health and monitored for osteonecrosis of the jaw		Khosla[16]
The serum creatinine levels of women taking intravenous zoledronic acid should be monitored for renal toxicity at baseline, before each infusion and at the final visit		Z-FAST,[17] ZO-FAST[18]
Clinicians should conduct a bone mineral density scan prior to prescribing bisphosphonates Clinicians should be aware of baseline tests (biochemistry including creatinine, serum calcium and vitamin D) and contraindications prior to prescribing bisphosphonates		
Women taking bisphosphonates should be reviewed regularly and monitored for adverse events by clinicians familiar with the use of bisphosphonates		

[a] The upfront groups received intravenous zoledronic acid immediately after random assignment.
[b] The delayed groups received intravenous zoledronic acid when either post-baseline lumbar spine or total hip T score decreased to less than -2.0 or a non-traumatic clinical fracture occurred.

Statements of Evidence

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

STATEMENTS	LEVEL OF EVIDENCE[4]	REFERENCE
In women with *early breast cancer* who are receiving or have received systemic therapy:		
Bone health		
Short-term use of any bisphosphonate (up to 4 years) can reduce lumbar spine, hip and femoral neck *bone mineral density* loss associated with treatment for early breast cancer at follow-up (1–5 years)	II	McCloskey,[5] Saarto,[6] ARIBON,[7] Kristensen,[8] REBBeCa,[9] SABRE,[10] ABCSG-12,[11] Hershman[12]
Bisphosphonates (clodronate, ibandronate, risedronate and zoledronic acid) significantly reduce the incidence of osteoporosis	I	CA[32a]
The short-term use of bisphosphonates does not significantly affect the incidence of bone fractures within a follow-up period of 1–5 years The longer-term impact of bisphosphonates on bone fractures is unknown	I	Valachis[19]
Overall survival[b]		
Bisphosphonates (clodronate, risedronate and zoledronic acid) do not significantly affect overall survival	I	CA[32a]
Cancer *recurrence* and metastases		
Oral bisphosphonates (clodronate and risedronate) do not significantly affect cancer recurrence	I	CA[32a]
Bisphosphonates (clodronate, pamidronate and zoledronic acid) do not significantly reduce the risk of developing bone metastases	I II	Cochrane[20] Diel,[21] Kristensen,[8] ABCSG-12[11]
Oral clodronate does not significantly reduce the risk of developing visceral metastases	I II	Cochrane[20] Diel[21]
Disease-free survival and recurrence-free survival[b]		
In premenopausal women undergoing *ovarian suppression* in combination with *endocrine therapy* (without *adjuvant* chemotherapy), zoledronic acid is associated with significantly longer disease-free survival and recurrence-free survival	II	ABCSG-12[11,22]

STATEMENTS	LEVEL OF EVIDENCE[4]	REFERENCE
Quality of life		
There are no studies on bisphosphonates in early breast cancer that report on quality of life		
Type of bisphosphonate		
There are no studies comparing different types of bisphosphonate		
Schedule and duration of administration		
There are no studies comparing different durations of bisphosphonate use		
Clinical studies evaluating bisphosphonates have been limited to therapy no greater than 5 years There is no evidence on the continuation of bisphosphonates beyond 5 years		
The administration schedules used in trials of bisphosphonate are: • Intravenous zoledronic acid:		
- 4mg every 6 months for 3 years[c]		ABCSG-12[11,23]
- 4mg every 3 months for 1 year		Hershman[12]
- 4mg every 6 months for 5 years		Hines 2009b,[24] Z-FAST,[17] ZO-FAST[18]
• Oral clodronate: 1600mg daily for 2–3 years		Saarto,[6] McCloskey[5]
• Oral ibandronate: 150mg every 4 weeks for 2 years		ARIBON[7]
• Oral pamidronate: 150mg twice daily for 4 years		Kristensen[8]
• Oral risedronate: 35mg weekly for 1–2 years		Hines 2009a,[25] REBBeCA,[9,26-28] SABRE[10]
In postmenopausal women, the upfront[d] addition of intravenous zoledronic acid (4mg every 6 months) to *aromatase inhibitors* has the following benefits when compared to delayed[e] treatment: • significantly improves disease-free survival • significantly reduces bone mineral density loss However, it may be associated with increased adverse events	II	ZO-FAST[29] Hines 2009b,[24] Z-FAST,[30] ZO-FAST,[18] Z-FAST/ZO-FAST[13]
In postmenopausal women with *osteopenia*, the upfront addition of intravenous zoledronic acid to *aromatase inhibitors* significantly reduces the incidence of *osteoporosis* at 1 and 3 years follow-up		Z-FAST/ZO-FAST,[13] ZO-FAST[29]
Adverse events[f]		
Bisphosphonates are associated with mild and infrequent toxicity	II	ARIBON,[7]

STATEMENTS	LEVEL OF EVIDENCE[4]	REFERENCE
Serious adverse events reported in bisphosphonate-treated populations ranged from <1% to 10.4%; however no statistically significant differences were reported between women taking bisphosphonates and no bisphosphonates in these trials		Kristensen,[8] Hines 2009a,[25] REBBeCa,[9] SABRE,[10] ABCSG-12,[11] Hershman,[12] Hines 2009b,[24] Z-FAST,[30] ZO-FAST,[18] Z-FAST/ZO-FAST[13]
Intravenous zoledronic acid significantly increases the incidence of osteonecrosis of the jaw; although the overall incidence is extremely low in women with early breast cancer (13 out of 5,312 women taking bisphosphonates; 0.2%)	I	Mauri 2009[31]
In premenopausal women undergoing ovarian suppression in combination with endocrine therapy, intravenous zoledronic acid may increase adverse events including bone pain, *arthralgia*, fever and nausea/vomiting	II	ABCSG-12[11]
All patients were screened for adequate renal function before inclusion to the adjuvant trials on zoledronic acid, and renal monitoring was conducted regularly throughout trial duration		ABCSG-12,[11] Hershman,[12] Hines 2009b,[24] Z-FAST,[30] ZO-FAST[18]

[a] Statement based on a meta-analysis undertaken as part of the Cancer Australia systematic review[32]

[b] The Cancer Australia systematic review does not include preliminary results from the AZURE trial. Further information can be found in the summary of results section of the guideline

[c] Protocol amendments, after 254 patients had been enrolled, reduced the dose of intravenous zoledronic acid from 8mg every 4 weeks to 4mg every 6 months

[d] The upfront groups received intravenous zoledronic acid immediately after random assignment

[e] The delayed groups received intravenous zoledronic acid when either post-baseline lumbar spine or total hip T score decreased to less than -2.0 or a non-traumatic clinical fracture occurred

[f] 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

Summary of Evidence

The statements and clinical practice recommendations about the use of bisphosphonates for women with *early breast cancer* are based on a Cancer Australia systematic review and meta-analysis (including available evidence published between 1 January 2007 and 18 August 2010)[32] and a Cochrane review and meta-analysis investigating the use of bisphosphonates for breast cancer (2005 and 2007 update).[20] Outcomes assessed include bone health, overall survival, cancer *recurrence* and metastases, quality of life and adverse events.

The Cochrane review and meta-analysis[20] included three trials on the effect of oral clodronate in women with early breast cancer on survival and *metastasis* compared to placebo or open control. Updated follow-up data from two trials identified in the Cochrane review were included in the Cancer Australia systematic review.

The Cancer Australia systematic review identified four systematic reviews and 13 published randomised controlled trials, which examined the effects of bisphosphonates for women with early breast cancer. The quality of all systematic reviews and randomised controlled trials was rated fair to good. The four systematic reviews assessed: the effect of oral clodronate on survival (Ha 2007[33]), the relationship between bisphosphonates and osteonecrosis of the jaw (Mauri 2009[31]), the impact of bisphosphonates on disease course (Mauri 2010[34]), and the impact of bisphosphonates on fracture prevention (Valachis 2010[19]).

Ten of the randomised controlled trials identified in the Cancer Australia systematic review compared bisphosphonates to placebo or no bisphosphonate: three oral clodronate trials, one oral ibandronate trial, one oral pamidronate trial, three oral risedronate trials and two intravenous zoledronic acid trials. The remaining three randomised controlled trials compared upfront[a] intravenous zoledronic acid with delayed[b] delivery.

For all trials, bisphosphonates were administered in addition to standard *adjuvant* treatment, such as *chemotherapy*, *endocrine therapy* and *radiotherapy*.

Meta-analyses were conducted using the results from earlier systematic reviews[20,34] and the subsequently published randomised controlled trials identified in the Cancer Australia systematic review to analyse the effect of bisphosphonates on overall survival, cancer recurrence, metastasis, and incidence of *osteoporosis* and fracture.

(See Table 1 – Summary of trials)

[a] The upfront groups received intravenous zoledronic acid immediately after random assignment

[b] The delayed groups received intravenous zoledronic acid when either post-baseline lumbar spine or total hip T score decreased to less than -2.0 or a non-traumatic clinical fracture occurred

Details of Trials or Studies

Table 1. Summary of trials

Study Follow-up *Quality*	Population	Intervention*	Comparator*
Clodronate			
Diel 2008[21,35] Median 8.5yr follow-up *Fair*	Women with T1-4, N0-2 breast cancer, no distant metastases who received *adjuvant endocrine therapy* or *chemotherapy* with or without radiotherapy	Clodronate 1600mg/d for 2yrs (N=157)	Standard care for 2yrs (N=145)
McCloskey 2010[5] 2yr follow-up *Fair*	Women with primary breast cancer without *metastasis* having chemotherapy, endocrine therapy and/or *radiotherapy*, according to local protocols	Clodronate 1600mg/d for 2yrs (N=419)	Placebo for 2yrs (N=432)
Saarto 2008[6] 10yr follow-up *Fair*	Pre/postmenopausal women with breast cancer who received postoperative radiotherapy; premenopausal women who received chemotherapy	**Premenopausal:** Clodronate 1600mg/d for 3yrs (N=20) **Postmenopausal:** Clodronate 1600mg/d for 3yrs & tamoxifen 20mg (N=14) or toremifene 60mg/d (N=10) for 3yrs	**Premenopausal:** Standard care for 3yrs (N=35) **Postmenopausal:** Tamoxifen 20mg (N=11) or toremifene 60mg/d (N=6) for 3yrs
Ibandronate			
ARIBON[7] 2yr follow-up *Fair*	Osteopenic, postmenopausal women with ER+ breast cancer who received anastrozole	Ibandronate 150mg every 4wks for 2yrs (N=25)	Placebo every 4wks for 2yrs (N=25)
Pamidronate			
Kristensen 2008[8] 10yr follow-up (4yr BMD)	Women with no distant metastases and either:	Pamidronate 150mg twice daily for 4yrs (N=460)	Standard care for 4yrs (N=493)

Study Follow-up *Quality*	Population	Intervention*	Comparator*
Fair	1) premenopausal, *grade* 2-3 breast cancer #5cm without *lymph* node metastasis; 2) premenopausal, HR-ve/ unknown breast cancer & axillary lymph node metastases or primary tumour >5cm; 3) postmenopausal, HR-ve breast cancer & axillary lymph node metastasis or primary tumour >5cm Patients received adjuvant chemotherapy; locoregional radiotherapy was given according to local guidelines, and endocrine therapy was avoided		
Risedronate			
Hines 2009a[25] 1yr follow-up *Good*	Premenopausal women with *stage* I-IIIb breast cancer with adjuvant/neoadjuvant chemotherapy scheduled with or without tamoxifen	Risedronate 35mg weekly for 1yr (N=108)	Placebo weekly for 1yr (N=108)
REBBeCa[9,26-28] 2yr follow-up *Good*	Women with breast cancer, <8yrs postmenopausal, after chemotherapy with or without endocrine therapy	Risedronate 35mg weekly for 2yrs (N=43)	Placebo weekly for 2yrs (N=44)
SABRE[10]	Postmenopausal women with non-	Risedronate 35mg weekly for 2yrs (N=77)	Placebo weekly for 2yrs (N=77)

Study **Follow-up** *Quality*	**Population**	**Intervention***	**Comparator***
2yr follow-up *Good*	metastatic breast cancer, moderate fracture risk with anastrozole scheduled		
Zoledronic acid			
ABCSG-12[11,22-23] Median 5yr follow-up (5yr BMD) *Fair*	Premenopausal women with stage I-II ER+/PR+ breast cancer, <10 positive *lymph nodes*, standard therapy with goserelin scheduled Preoperative chemotherapy was allowed however no patients received adjuvant chemotherapy; postoperative radiotherapy was given according to local guidelines	**GTZ:** Goserelin 3.6mg s.c. every 4wks & tamoxifen 20mg/d & ZA IV 8mg every 4wks for 3yrs (N=449)[§] **GAZ:** Goserelin 3.6mg s.c. every 4 wks & anastrozole 1mg/d & ZA IV 8mg every 4wks for 3yrs (N=450)[§]	**GT:** Goserelin 3.6mg s.c. every 4 wks & tamoxifen 20mg/d for 3yrs (N=451) **GA:** Goserelin 3.6mg s.c. every 4wks & anastrozole 1mg/d for 3yrs (N=453)
Hershman 2010[12] 2yr BMD follow-up; 1yr AEs, recurrence *Fair*	Premenopausal women with non-metastatic breast cancer receiving chemotherapy	ZA IV 4mg every 3mths for 1yr (N=57)	Placebo for 1yr (N=57)
Hines 2009b[24] 2yr follow-up *Fair*	Postmenopausal women with stage I-IIIa ER+/PR+ breast cancer without metastasis, #6yrs tamoxifen completed	Letrozole 2.5mg/d for 5yrs + upfront[†] ZA IV 4mg every 6mths for 5yrs or until *recurrence* (N=279)	Letrozole 2.5mg/d for 5yrs + delayed[‡] ZA IV 4mg every 6mths for 5yrs or until recurrence (N=279)
Z-FAST[17] 3yr follow-up *Fair*	Postmenopausal women with stage I-IIIa ER+/PR+ breast cancer	Letrozole 2.5mg/d for 5yrs + upfront[†] ZA IV 4mg every 6mths for 5yrs (N=301)	Letrozole 2.5mg/d for 5yrs + delayed[‡] ZA IV 4mg every 6mths for 5yrs (N=301)

Study **Follow-up** *Quality*	**Population**	**Intervention***	**Comparator***
ZO-FAST[18] 1yr follow-up *Fair*	Postmenopausal women with stage I-IIIa ER+/PR+ breast cancer	Letrozole 2.5mg/d for 5yrs + upfront† ZA IV 4mg every 6mths for 5yrs (N=532)	Letrozole 2.5mg/d for 5yrs + delayed‡ ZA IV 4mg every 6mths for 5yrs (N=533)

Abbreviations: AE = adverse event; BMD = bone mineral density; ER+ = *oestrogen* receptor-positive; GA = goserelin & anastrozole; GAZ = goserelin & anastrozole & zoledronic acid; GT = goserelin & tamoxifen; GTZ = goserelin & tamoxifen & zoledronic acid; HR- = hormone receptor-negative; IV = intravenous; PR+ = *progesterone* receptor-positive; s.c. = subcutaneous; ZA = zoledronic acid

*administered orally unless otherwise specified; §protocol amendments, after 254 patients had been enrolled, reduced the dose of intravenous zoledronic acid from 8mg every 4 weeks to 4mg every 6 months; †administered immediately after random assignment; ‡administered when either post-baseline lumbar spine or total hip T score decreased to less than -2.0 or a non-traumatic clinical fracture occurred

Summary of Trial or Study Results

Bone health

Chemotherapy and some *endocrine therapies* (aromatase inhibitors and ovarian suppression) are associated with *bone mineral density* (BMD) loss. The majority of trials identified in the Cancer Australia systematic review[32] reported that patients were assigned to receive calcium and vitamin D supplements, which could impact on their bone health. Eight trials reported that short-term use of bisphosphonates (up to four years) was associated with significantly reduced lumbar spine, hip and femoral neck BMD loss at follow-up. The patient populations and breast cancer treatment regimens used in each trial varied, and the follow-up periods ranged from one to five years after completion of bisphosphonates.

A meta-analysis[32] of four trials showed that bisphosphonates significantly reduced the incidence of *osteoporosis*. All trials favoured the bisphosphonates group; however the results are largely influenced by the large ABCSG-12 trial[23] of intravenous zoledronic acid in premenopausal women undergoing *ovarian suppression* (without *adjuvant* chemotherapy), which was the only individual trial to show a significant reduction in incidence of osteoporosis.

The effect of bisphosphonates on *osteopenia* (a condition where BMD is lower than normal but not low enough to be classified as osteoporosis) is unclear, as the results differ by trial. The ABCSG-12 trial[23] reported a significant reduction in incidence of osteopenia at three-year follow-up for participants receiving zoledronic acid in addition to goserelin and anastrozole, or goserelin and tamoxifen; yet five-year follow-up results were only significant for addition of zoledronic acid to goserelin and anastrozole. Results from other trials of clodronate and risedronate were not significant.

A meta-analysis[19] of 14 randomised controlled trials and meta-analysis[32] of five randomised controlled trials showed that short-term use of bisphosphonates (up to five years) did not significantly reduce the incidence of fractures at follow-up. As the trials generally had short follow-up periods (one to five years), it is unknown whether improvements in BMD could have long-term effects on the incidence of fractures. Also, the studies were not powered to detect a significant difference for fracture outcome.

Australian guidelines[36] on the prevention and management of osteoporosis state that there is high level evidence to support the effectiveness of bisphosphonates in reducing the risk of vertebral and non-vertebral fractures and increasing BMD in postmenopausal women with osteoporosis in the general population. The guidelines also state that healthy lifestyle choices (such as adequate vitamin D, healthy weight and body mass index, not smoking and limiting alcohol consumption) minimise the risk of developing osteoporosis.

The most appropriate protocol for monitoring bone mineral density has not been addressed as a clinical question. The trials included in the Cancer Australia systematic review monitored BMD at baseline and at regular intervals throughout the duration of the trials. While not included in the scope of this guideline, secondary causes of low BMD, including vitamin D deficiency, hyperthyroidism and primary hyperparathyroidism, have been observed to be common in postmenopausal breast cancer patients.[37] A detailed analysis of secondary causes of low BMD was not undertaken for this guideline.

Overall survival

The evidence on overall survival is complex, as different trials with different patient populations and treatment regimens have reported varying results. The Cancer Australia meta-analysis[32] of five randomised controlled trials found that bisphosphonates (clodronate, risedronate and zoledronic acid) do not significantly affect overall survival. An earlier Cochrane meta-analysis[20] of three oral clodronate trials reported that oral clodronate may improve overall

survival at follow-up of 4–5.5 years. More recent follow-up data from two of these trials was included in the Cancer Australia meta-analysis, which found no significant difference in overall survival associated with bisphosphonates, although the trials were not designed to show a significant difference in relation to mortality or overall survival.

Subgroup analysis of 1,100 out of 3,360 women of preliminary results from the AZURE trial showed that intravenous zoledronic acid had a significant effect on overall survival for women with well-established *menopause* (ie more than 5 years after menopause).[38] Women in this trial had *stage* II/III breast cancer, scheduled to receive (neo) adjuvant chemotherapy and/or *endocrine therapy*.[39] The full results on overall survival from this trial are not yet published.

Cancer *recurrence* and metastases

The Cancer Australia meta-analysis[32] of six randomised controlled trials of clodronate, risedronate and zoledronic acid showed that bisphosphonates did not significantly affect overall cancer recurrence.

The Cochrane systematic review[20] and three randomised controlled trials[8,11,21] reported that the risk of developing bone metastases was not significantly reduced with bisphosphonates (clodronate, pamidronate, zoledronic acid). The Cochrane systematic review[20] and recent follow-up data from one randomised controlled trial[21] reported that oral clodronate does not significantly reduce risk of developing visceral metastases.

Disease-free survival, *recurrence-free survival* and survival without metastasis

The evidence on disease-free survival is complex, as different trials with different patient populations and treatment regimens have reported varying results. The large ABCSG-12 trial[11] in premenopausal women undergoing ovarian suppression in combination with endocrine therapy (without adjuvant chemotherapy) found that intravenous zoledronic acid significantly improved disease-free survival and recurrence-free survival. Longer follow-up data recently reported from this trial support these findings.[22] The primary end point of this trial was disease-free survival, defined as time from randomisation to the first occurrence of one or more of the following: a local or regional recurrence, cancer in the *contralateral breast*, distant *metastasis*, second primary *carcinoma*, or death from any cause.

Preliminary results from the large AZURE trial of women with stage II/III breast cancer, scheduled to receive (neo) adjuvant chemotherapy and/or endocrine therapy found no significant effect of intravenous zoledronic acid on disease-free survival after a median follow-up of 59 months.[39] The full results on disease-free survival from this trial are not yet published.

A trial[8] comparing oral pamidronate with standard care in pre- and postmenopausal women reported no significant impact on survival without *bone metastasis*.

Schedule and duration of administration

No bisphosphonate is currently subsidised on the *Pharmaceutical Benefits Scheme* for women with *early breast cancer*.[40] Doses and schedules identified in this guideline are based on individual trials in women with early breast cancer; however there are no standard schedules and there is much variation among trials.

Most trials administered bisphosphonates over a period of one to five years. No studies comparing different durations of bisphosphonate use, or use beyond five years were identified.

Three trials[13,18,24,29-30] compared upfront to delayed intravenous zoledronic acid, in combination with *aromatase inhibitors* for postmenopausal women with early breast cancer. Upfront zoledronic acid significantly improved disease-free survival[29] and significantly reduced BMD loss associated with treatment for early breast

cancer.[13,18,24,30] However, the addition of upfront zoledronic acid to *aromatase inhibitors* was associated with increased adverse events, such as pyrexia (fever), bone pain and headache. An integrated analysis[13] of two trials and recent follow-up data from the ZO-FAST trial[29] found that upfront zoledronic acid significantly reduced the incidence of severe osteopenia/osteoporosis (T score less than -2.0) in premenopausal women with mild-moderate osteopenia (T score of -1.0 or lower and -2.0 or greater) when compared to delayed zoledronic acid. This effect was significant at one and three year follow-up.

Recent results from the CALGB 79809 trial[41] report that zoledronic acid prevents bone loss in premenopausal women who develop ovarian failure due to chemotherapy. The upfront addition of intravenous zoledronic acid to adjuvant chemotherapy (within 1–3 months of randomisation) led to a significantly greater reduction in BMD loss compared to delaying addition of zoledronic acid for one year.

Adverse events

Ten trials[32] reported on adverse events or toxicity. Minimal serious toxicity was reported, with serious adverse events reported for <1% to 10.4% of women taking bisphosphonates. In these trials, there were no statistically significant differences in reported toxicity between women taking bisphosphonates and no bisphosphonates. Trials of ibandronate,[7] pamidronate,[8] risedronate[9-10,25] and zoledronic acid[12] found that bisphosphonates were well tolerated compared with placebo. One trial[25] found that risedronate benefited patients by reducing incidence of *arthralgia* and chest pain, compared with placebo. The ABCSG-12 trial[11] of zoledronic acid in premenopausal women with ovarian suppression (without adjuvant chemotherapy) reported a significant increase in adverse events associated with zoledronic acid, including arthralgia, bone pain, fever and nausea/vomiting. There were no confirmed cases of osteonecrosis of the jaw (ONJ) in this trial.

A literature review[42] on bisphosphonate-related adverse effects identified gastrointestinal toxicity, acute-phase reactions and renal toxicity as the most common adverse events of bisphosphonates. Renal toxicity was associated with intravenous bisphosphonates, mainly zoledronic acid and to a lesser extent pamidronate, while intravenous ibandronate and oral bisphosphonates were identified as having a safety profile similar to placebo with regard to renal toxicity. The trials identified in the Cancer Australia systematic review[32] reported no incidences of renal toxicity; however this is likely influenced by the trial exclusion criteria, as many studies excluded patients with renal dysfunction.

Some side effects of bisphosphonates, which may affect women on an individual basis, are presented in Table 2.

Table 2. Bisphosphonates and their side effects[20,32,40,43]

See the statements of evidence for further evidence on adverse effects of bisphosphonates.

Agent	Characteristic side effects
Clodronate	Gastrointestinal toxicity, hypocalcaemia
Ibandronate	Gastrointestinal toxicity, arthralgia
Pamidronate	Gastrointestinal toxicity, fever, *hypocalcaemia*, *phlebitis*, flu-like symptoms, hypophosphataemia
Risedronate	Gastrointestinal toxicity, arthralgia, chest pain
Zoledronic acid	Anaemia, fever, nausea, fatigue, hypocalcaemia, renal toxicity, nervous system disorders, flu-like symptoms, arthralgia, *myalgia*, hypophosphataemia

Osteonecrosis of the jaw

A taskforce of the American Society for Bone and Mineral Research conducted a review of bisphosphonate-associated ONJ in 2007.[16] The true incidence of bisphosphonate-associated ONJ is unknown; however the estimated incidence in patients with malignancy seems to range between 1% and 10%. While the taskforce recognised that the evidence on *risk factors* predisposing to bisphosphonate-associated 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.

One systematic review and meta-analysis[31] of 15 randomised controlled trials assessed the relationship between ONJ and bisphosphonate use as adjuvant breast cancer treatment. ONJ was identified in the review as a rare event, occurring in 13 of the 5,312 patients receiving bisphosphonates (0.2%) and occurring in one of the 5,382 patients in the *control group* (0.02%). All 13 ONJ occurrences in the bisphosphonates group were in patients taking zoledronic acid, and the meta-analysis showed a significant increase in ONJ with zoledronic acid compared with no bisphosphonates. Further published data from the AZURE trial[44] on the safety profile of zoledronic acid reported 11 confirmed cases of ONJ from a total of 1,665 women receiving zoledronic acid (0.7%). No cases of ONJ were reported in the group of women not receiving zoledronic acid.

Limited information is available evaluating the effect of dental preventive measures on incidence of bisphosphonate-associated ONJ in cancer patients. In the advanced cancer setting, a retrospective non-randomised study[45] 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 intravenous zoledronic acid therapy had significantly lower rates of bisphosphonate-associated ONJ than patients who did not receive any preventive measures (1.7% vs. 7.8% respectively, p=0.016). American expert panels[14-15] 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.

Atypical fractures

While not included in the scope of this guideline, atypical femoral fractures have been reported to be associated with bisphosphonate use. A recent Swedish analysis[46] of women aged 55 years and older with a fracture identified that bisphosphonate use was associated with atypical fractures; however the *absolute risk* was small [0.0005 (0.0004-0.0007)]. A detailed analysis of atypical fractures was not undertaken for this guideline.

Quality of life

Quality of life, including the impact of adverse events on quality of life, was not a reported outcome in the trials identified in the systematic review. Further research is required to determine the short- and long-term effects of bisphosphonates on quality of life.

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. There are ongoing studies comparing denosumab with placebo in women with early breast cancer (D-CARE,[47] ABCSG-18,[48] NCT00089661[49]), and evidence from one large study[50] in the *advanced breast cancer* setting has found that denosumab may result in improved outcomes in delaying or preventing skeletal-related events compared to zoledronic acid, with similar toxicity.

Strengths and Weaknesses of the Evidence

The evidence included in this guideline is mostly based on randomised controlled trials. The quality of all included systematic reviews and randomised controlled trials was rated fair to good. The variations in patient populations and breast cancer treatment regimens used in each trial may impact the generalisability of some of the trial results. While participant numbers in the randomised controlled trials varied from 50 to 1,803, the majority of trials had more than 200 participants. The Cancer Australia meta-analysis results for some outcomes were influenced by one of the larger trials, ABCSG-12, which included a select population of premenopausal women treated with *endocrine therapy* and *ovarian suppression* (without *adjuvant* chemotherapy). Another limitation of the evidence is the paucity of information on the long-term effects of bisphosphonates on patients, as follow-up results beyond 10 years have not been reported. Information about the optimal duration and schedule of bisphosphonate treatment for women with *early breast cancer* is not yet available, nor is evidence available about how bisphosphonates affect quality of life for women with early breast cancer.

Unanswered Questions

- What is the optimal schedule and duration for use of bisphosphonates?
- What are the longer-term effects of bisphosphonate use (beyond 1–5 years)?
- What are the relative harms/benefits of different bisphosphonates?
- How do bisphosphonates affect overall quality of life?
- What baseline tests should be used to determine who could benefit from bisphosphonates?
- Are there certain subgroups who would benefit most from different bisphosphonates?
- What is the relationship between bisphosphonate type and dosage and osteonecrosis of the jaw?
- What are the long term effects of improvements in *bone mineral density* on future bone events, such as fractures?
- 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?
- What are the optimal tests and schedules for monitoring women taking bisphosphonates?

Ongoing and Additional Trials or Studies

A number of additional studies are investigating the use of bisphosphonates for early breast cancer:

- five trials investigating the use of bisphosphonates in combination with *chemotherapy* and/or hormone therapy for *adjuvant* treatment of *early breast cancer* (zoledronic acid: HOBOE,[51] CZOL446GDE13;[52] clodronate: NSABP B-34;[53] ibandronate: GAIN,[54] TEAM IIB[55])
- one trial investigating the use of zoledronic acid in combination with chemotherapy and/or hormone therapy for adjuvant or *neoadjuvant* treatment of high risk localised breast cancer (AZURE[56])[a]
- four trials investigating upfront versus delayed use of zoledronic acid in combination with chemotherapy and/or hormone therapy for adjuvant treatment of early breast cancer (NCT00376740,[57] CFEM345D2405,[58] CALGB-79809, [59b] JPRN-UMIN000001104[60])
- one trial investigating the use of zoledronic acid in combination with letrozole for extended adjuvant treatment of primary breast cancer (CFEM345DDE09[61])
- one trial comparing zoledronic acid with clodronate or ibandronate for adjuvant treatment of early breast cancer in combination with chemotherapy and/or hormone therapy (SWOG-S0307[62])
- two trials investigating the use of risedronate in preventing bone loss in postmenopausal women on hormonal therapy (REBBeCA II,[63] RISAROS[64])
- three trials investigating the use of zoledronic acid in combination with chemotherapy and/or hormone therapy for neoadjuvant treatment of early breast cancer (CZOL446GDE19,[65] CZOL446GCA08,[66] ANZAC[67])
- one trial investigating the postoperative use of zoledronic acid in breast cancer patients after neoadjuvant chemotherapy (NATAN[68]).

[a] Preliminary results from AZURE were presented at San Antonio Breast Cancer Symposium 2010. Data on the safety profile of zoledronic acid were published in 2011

[b] Results from CALGB-79809 were published in 2011

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Note – Recent results and information from Coleman (2010 (#39), 2011 (#44)), Eidtmann (2010)(#29), Gnant (2011) (#22), Schilcher (2011)(#46) and Shapiro (2011)(#41) are included in this guideline, although these results were published after the Cancer Australia systematic review was conducted.

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* 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.

External review

Cancer Australia acknowledges those who gave their time to provide comment on the draft guideline recommendations as part of the external review process.

Topic-specific guideline development process

Priority topic areas for Cancer Australia 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

Precautionary information, 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

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Glossary

Adjuvant – treatment given in addition to primary (initial) treatment. For breast cancer, the primary treatment is surgery and adjuvant treatments include *chemotherapy*, *radiotherapy*, *hormonal therapies* and targeted therapies

Anaemia – a condition in which there are fewer red blood cells in the blood than normal

Aromatase inhibitors – types of hormonal therapy used in the treatment of breast cancer

Arthralgia – pain in the joints

Atypical fractures – stress fractures in compact bone that occur at sites with high tensional stress

Bone metastasis – cancer that has spread to the bone

Bone mineral density (BMD) – defined using the T score (how dense the bone is compared to the expected bone density of a young healthy adult) and measured from various places including lumbar spine, hip and femoral neck. A normal bone mineral density is T score greater than -1.0

Contralateral breast – the other breast from the initial site of breast cancer

Disease-free survival – time from randomisation to the first occurrence of one or more of the following: a local or regional recurrence, cancer in the contralateral breast, distant metastasis, second primary *carcinoma*, or death from any cause

Endocrine therapy – a type of hormonal treatment that acts to inhibit the grown of breast cancer cells that have *hormone receptors* (e.g. ovarian suppression, aromatase inhibitors and selective *oestrogen* receptor modulators)

ER+ (oestrogen receptor-positive) breast cancer – a type of breast cancer in which the growth of cancer cells is affected by the female hormone oestrogen

Hypocalcaemia – abnormally low calcium levels

Hypophosphataemia – abnormally low phosphate levels

Lymph nodes – glands in the armpit and other parts of the body that protect the body from infection. *Lymph nodes* may be fixed or moveable

Metastasis – the secondary or distant spread of cancer, away from its initial site in the body

Myalgia – muscle pain

Neoadjuvant – administration of therapy before the main treatment (e.g. prior to surgery)

Osteonecrosis of the jaw (ONJ) – death of a section of the jaw

Osteopenia – lower bone mineral density than normal but not low enough to be classified as osteoporosis. *Osteopenia* may be a precursor to osteoporosis. Defined in trials as bone mineral density T score greater than -2.5 and less than -1.0

Osteoporosis – systemic skeletal disease that causes the bones to become thin, weak and fragile, and leads to increased risk of fracture. Defined in trials as bone mineral density T score of -2.5 or lower

Ovarian suppression – therapy to stop functioning of the *ovaries* and prevent them from producing oestrogen

Phlebitis – inflammation of a vein

PR+ (progesterone receptor-positive) breast cancer – a type of breast cancer in which the growth of cancer cells is affected by the female hormone progesterone

Recurrence-free survival – time from randomisation to the first occurrence of local or regional recurrence

Systemic therapy – drugs such as chemotherapy or hormonal therapy that treat the whole body to destroy cancer cells **Targeted therapy** – drugs that stop the growth of particular types of cancer cells

Visceral metastasis – cancer that has spread to other internal organ(s)