An addendum to this Public Summary Document (PSD) has been included at the end of the document.

6.04 Zoledronic acid  
**Injection concentrate for I.V. infusion 4 mg (as monohydrate) in 5 mL  
APO-Zoledronic Acid®  
Apotex Pty Ltd**

1. **Purpose** 
   1. To seek the Pharmaceutical Benefits Advisory Committee’s (PBAC) consideration of whether it would be appropriate to amend the current listing for zoledronic acid to include the adjuvant management of breast cancer in post-menopausal women.
2. **Background**
   1. In July 2021, members of the Medical Oncology Group of Australia (MOGA) and Breast Cancer Network Australia (BCNA) prepared a presentation on the evidence base supporting the listing of zoledronic acid for the adjuvant management of early breast cancer on the Pharmaceutical Benefits Scheme (PBS).

Committee-In-Confidence

* 1. ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |.

**End Committee-In-Confidence**

TGA Registration

* 1. The current TGA registered indications for the 4 mg/5 mL presentation of zoledronic acid are:
* Prevention of skeletal-related events (pathological fracture, spinal cord compression, radiation to bone or surgery to bone) in patients with advanced malignancies involving bone.
* Treatment of tumour-induced hypercalcaemia.
  1. The recommended dosing for the above indications is 4 mg given as an intravenous infusion lasting no less than 15 minutes, every 3 to 4 weeks.
  2. The 5 mg vial has marketing approval for the following indications:
* Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures.
* Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures.
* To increase bone mineral density in men with osteoporosis.
* To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use.
* To prevent glucocorticoid-induced bone mineral density loss.
* Treatment of Paget’s disease of bone
  1. The recommended dosing of the 5 mg vial is one 5 mg infusion, annually.

International subsidy arrangements

* 1. Zoledronic acid is used (off-label) for adjuvant management of early breast cancer in post-menopausal women in New Zealand, UK, Canada, and several countries in Western Europe. It is also recommended in various clinical practice guidelines (e.g., ASCO, ESMO).
  2. Zoledronic acid has been subsidised in New Zealand for adjuvant management of early breast cancer since 2017, with a treatment duration of 2 years. In April 2022, subsidy was extended to a treatment duration of 3 years[[1]](#footnote-1). The requirements of subsidy are as follows:
* Treatment to be used as adjuvant therapy for early breast cancer.
* Patient has been amenorrhoeic for 12 months or greater, either naturally or induced, with endocrine levels consistent with a postmenopausal state and
* Treatment to be administered at a minimum interval of 6-monthly for a maximum of 3 years.
  1. In the United Kingdom, in 2018, NICE recommended[[2]](#footnote-2):
* Offer bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node‑positive invasive breast cancer.
* Consider bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy for postmenopausal women with node‑negative invasive breast cancer and a high risk of recurrence.
* Health practitioners discuss the benefits and risks of bisphosphonate treatment with women, particularly the risk of osteonecrosis of the jaw, atypical femoral fractures and osteonecrosis of the external auditory canal.

Current PBS listing

* 1. Zoledronic acid (4 mg vial) was first listed on the PBS for bone metastases from breast cancer and prostate cancer in 2003, and subsequently for multiple myeloma and hypercalcaemia of malignancy. The dosing interval is monthly.
  2. Other bisphosphonates listed for bone metastases are clondronate, pamidronate and ibandronic acid. Denosumab was listed with a similar restriction in 2011.
  3. Zoledronic acid (5 mg vial) was listed on the PBS for osteoporosis in 2008. The dosing interval for the management of osteoporosis is 12-months.
  4. Current PBS listings for zoledronic acid (5 mg vial) are not for the prevention of osteoporosis, but for treatment of osteoporosis, established osteoporosis and corticosteroid-induced osteoporosis for patients:
* older than 70 years with bone mineral density (BMD) T-score of -3.0 or less
* on long-term, high-dose corticosteroid use and BMD T-score of -1.0 or less
* who have experienced minimal-trauma fracture due to osteoporosis.
  1. Zoledronic acid (5 mg vial) is also currently listed on the PBS for the treatment of symptomatic Paget disease of bone.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

1. **Requested Listing**
   1. Add new indication to zoledronic acid as follows:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of**  **Rpts** | **Available brands** |
| ZOLEDRONIC ACID | | | | | | | |
| zoledronic acid 4 mg/5 mL injection, 5 mL vial | | | NEW | 1 | 1 | 0 | APO-Zoledronic Acid |
| **Restriction Summary / Treatment of Concept:** | | | | | | | |
| **Concept ID** | | **Category / Program:** Section 100 – Highly Specialised Drugs Public/Private hospitals | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (STREAMLINED | | | | | |
| Prescribing rule level |  |  | | | | | |
|  | | **Indication:** Adjuvant management of breast cancer | | | | | |
|  | | **Clinical criteria:** Patient must be post-menopausal | | | | | |
|  | | **Administrative Advice:** Patient must not undergo treatment for more than 3 years. | | | | | |

* 1. The recommended dose provided by MOGA/BCNA for the proposed indication was 4 mg IV every six months for three years.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

1. **Population and the disease**
   1. Breast cancer is the most common cancer in women. In Australia, most cases (approximately 87%) are diagnosed at an early localised stage.
   2. Bone is a common site of metastases for women with breast cancer. Bisphosphonates act by inhibiting osteoclast-mediated bone resorption and affect T-cell function which in turn, could prevent or delay recurrence of bone disease.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

1. **Consideration of the evidence**

Sponsor hearing

* 1. There was no hearing for this item.

Clinical trials and claim

* 1. Individual studies of adjuvant bisphosphonate in early breast cancer reported inconsistent results, which could be due to random variation associated with the small number of recurrences and deaths that occur for follow-up of 5 years. A related problem is that, in a particular individual study, there might not be enough recurrences and deaths to identify consistent effects in the all-comers population versus a particular subgroup, for example, postmenopausal women.
  2. To alleviate these statistical problems, an individual-patient data (IPD) meta-analysis was conducted by the Early Breast Cancer Trialists' Collaborative Group and published in 2015[[3]](#footnote-3).
  3. Summary of women and treatments included in the EBCTCG meta-analysis:
* 18,766 women enrolled in 26 randomised control trials.
* 11,767 women were postmenopausal, 6171 women were premenopausal and 828 women were perimenopausal
* zoledronic acid (50%) and clodronate (27%) were the most commonly used bisphosphonates
* median follow-up was 5·6 woman-years (IQR 3·7–8·0). 3453 women had a recurrence, 2106 died.
* the mean scheduled treatment duration was 3·4 years; 18 206 (97%) of 18 766 participants were in trials of 2–5 years of treatment.
* subgroup analyses by menopausal and nodal status were not published separately for zoledronic acid or clodronate (NICE did a 2018 systematic review of data specifically for zoledronic acid and the other bisphosphonates, see below)
  1. Among all women in the EBCTCG meta-analysis (n=18,766), the absolute 10-year risk with bisphosphonates compared with control was reduced by:
* 1.4% for distant recurrence (20.4% compared with 21.8%, p=0.03)
* 1.1% for bone recurrence (7.8% compared with 9.0%, p=0.004), and
* 1.7% for breast cancer mortality (16.6% compared with 18.4%, p=0.04).
  1. A subgroup analysis found that in postmenopausal women (n=11,767) the absolute 10-year risk with bisphosphonates compared with control was reduced by:
* 3.0% for breast cancer recurrence (22.8% compared with 25.8%, p=0.002)
* 3.4% for distant recurrence (17.9% compared with 21.2%, p=0.0003)
* 2.2% for bone recurrence (6.6% compared with 8.8%, p=0.0002) and
* 3.3% for breast cancer mortality (14.7% compared with 18.0%, p=0.002)
* 2.3% for all-cause mortality (21.1% compared with 23.5%, p=0.005).

The same benefits were not seen in premenopausal women.

* 1. The main conclusion from the study was: ‘Adjuvant bisphosphonates reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival, but there is definite benefit only in women who were postmenopausal when treatment began.’
  2. Similar findings were reported from a 2017 Cochrane meta-analysis[[4]](#footnote-4).
  3. The absolute benefit for breast-cancer mortality for postmenopausal women of 3.3% at 10 years compares to the estimated absolute benefit of anthracycline containing chemotherapy over CMF (cyclophosphamide, methotrexate and 5-fluorouracil) of 3.0% at 5 years and taxanes in addition to anthracycline chemotherapy regimens, a 3.2% gain at 8 years[[5]](#footnote-5).
  4. In 2018 NICE conducted a systematic review and economic analysis, separately for zoledronic acid and each of the other major bisphosphonates. NICE concluded that the cost-effectiveness results largely mirror the clinical effectiveness inputs and use in post-menopausal women, where zoledronic acid improved overall and disease-free survival, is likely to be cost-effective[[6]](#footnote-6).
  5. The table below summarises the 2015 Early Breast Cancer Trialists' Collaborative Group Individual-patient data meta-analysis.

**Table 1: Hazard ratios and Kaplan-Meier 10-year risk, bisphosphonate versus no-treatment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | recurrence-free survival | | overall survival | | bone fracture | |
|  | HR  (95% CI) | 10-year risk  bisphosphonate versus  no treatment | HR  (95% CI) | 10-year risk  bisphosphonate versus  no treatment | HR  (95% CI) | 10-year risk  bisphosphonate versus  no treatment |
| all-comers | 0.94  (0.87, 1.01) | 24.9%  25.9% | 0.92  (0.85, 1.00) | 20.8%  22.3% | 0.85  (0.75, 0.97) | 9.1%  10.4% |
| pre-menopausal | 1.02  (0.91, 1.15) | 29.4%  28.7% | 1.01  (0.89, 1.16) | 22.3%  22.3% | 0.98  (0.76, 1.26) | 8.9%  9.7% |
| post-menopausal | 0.86  (0.78, 0.94) | 22.8%  25.8% | 0.86  (0.77, 0.96) | 21.1%  23.5% | 0.83  (0.71, 0.98) | 9.1%  10.3% |
| N0  N1 – N3  N4+ | 0.85  (0.68, 1.06)  1.03  (0.89, 1.19)  0.88  (0.74, 1.06) | 10.7%  12.3%  18.2%  19.4%  43.6%  47.6% | 0.74a  (0.55, 1.01)  1.02a  (0.84, 1.23)  0.87a  (0.71, 1.06) | 4.9%a  6.7%a  10.3%a  11.6%a  32.7%a  35.6%a | not  available | not  available |

(a) breast-cancer mortality, not OS

* 1. The table below summarises the 2018 NICE aggregate data meta-analysis.

**Table 2: Hazard ratios and Kaplan-Meier 5.6-year risk, zoledronic acid versus no-treatment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | recurrence-free survival | | overall survival | | bone fracture | |
|  | HR  (95% CI) | 5.6-year risk  zoledronic acid versus  no treatment | HR  (95% CI) | 5.6-year risk  zoledronic acid versus  no treatment | HR  (95% CI) | 5.6-year risk  zoledronic acid versus  no treatment |
| all-comers | 1.09  (0.31, 3.85) | 24.8%  22.8% | 0.93  (0.81, 1.07) | 16.0%  14.9% | 0.80  (0.64, 1.00) | not  available |
| pre-menopausal | not available | | | | | |
| post-menopausal | 0.88  (0.73, 1.07) | 26.4%  23.3% | 0.90  (0.73, 1.11) | 23.3%  20.9% | not  available | |
| node positive | 0.67  (0.45, 0.99) | 26.4%  17.7% | 0.62  (0.34, 1.14) | 25.3%  14.4% |

Source: <https://www.nice.org.uk/guidance/ng101/evidence/evidence-review-g-adjuvant-bisphosphonates-pdf-4904666612>

* 1. The results for zoledronic acid were similar in size (e.g. 2% to 3% absolute improvement in OS) to those for all bisphosphonates combined (from the EBCTC 2015 IPD meta-analysis) but were not statistically significant due to the smaller sample size.
  2. The PBAC considered that the data supported the claim of zoledronic acid providing an improvement in overall and disease-free survival for post-menopausal women.

Safety

* 1. Zoledronic acid has been used in clinical practice for more than 20 years and its safety profile is considered fully characterised.
  2. For patients with metastatic breast cancer (4-weekly dosing), the product label includes the following information:

Renal function impairment

* In a pooled analysis of safety data from registration trials for the prevention of skeletal-related events in patients with advanced malignancy involving bone, the frequency of renal function impairment adverse events suspected to be related to zoledronic acid was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumours (3.2%). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended.

Osteonecrosis

* Cases of osteonecrosis (primarily of the jaw but also of other anatomical sites including hip, femur and external auditory canal) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many patients with osteonecrosis of the jaw had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, anti-angiogenic drugs, radiotherapy, corticosteroids) and comorbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease).

Acute phase reaction

* This adverse drug reaction consists of a constellation of symptoms that includes pyrexia, fatigue, bone pain, chills, influenza-like illness, arthritis with subsequent joint swelling. The onset time is ≤ 3 days post-zoledronic-acid infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms; these symptoms usually resolve within a few days.
  1. In the adjuvant setting, the risk of adverse events from zoledronic acid is lower than in the metastatic setting. The 2017 Cochrane review reported that toxicities in the adjuvant setting were generally mild. Osteonecrosis of the jaw was rare, occurring less than 0.5% in the adjuvant setting (high-quality evidence)[[7]](#footnote-7).
  2. The PBAC considered the safety profile of zoledronic acid was well established and the risk of adverse events did not outweigh the potential benefits in the proposed indication. The PBAC considered that prescribers would be best placed to consider and discuss the specific risk to their patient in relation to the potential benefits at the time of prescribing.

Economic Analysis

* 1. An economic analysis, that adjusted the NICE analysis to the Australian context, was conducted. There have been no major new studies published since the 2018 NICE analysis that would materially change the efficacy and safety inputs into the economic analysis.

**Table 3: Summary of economic analysis**

|  |  |
| --- | --- |
| Time horizon | 50 years |
| Discount rate | 3.5% as per NICE reference case |
| Structure of model | Partitioned survival analysis   * alive without progressive disease * alive with progressive disease * dead |
| Groups | * all-comers * node positive * post-menopausal |
| Efficacy inputs | Hazard ratios for DFS/RFS and OS from the NICE systematic review were applied to baseline rates for recurrence and deaths from baseline absolute values for overall and disease free survival from the combined evidence for the comparison between zoledronic acid and no treatment in post-menopausal women (using the values from the no treatment arm). For example, for post-menopausal women, OS was estimated to be 76.7% and DFS was estimated to be 73.6% at 5.6 years. |
| Mortality of general population | 2013 – 2015 lifetables for England and Wales |
| Incidence of osteonecrosis of jaw | 1%  Cost: $US 1667 from Najm (2014) |
| Utilities | Taken from NICE evaluation of neoadjuvant pertuzumab  e.g., progressed/recurrence: 0.810 |

**Table 4: Incremental QALY (discounted at 3.5%) 50-year time horizon versus no treatment**

|  |  |
| --- | --- |
| All-comers | 0.09 |
| Node positive | 0.71 |
| Post-menopausal | 0.18 |

Source: Tables 12 -14, p31 of 169 [www.nice.org.uk/guidance/ng101/evidence/evidence-review-g-adjuvant-bisphosphonates-pdf-4904666612](file:///\\central.health\DFSApps\ServerApps\Staging\PEB%20-%20Common\PBAC%20Intracycle%20Meeting%20December%202022\Working%20documents\Draft%20minutes\5.%20With%20discussants\www.nice.org.uk\guidance\ng101\evidence\evidence-review-g-adjuvant-bisphosphonates-pdf-4904666612)

post-menopausal refers to all post-menopausal women, not the subgroup of high-risk or node-positive post-menopausal women

* 1. Using incremental QALYs from the 2018 NICE analysis and Australian drug acquisition costs estimated based on current AEMP of $70 and 7 treatments required over 3-year course = $490 per patient.

**Table 5: Cost per QALY, based on NICE QALY estimates**

|  |  |
| --- | --- |
| Group | ICER |
| All-comers | $490/0.09 = $5444 per QALY |
| Node positive | $490/0.71 = $690 per QALY |
| Postmenopausal | $490/0.18 = $2722 per QALY |

* 1. The ICER in the postmenopausal group might be less per QALY than the point estimate in Table 5 because:
* reductions in the risk of fractures were not included in the QALY estimates
* cost offsets due to fewer recurrences were not included
  1. The ICER in the postmenopausal group might be more per QALY than the point estimate in Table 5 because:
* A discount rate of 3.5% was used over a 50-year time horizon, rather than the 5.0% as per PBAC guidelines.
  1. Administration costs were not included in the financial estimates. Infusions for bisphosphonates do not have a specific Medicare Benefits Schedule (MBS) item number and are billed under consultation item numbers. As consultation item number costs are not generally included in the cost estimates for PBS listings they have been excluded here.
  2. Zoledronic acid in adjuvant breast cancer has the highest efficacy in post-menopausal Australian women. Efficacy in the all-comers group is driven by benefit in the post-menopausal group.
  3. In its consideration, NICE concluded:
* the economic analysis is subject to uncertainty
* however, the cost-effectiveness results largely mirror the clinical effectiveness inputs
* use in groups where zoledronic acid improved overall and disease-free survival is likely to be cost-effective[[8]](#footnote-8)

Estimated PBS utilisation and financial implications

* 1. The proposed approved ex-manufacturer price (AEMP) of $70 is equivalent to the current price for the existing listing for this product.
  2. Table 6 presents the estimated extent of use, cost of zoledronic acid to the PBS/RPBS and the net financial implications to the PBS/RPBS. As there is no testing or medical imaging associated with this listing, there is no impact on the MBS. As there is no change in dispensing volumes or the service delivery model associated with this listing, there is no impact anticipated on Services Australia.
  3. The estimated net financial impact to the PBS/RPBS for the listing is $30 million to < $40 million over six years.

**Table 6: Estimated use and financial impact**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** | | | | | | |
| Number of patients treated (initiating) | |　 1 | |　 1 | |　 1 | |　 1 | |　 1 | |　 1 |
| Number of patients treated (continuing) | |　 2 | |　 1 | |　 3 | |　 3 | |　 3 | |　 3 |
| Number of scripts dispenseda | |　 4 | |　 5 | |　 6 | |　 7 | |　 7 | |　 7 |
| **Drug costs to PBS** | | | | | | |
| Cost of zoledronic acid to PBS ($) | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 |
| Less co-payments ($) | |　 9 | |　 9 | |　 9 | |　 9 | |　 9 | |　 9 |
| Net cost to PBS ($) | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 |
| **Drug costs to RPBS** | | | | | | |
| Cost of zoledronic acid to RPBS ($) | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 |
| Less co-payments ($) | |　 9 | |　 9 | |　 9 | |　 9 | |　 9 | |　 9 |
| Net cost to RPBS ($) | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 |
| **Estimated net financial implications** | | | | | | |
| Net cost to PBS+RPBS ($) | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 |

a Assuming 3 script per patient per year in year 1 and 2 scripts per patient per year in years 2 and 3.

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

*The redacted values correspond to the following ranges:*

*1 10,000 to < 20,000*

*2 < 500*

*3 20,000 to < 30,000*

*4 30,000 to < 40,000*

*5 50,000 to < 60,000*

*6 70,000 to < 80,000*

*7 80,000 to < 90,000*

*8 $0 to < $10 million*

*9 net cost saving*

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

1. **PBAC Outcome**
   1. The PBAC deferred making a recommendation to amend the circumstances under which zoledronic acid, injection concentrate for I.V. infusion 4 mg (as monohydrate) in 5 mL, is available on the PBS to include the adjuvant management of breast cancer in post-menopausal women as the TGA Delegate’s Overview was not available at the time of PBAC consideration. However, the PBAC was of a mind to recommend listing on the basis of its assessment that the cost-effectiveness of zoledronic acid would be acceptable in this population at the equivalent price as the existing listing.
   2. The PBAC noted the financial estimates presented were intended to provide an upper estimate of the potential financial impact.

**Outcome:**

Deferred

**Addendum to the December 2022 PBAC Public Summary Document:**

4.05 Zoledronic Acid,  
Injection concentrate for I.V. infusion 4 mg (as monohydrate) in 5 mL  
APO-Zoledronic Acid®  
Apotex Pty Ltd

1. Background
   1. At its December 2022 meeting, the PBAC deferred making a recommendation to amend the circumstances under which zoledronic acid, injection concentrate for I.V. infusion 4 mg (as monohydrate) in 5 mL, is available on the PBS to include the adjuvant management of breast cancer in post-menopausal women as the TGA Delegate’s Overview was not available at the time of PBAC consideration. However, the PBAC was of a mind to recommend listing on the basis of its assessment that the cost-effectiveness of zoledronic acid would be acceptable in this population at the equivalent price as the existing listing.
2. Consideration of the Evidence

TGA Delegate’s Overview

* 1. The TGA Delegate’s Overview and ACM advice were provided prior to the July 2023 PBAC meeting. The final decision is expected in July 2023.
  2. The Delegate’s Overview proposed the following indication to be included in the Product Information for zoledronic acid:

*Zoledronic acid is indicated as an adjunct to adjuvant treatment for women with early breast cancer who are in established menopause*

* 1. The Delegate’s Overview proposed two treatment regimens will be registered for the product:
* 4 mg IV 6 monthly for 3 years
* 4 mg IV 3 monthly for 2 years
  1. The December 2022 PBAC submission presented the 6 monthly for 3 years dosing regimen as this is the most commonly used regimen in the available studies and is favoured in current Australian clinical practice. The Delegate’s Overview supports this.

Revised financial estimates

* 1. The December 2022 paper assumed the 3 year regimen may involve a loading dose in year 1, resulting in 7 doses provided per patient over 3 years (3 doses in year one, then 2 doses in years 2 and 3). The Delegate’s Overview has indicated that the 3 year regimen is a 6 dose treatment course over 3 years.
  2. Based on this an updated financial analysis is provided in Table 7 which results in a lower total financial impact of $20 million to < $30 million over the forward estimates (compared to $30 million to < $40 million presented in December 2022).

Table 7: Revised financial impact based on 6 dose treatment course

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** | | | | | | |
| Number of patients treated (initiating) | |　 1 | |　 1 | |　 1 | |　 1 | |　 1 | |　 1 |
| Number of patients treated (continuing) | |　 2 | |　 1 | |　 3 | |　 3 | |　 3 | |　 3 |
| Number of scripts dispenseda | |　 3 | |　 4 | |　 5 | |　 6 | |　 6 | |　 6 |
| **Drug costs to PBS** | | | | | | |
| Cost of zoledronic acid to PBS ($) | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 |
| Less co-payments ($) | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 |
| Net cost to PBS ($) | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 |
| **Drug costs to RPBS** | | | | | | |
| Cost of zoledronic acid to RPBS ($) | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 |
| Less co-payments ($) | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 | |　 8 |
| Net cost to RPBS ($) | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 |
| **Estimated net financial implications** | | | | | | |
| Net cost to PBS+RPBS ($) | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 |

a Assumes patients receive 2 dose per year for 3 years

*The redacted values correspond to the following ranges:*

*1 10,000 to < 20,000*

*2 < 500*

*3 20,000 to < 30,000*

*4 40,000 to < 50,000*

*5 60,000 to < 70,000*

*6 70,000 to < 80,000*

*7 $0 to < $10 million*

*8 net cost saving*

* 1. The revised treatment regimen also resulted in a lower cost per patient of $420 based on 6 doses at current AEMP ($70). Using incremental QALYs from the 2018 NICE analysis (Table 4), the revised ICER’s are now presented in Table 8.

**Table 8****: Cost per QALY, based on NICE QALY estimates**

|  |  |
| --- | --- |
| Group | ICER |
| All-comers | $420/0.09 = $4667 per QALY |
| Node positive | $420/0.71 = $591 per QALY |
| Postmenopausal | $420/0.18 = $2333 per QALY |

Sensitivity analysis

* 1. The alternative 3 monthly dosing for 2 years treatment regimen will result in patients utilising 8 doses over 2 years. It is anticipated the uptake of this regimen in Australian practice will be low based on available evidence.
  2. A sensitivity analysis modelling all patients utilising the alternative regimen which results in a higher cost per patient is provided at Table 9. The sensitivity analysis provides an estimate of the upper limit of the potential financial impact of $30 million to < $40 million over the forward estimates.

Table 9: Sensitivity analysis based on 3 monthly 2 year treatment regimen

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **Year 6** |
| --- | --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** | | | | | | |
| Number of patients treated (initiating) | |　 1 | |　 1 | |　 1 | |　 1 | |　 1 | |　 1 |
| Number of patients treated (continuing) | |　 2 | |　 1 | |　 1 | |　 1 | |　 1 | |　 1 |
| Number of scripts dispenseda | |　 3 | |　 4 | |　 5 | |　 5 | |　 5 | |　 5 |
| **Drug costs to PBS** | | | | | | |
| Cost of zoledronic acid to PBS ($) | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 |
| Less co-payments ($) | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 |
| Net cost to PBS ($) | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 |
| **Drug costs to RPBS** | | | | | | |
| Cost of zoledronic acid to RPBS ($) | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 |
| Less co-payments ($) | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 | |　 7 |
| Net cost to RPBS ($) | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 |
| **Estimated net financial implications** | | | | | | |
| Net cost to PBS+RPBS ($) | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 | |　 6 |

a Assumes patients are receiving 4 doses per year at 3 monthly intervals

*The redacted values correspond to the following ranges:*

*1 10,000 to < 20,000*

*2 < 500*

*3 40,000 to < 50,000*

*4 80,000 to < 90,000*

*5 90,000 to < 100,000*

*6 $0 to < $10 million*

*7 net cost saving*

* 1. Cost per patient in the sensitivity analysis is $560 based on 8 doses at current AEMP ($70) and resulted in the ICER’s in Table 10.

**Table 10: Sensitivity analysis - Cost per QALY, based on NICE QALY estimates**

|  |  |
| --- | --- |
| Group | ICER |
| All-comers | $560/0.09 = $6222 per QALY |
| Node positive | $560/0.71 = $789 per QALY |
| Postmenopausal | $560/0.18 = $3111 per QALY |

1. PBAC outcome
   1. The PBAC recommended the amendment of the existing listing of zoledronic acid, injection concentrate for I.V. infusion 4 mg (as monohydrate) in 5 mL (APO-Zoledronic Acid) on the Pharmaceutical Benefits Scheme (PBS), to include the adjuvant management of breast cancer in post-menopausal women on the basis of acceptable cost-effectiveness in this population at the existing PBS price.
   2. The PBAC noted the revised financial estimates and sensitivity analysis and while it considered that the base case presented in the revised estimates was the most likely scenario, it considered that the listing would be suitably cost-effective in either scenario at the requested price.
   3. The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

**Outcome:**

Recommended

1. Recommended listing

Amend existing listing as follows:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT**  **medicinal product pack** | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of**  **Rpts** | **Available brands** |
| ZOLEDRONIC ACID | | | | | | |
| zoledronic acid 4 mg/5 mL injection, 5 mL vial | | NEW | 1 | 1 | 0 | APO-Zoledronic Acid |
| **Restriction Summary / Treatment of Concept:** | | | | | | |
|  | **Category / Program:** Section 100 – Highly Specialised Drugs Public/Private hospitals | | | | | |
| **Prescriber type:** Medical Practitioners | | | | | |
| **Restriction type:** Authority Required (STREAMLINED) | | | | | |
|  | **Indication:** Adjuvant management of breast cancer | | | | | |
|  | **Population Criteria:** Patient must be post-menopausal | | | | | |
|  | **Treatment Criteria:** Patient must not be undergoing PBS-subsidised treatment with this drug for this indication for more than 36 months. | | | | | |

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

1. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

1. Sponsor’s Comment

The Sponsor welcomes the PBAC’s decision to recommend zoledronic acid for adjuvant management of early breast cancer in post-menopausal women and will work with PBAC and the Department of Health and Aged Care to provide access for these patients in need.

1. https://schedule.pharmac.govt.nz/2022/08/01/SA2109.pdf [↑](#footnote-ref-1)
2. www.nice.org.uk/guidance/ng101/chapter/Recommendations#bisphosphonate-therapy [↑](#footnote-ref-2)
3. Early Breast Cancer Trialists' Collaborative Group. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. The Lancet. 2015 Oct 3;386(10001):1353-61 [↑](#footnote-ref-3)
4. O'Carrigan B, Wong MH, Willson ML, Stockler MR, Pavlakis N, Goodwin A. Bisphosphonates and other bone agents for breast cancer. Cochrane database of systematic reviews. 2017(10) [↑](#footnote-ref-4)
5. Early Breast Cancer Trialists' Collaborative Group, Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials, Lancet 365 (9472) (2005) 1687–1717. [↑](#footnote-ref-5)
6. www.nice.org.uk/guidance/ng101/evidence/evidence-review-g-adjuvant-bisphosphonates-pdf-4904666612 [↑](#footnote-ref-6)
7. O'Carrigan B, Wong MH, Willson ML, Stockler MR, Pavlakis N, Goodwin A. Bisphosphonates and other bone agents for breast cancer. Cochrane database of systematic reviews. 2017(10) [↑](#footnote-ref-7)
8. [www.nice.org.uk/guidance/ng101/evidence/evidence-review-g-adjuvant-bisphosphonates-pdf-4904666612](file:///\\central.health\DFSApps\ServerApps\Staging\PEB%20-%20Common\PBAC%20Intracycle%20Meeting%20December%202022\Working%20documents\Draft%20minutes\5.%20With%20discussants\www.nice.org.uk\guidance\ng101\evidence\evidence-review-g-adjuvant-bisphosphonates-pdf-4904666612) (p33 of 169) [↑](#footnote-ref-8)