

ATC codes: **M05BA08**

Indication	Malignant neoplasm metastasis in bone or bone marrow	ICD11 code: 2E43
INN	Zoledronic acid	
Medicine type	Chemical agent	
List type	Complementary	
Formulations	Parenteral > General injections > IV: 4 mg per 5 mL in 5 mL vial ; 4 mg per 100 mL in 100 mL bottle	
EML status history	First added in 2017 (TRS 1006)	
Sex	All	
Age	Adolescents and adults	
Therapeutic alternatives	The recommendation is for this specific medicine	
Patent information	Patents have expired in most jurisdictions Read more about patents . 	

Tags

Cancer

Cancer supportive care

Wikipedia

Zoledronic acid 

DrugBank

Zoledronic acid 

Expert Committee recommendation

In relation to the application, the Expert Committee noted that it did not follow the standard template, and some important elements of the evaluation were missing or inadequately addressed. Despite these shortcomings, the Expert Committee considered that zoledronic acid has been shown to be a valid treatment option for use in patients with malignancy-related bone disease. Based on the positive evaluation, the Committee recommended zoledronic acid be added to the complementary list of the EML for this indication. The Committee did not recommend listing with a square box, as it considered the evidence presented in the application for alternative bisphosphonates was not adequate to support their inclusion on the EML. The Expert Committee recommended the establishment of an EML cancer medicines working group to coordinate comprehensive evaluation of available treatment options for different cancers. In particular, noting the role of zoledronic in the management of bone metastases associated with multiple myeloma, and that multiple myeloma was not included in the 2015 review of cancer medicines on the EML, the Committee highlighted the need for the working group to evaluate treatments for multiple myeloma as a priority for EML inclusion.

Background

Bisphosphonates have not previously been considered by the Expert Committee for addition to the EML.

Public health relevance

The skeleton is one of the most common locations to which cancer metastasizes. The propensity for solid tumour malignancies to metastasize to bone varies: bone metastases will develop in 65–75% of patients with advanced prostate cancer and 70% of patients who die of breast cancer. The incidence of bone metastases is lower in patients with lung, colon, stomach, bladder and

other cancers (15–30%), and only 5% of patients with certain gastrointestinal malignancies (1). In patients with multiple myeloma, 60% of patients will have bone lesions at the time of presentation and nearly all patients will develop bone lesions during the course of the disease (2). Bone metastases can cause skeletal-related events (SREs) including fractures, spinal cord compression, hypercalcaemia and significant pain, which can then necessitate treatment with radiation and/or chemotherapy or surgical intervention in the case of fractures or spinal complications. In patients with bone metastases treated with systemic anticancer regimens and no bisphosphonates, SREs occur in 46–64% of patients within 2 years (depending on the underlying malignancy), contributing importantly to the significant overall morbidity of advanced cancer (3–5).

Benefits

Bisphosphonates are specific inhibitors of osteoclasts, and their use in cancer patients prevents the increased bone resorption that accompanies metastatic bone disease (6, 7). Through this mechanism, bisphosphonates reduce complications or SREs such as fractures, the need for palliative radiotherapy to relieve pain, spinal cord compression and hypercalcaemia from bone metastases (8, 9). They can also reduce bone pain and analgesic requirements (10, 11) and improve quality of life (3, 12, 13). In the absence of a bisphosphonate, SREs occur in around one half to two thirds of patients (depending on the underlying malignancy and concomitant cancer treatments) (3–5), contributing significant morbidity to the clinical course of the underlying disease and increasing the health care costs of treating advanced malignancy (8, 14). Bisphosphonates reduce the number of breast cancer patients experiencing an SRE, extend the time to first and subsequent SREs, and prevent around a third of all skeletal morbidity (4, 5, 13, 15). Zoledronic acid is likely to be the most effective agent (16–18), reducing by 41% the overall risk of SREs when compared with placebo (19). Placebo-controlled trials have also shown benefits for oral clodronate (20–22), IV (23, 24) and oral (24, 25) ibandronate and pamidronate (3, 13, 15) but to a lesser extent than zoledronic acid (17). In hormone-resistant prostate cancer, inhibition of bone resorption is also of clinical relevance despite the osteoblastic nature of most prostate bone metastases (26, 27). However, only zoledronic acid has shown significant benefits in terms of reducing SREs (4, 28), although IV ibandronate has similar efficacy to palliative radiotherapy for the acute relief of bone pain (11). In this disease setting, zoledronic acid reduced the number of patients experiencing an SRE by 9% (33% vs 44%), increased the median length of time to first SREs (>420 days vs 321 days), reduced the overall risk of SREs by 36% and improved pain scores (4). Similarly, in non-breast and non-prostate solid tumours (50% non-small cell lung cancer and 50% miscellaneous other solid tumours), zoledronic acid increased the median time to the first event (230 days vs 163 days) and reduced the overall risk for SREs by 31% (4, 29). In multiple myeloma (30), bisphosphonates reduce vertebral fractures, SREs and bone pain (relative risk of 0.74, 0.80 and 0.75, respectively) with oral clodronate (31, 32), pamidronate (33) and zoledronic acid (16, 17) having similar effects on skeletal morbidity. However, zoledronic acid improved overall survival when compared with oral clodronate and extended survival by 3 months (34).

Harms

Several risks are associated with treatment with bisphosphonates and require monitoring (8, 35). Intravenous bisphosphonates are commonly associated with the acute-phase response (fever and influenza-like symptoms), and bone/joint pain. Less common side-effects include kidney injury (36), ocular inflammation (37) and atrial fibrillation (38). Osteonecrosis of the jaw (ONJ) is a significant clinical problem associated with long-term bisphosphonate use (39). The frequency of ONJ is 1–2% of patients for each year on monthly IV bisphosphonate therapy (40, 41); the risk may be less with daily oral agents or with a 3-monthly schedule of IV treatment (42). It is recommended that patients have a dental examination and preventive dental work (such as tooth extraction) before administration of bisphosphonate therapy; invasive dental work should be avoided (42). When extraction or jaw surgery cannot be avoided, prophylactic antibiotics should be given. The bisphosphonate should be discontinued until healing is complete unless the patient has ongoing significant symptomatic bone disease. Patients are also at risk of hypocalcaemia. Vitamin D supplementation is recommended and most patients should be placed also on calcium supplementation, which should be individualized on the basis of the characteristics of the malignancy and renal function (43). Atypical femoral fractures (subtrochanteric and diaphyseal regions) can also occur rarely (<1 in 1000) and may be related to long-term suppression of bone remodelling induced by bisphosphonate treatments (44).

Additional evidence

N/A

Cost / cost effectiveness

In 2015, the MSF International Medical Products Price Guide (45) reported a median buyer price for zoledronic acid 4 mg/5 mL vial of US\$ 23.45.

WHO guidelines

The WHO Guidelines for management of cancer pain are currently under review.

Availability

Ibandronate and clodronate are not approved in USA.

Other considerations

Treatment should be continued throughout the course of the disease. However, to reduce the risk of treatment complications, interruption after 12–24 months should be considered in patients in remission and restarted on progression (46, 47). Administration of zoledronic acid every 12 weeks may be as effective as the approved 4-weekly schedule (48–50).

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin Cancer Res.* 2006;12(20 Pt 2):6243s–9s.
2. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc.* 2003;78(1):21–33.
3. Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer.* 2000;88(5):1082–90.
4. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst.* 2002;94(19):1458–68.
5. Rosen LS, Gordon D, Tchekmedyian S, Yanagihara R, Hirsh V, Krzakowski M et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial – the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol.* 2003;21(16):3150–7.
6. Fleisch H. Bisphosphonates: mechanisms of action. *Endocr Rev.* 1998;19(1):80–100.
7. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med.* 2004;350(16):1655–64.
8. Coleman R, Body JJ, Aapro M, Hadji P, Herrstedt J. Bone health in cancer patients: ESMO clinical practice guidelines. *Ann Oncol.* 2014;25(Suppl 3):iii124–37.
9. Palmieri C, Fullarton JR, Brown J. Comparative efficacy of bisphosphonates in metastatic breast and prostate cancer and multiple myeloma: a mixed-treatment meta-analysis. *Clin Cancer Res.* 2013;19(24):6863–72.
10. Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev.* 2002;(2):CD002068.
11. Hoskin P, Sundar S, Reczko K, Forsyth S, Mithal N, Sizer B et al. A multicenter randomized trial of ibandronate compared with single-dose radiotherapy for localized metastatic bone pain in prostate cancer. *J Natl Cancer Inst.* 2015;107(10):ii.
12. Wong MH, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev.* 2012;(2):CD003474.
13. Hortobagyi GN, Theriault RL, Porter L, Blayney D, Lipton A, Sinoff C et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med.* 1996;335(24):1785–91.
14. Hechmati G, Cure S, Gouepo A, Hoefeler H, Lorusso V, Luftner D et al. Cost of skeletal-related events in European patients with solid tumours and bone metastases: data from a prospective multinational observational study. *J Med Econ.* 2013;16(5):691–700.
15. Theriault RL, Lipton A, Hortobagyi GN, Leff R, Gluck S, Stewart JF et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol.* 1999;17(3):846–54.
16. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J.* 2001;7(5):377–87.
17. Rosen LS, Gordon D, Kaminski M, Howell A, Belch A, Mackey J et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer.* 2003;98(8):1735–44.
18. Barrett-Lee P, Casbard A, Abraham J, Hood K, Coleman R, Simmonds P et al. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. *Lancet Oncol.* 2014;15(1):114–22.
19. Kohno N, Aogi K, Minami H, Nakamura S, Asaga T, Iino Y 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.
20. Tubiana-Hulin M, Beuzeboc P, Mauriac L, Barbet N, Frenay M, Monnier A et al. [Double-blinded controlled study comparing clodronate versus placebo in patients with breast cancer bone metastases]. *Bull Cancer.* 2001;88(7):701–7.
21. Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J Clin Oncol.* 1993;11(1):59–65.
22. Kristensen B, Ejlersen B, Groenvold M, Hein S, Loft H, Mouridsen HT. Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J Intern Med.* 1999;246(1):67–74.
23. Body JJ, Diel IJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA 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.
24. Body JJ, Lichinitser M, Tjulandin S, Garnerio P, Bergstrom B. 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.
25. Body JJ, Diel IJ, Lichinitser M, Lazarev A, Pecherstorfer M, Bell R 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.

26. Saad F, McKiernan J, Eastham J. Rationale for zoledronic acid therapy in men with hormone-sensitive prostate cancer with or without bone metastasis. *Urol Oncol*. 2006;24(1):4–12.
27. Brown JE, Cook RJ, Major P, Lipton A, Saad F, Smith M et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst*. 2005;97(1):59–69.
28. Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol*. 2003;21(23):4277–84.
29. Rosen LS, Gordon D, Tchekmedyian NS, Yanagihara R, Hirsh V, Krzakowski M et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer*. 2004;100(12):2613–21.
30. Mhaskar R, Redzepovic J, Wheatley K, Clark OA, Miladinovic B, Glasmacher A et al. Bisphosphonates in multiple myeloma: a network meta-analysis. *Cochrane Database Syst Rev*. 2012;(5):CD003188.
31. Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med*. 1996;334(8):488–93.
32. McCloskey EV, MacLennan IC, Drayson MT, Chapman C, Dunn J, Kanis JA. A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. MRC Working Party on Leukaemia in Adults. *Br J Haematol*. 1998;100(2):317–25.
33. Lahtinen R, Laakso M, Palva I, Virkkunen P, Elomaa I. Randomised, placebo-controlled multicentre trial of clodronate in multiple myeloma. Finnish Leukaemia Group. *Lancet*. 1992;340(8827):1049–52.
34. Morgan GJ, Davies FE, Gregory WM, Cocks K, Bell SE, Szubert AJ et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet*. 2010;376(9757):1989–99.
35. Coleman RE. Risks and benefits of bisphosphonates. *Br J Cancer*. 2008;98(11):1736–40.
36. Guarneri V, Donati S, Nicolini M, Giovannelli S, D'Amico R, Conte PF. Renal safety and efficacy of i.v. bisphosphonates in patients with skeletal metastases treated for up to 10 years. *Oncologist*. 2005;10(10):842–8.
37. Sharma NS, Ooi JL, Masselos K, Hooper MJ, Francis IC. Zoledronic acid infusion and orbital inflammatory disease. *N Engl J Med*. 2008;359(13):1410–1.
38. Kim DH, Rogers JR, Fulchino LA, Kim CA, Solomon DH, Kim SC. Bisphosphonates and risk of cardiovascular events: a meta-analysis. *PLoS One*. 2015;10(4):e0122646.
39. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003;61(9):1115–7.
40. Saad F, Brown JE, Van Poznak C, Ibrahim T, Stemmer SM, Stopeck AT et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Ann Oncol*. 2012;23(5):1341–7.
41. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D 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.
42. Migliorati CA, Epstein JB, Abt E, Berenson JR. Osteonecrosis of the jaw and bisphosphonates in cancer: a narrative review. *Nat Rev Endocrinol*. 2011;7(1):34–42.
43. Simmons C, Amir E, Dranitsaris G, Clemons M, Wong B, Veith R et al. Altered calcium metabolism in patients on long-term bisphosphonate therapy for metastatic breast cancer. *Anticancer Res*. 2009;29(7):2707–11.
44. Edwards BJ, Sun M, West DP, Guindani M, Lin YH, Lu H et al. Incidence of atypical femur fractures in cancer patients: the MD Anderson Cancer Center experience. *J Bone Miner Res*. 2016;31(8):1569–76.
45. International Medical Products Price Guide. Arlington, VA: Management Sciences for Health; 2015 (<http://mshpriceguide.org/en/search-results-by-name-2/?searchYear=2015&searchString=Zoledronic+Acid&searchType=Name>, accessed 26 April 2017).
46. Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. *J Clin Oncol*. 2007;25(17):2464–72.
47. Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, Raje N et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol*. 2013;31(18):2347–57.
48. Amadori D, Aglietta M, Alessi B, Gianni L, Ibrahim T, Farina G et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. *Lancet Oncol*. 2013;14(7):663–70.
49. Hortobagyi GN, Van Poznak C, Harker WG, Gradishar WJ, Chew H, Dakhil SR et al. Continued treatment effect of zoledronic acid dosing every 12 vs 4 weeks in women with breast cancer metastatic to bone: the OPTIMIZE-2 Randomized Clinical Trial. *JAMA Oncol*. 2017;3(7):906–12.
50. Ibrahim MF, Mazzearello S, Shorr R, Vandermeer L, Jacobs C, Hilton J et al. Should de-escalation of bone-targeting agents be standard of care for patients with bone metastases from breast cancer? A systematic review and meta-analysis. *Ann Oncol*. 2015;26(11):2205–13.

