South African National Department of Health
Brief Report – Evaluation of previous class recommendation
Component: Tertiary

TITLE: Bisphosphonates for multiple myeloma associated bone disease

Date: October 2023

Date of previous review: 25 July 2013

Key findings

- In 2013 intravenous bisphosphonates were reviewed for supportive management for patients with multiple myeloma, for the reduction of pain and skeletal related events (SKEs). Intravenous bisphosphonates, as a class, were recommended for inclusion on the Tertiary/Quaternary Essential Medicines List. Zoledronate had historically been on National Contract however during the previous contract cycle, ibandronate achieved a more favourable price, resulting in being awarded on contract.
- A motivation was received from the Western Cape Pharmacy and Therapeutics Committee (2022), requesting that the bisphosphonates not be considered a class in this indication and that zoledronate be the preferred agent.
- We conducted a literature review and an updated search yielded 10 results. One document was selected for inclusion (systematic review and meta-analysis). The review was assessed as high quality (AMSTAR 2). A Risk of Bias 1 assessment extracted from the review showed many of the trials were considered 'high risk'.
- *Overall Survival*
  - Ibandronate was found not be superior to placebo (HR) 1.07 (95% CI 0.69 to 1.64), 1 trial, n = 198, i^2 = 0% P=0.77 - low quality.
  - Zoledronate was found to be superior to control (HR 0.57, 95% CI 0.43 to 0.75), 3 trials, n=402, i^2 = 0%, P<0.0001 – low quality.
  - On network meta-analysis, zoledronate may be superior to ibandronate however estimate crossed the null (HR 0.67 95% CI [0.29 to 1.31] – low certainty of evidence.
- *Progression-Free Survival (PFS)*
  - No studies reported on this outcome for ibandronate.
  - Zoledronate was found to be superior to control (HR 0.7, 95% CI [0.52 to 0.95], P=0.02, i^2=43.5%, n = 705) – very low quality.
  - Network meta-analysis not conducted.
- *Skeletal Related Events*
  - Ibandronate was found not be superior to control (RR 1.04, 95% CI [0.8 to 1.35]; P=0.78, n = 198, 1 trial) – moderated quality.
  - Zoledronate was found to be superior to control (RR 0.49, 95% CI [0.28 to 0.89]; P=0.02; i^2=51%, n = 711, 4 trials) – moderate quality.
  - On network meta-analysis, zoledronate is likely to be superior to ibandronate (HR 0.56 95% CI [0.26 to 0.98]) – moderate certainty of evidence.
- There was no significant difference in frequency in either gastrointestinal symptoms or hypocalcaemia with the use of bisphosphonates compared with placebo or no treatment (Gastrointestinal symptoms: RR 1.23, 95% CI 0.95 to 1.59; seven studies; 1829 participants; low-quality evidence; hypocalcaemia: RR 2.19, 95% CI 0.49 to 9.74; three studies; 1090 participants; low-quality evidence).
- Zoledronate was found to be superior compared to control for overall survival, PFS and skeletal related events outcomes; and in a network meta-analysis was found to be superior to ibandronate for skeletal related events. There was no data for ibandronate for progression free survival.

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

The Tertiary and Quaternary Expert Review Committee recommends that bisphosphonates not be regarded as a class in the management of multiple myeloma associated bone disease and that zoledonate be specified in this indication.

Rationale: The evidence shows that zoledronate offers a statistically significant benefit in terms of overall survival, progression free survival and skeletal related events. This recommendation is based on low to moderate quality evidence, involving small numbers of patients. The data for ibandronate was limited in this indication, and did not show any overall survival benefit.

Level of Evidence: *I (systematic review) – Grading for outcomes low to moderate*
Review Indicator: *New evidence of efficacy or safety*

(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

In 2013 intravenous bisphosphonates were reviewed for supportive management for patients with multiple myeloma, for the reduction of pain and skeletal related events (SKEs). Intravenous bisphosphonates were recommended for inclusion on the Essential Medicines List. *See review document – appendix 3.*

Zoledronate had historically been on National Contract but, during the previous contract cycle, ibandronate achieved a more favourable price. This meant that the contract was awarded to ibandronate and zoledronate was no longer available.

A motivation was received from the Western Cape Pharmacy and Therapeutics Committee, requesting that the bisphosphonates not be considered a class in this indication and that zoledronate be the preferred agent.

Currently, zoledronate and ibandronate are the only two intravenous bisphosphonates registered in South Africa. Previously pamidronate was registered in South Africa, however this product was discontinued and has not been available for a number of years.

This review investigates the evidence of the two available intravenous bisphosphonates for multiple myeloma associated bone disease.

METHODS

The evaluation comprised two parts; a rapid search update of evidence published since the last review, and an updated costing. The search was conducted in PubMed and the Cochrane Library in June 2023. The following PICO was utilised when assessing eligible studies.

Population	Patients with multiple myeloma associated bone disease
Intervention	Bisphosphonates (zoledronate acid and ibandronate)
Comparators	Other bisphosphonates, placebo
Outcomes	Overall survival Progression Free survival Skeletal related events (SRE) Adverse events including osteonecrosis of the jaw (ONJ)
Studies	Systematic reviews and meta-analyses

RESULTS

Search update

A Pubmed search was contacted limited to systematic reviews and meta-analyses:
((bisphosphonates[MeSH Terms]) AND (bone disease[MeSH Terms])) AND (multiple myeloma[MeSH Terms]) Filters: Meta-Analysis, Systematic Review

The search produced 10 results:

- 9 reviews were excluded:
    - 4 previous Cochrane iterations
    - 2 contained the incorrect comparator
    - 2 reviews did not meet the PICO
    - 1 review only included 1 study evaluating patients with multiple myeloma, this study was included in the Cochrane review (Mhaskar et al) identified which was recommended for inclusion

A summary of the excluded studies can be found in Appendix 2.

The following systematic review and meta-analysis were included:

- **Mhaskar R et.al**. Bisphosphonates in multiple myeloma: an updated network meta-analysis. Cochrane Database Systematic Review. 2017.[1]

Since Mhaskar et al only included one study where ibandronate was included, a search specifically for ibandronate randomised trials was undertaken: ((ibandronate[MeSH Terms]) AND (bone disease[MeSH Terms])) AND (multiple myeloma[MeSH Terms])

- *Only 3 results were identified:*
    - *One was not specific to Multiple myeloma*
    - *One only compared ibandronate to pamidronate (found pamidronate superior)*
    - *One (included in Mhaskar et al) evaluated ibandronate versus placebo*

Description of included study

One Cochrane review

Study	Study design	Nr of included trials/ participants	Types of participants	Interventions	Primary outcome
Mhaskar et.al. 2017[1]	Cochrane Review	24 RCTs included (7293 patients)	Patients with multiple myeloma	Any bisphosphonates vs placebo or other bisphosphonates	Primary outcome: overall survival and progression free survival

Internal validity

AMSTAR of 2 assessment

The Mhaskar *et al* 2017 systematic review was assessed as a high quality review (AMSTAR 2 assessment performed in duplicate by JR and KM).

Risk of bias of studies included in the review:

A Risk of Bias 1 assessment was conducted by Mhaskar *et al* 2017 (See Figure 1 below). Only 29% and 37% of trials reported method of generating randomization sequence and adequate allocation concealment. Double blinding was reported in 37% of trials, however only 4 of these studies reported blinding procedures. The remaining studies were open-label. Dropouts and withdrawals were reported in 62% of studies. Risk of reporting bias was considered low. Only one study (Gimseng *et al*. 2010) was evaluated as low risk of bias in all domains.

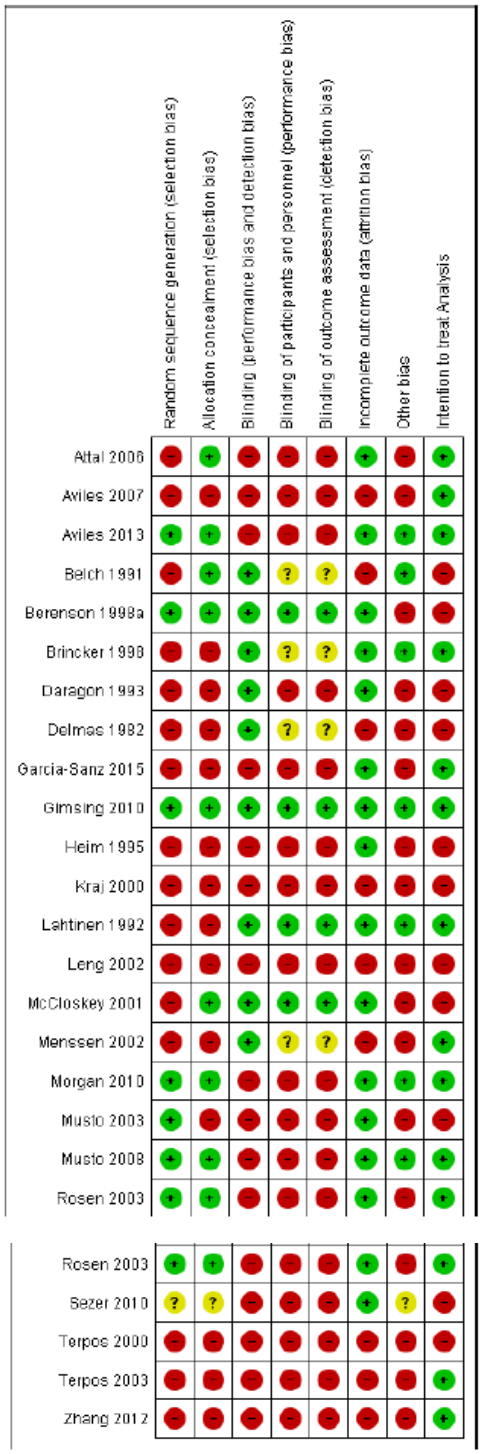
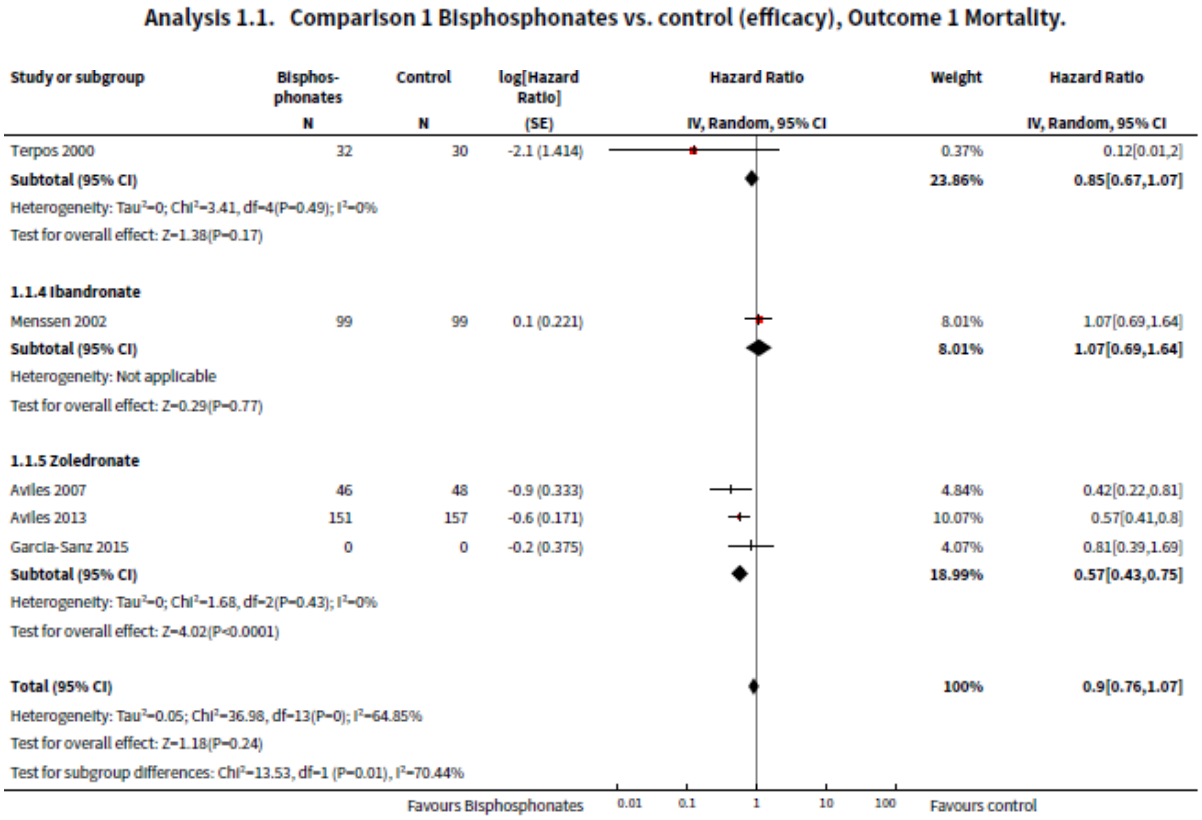


Figure 1: Risk of bias assessment Mhaskar et al

Effects of interventions

Overall survival

In the meta-analysis by Mhaskar et al., zoledronate and not ibandronate was found to offer a statistically significant benefit in terms of mortality when compared with control. [Zoledronate = HR 0.57, 95% CI 0.43 to 0.75; P<0.0001; i^2=0%, n = 402, 3 trials; ibandronate = HR 1.07 95% CI (0.69 to 1.64); P=0.77, n=198, 1 trial]. *See Table below.*



Meta-analysis bisphosphonates versus control – sub-group analysis – Overall Survival

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4 Ibandronate	1	198	Hazard Ratio (Random, 95% CI)	1.07 [0.69, 1.64]
1.5 Zoledronate	3	402	Hazard Ratio (Random, 95% CI)	0.57 [0.43, 0.75]

In the network meta-analysis conducted by Mhaskar et al for overall survival, it was found that zoledronate may be superior to ibandronate however the CI crossed the line of no effect (HR 0.67 95% CI [0.29 to 1.31]) – low certainty of evidence, downgraded for imprecision.

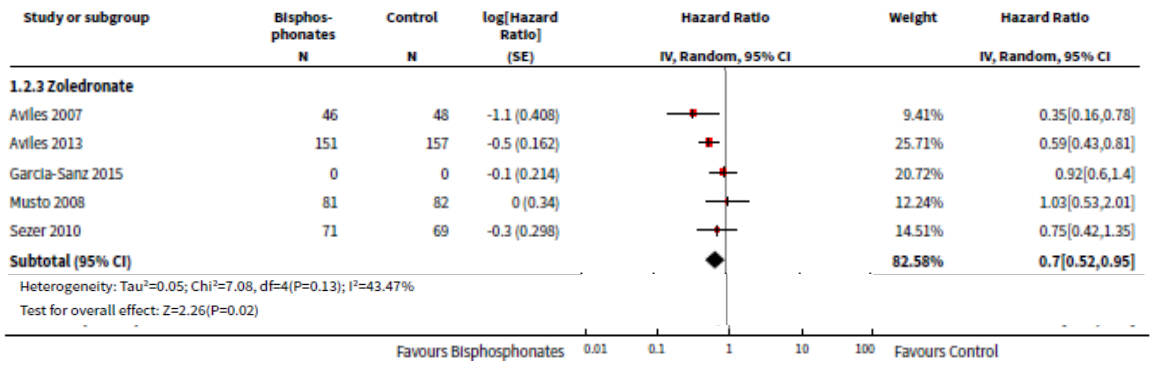
Indirect comparison of zoledronate to ibandronate reported by Mhaskar *et al*

Outcome	Treatment 1	Treatment 2	NRCTs	Patients	HR	95% CI	95% CI	Quality of evidence (GRADE)
Overall survival	Zoledronate	Ibandronate	16	5260	0.67	0.29	1.31	low

Progression Free survival

Five RCTs reported progression free survival for zoledronate. None evaluated ibandronate. Zoledronate was found to have a significant benefit when compared with control in terms of progression free survival (HR 0.7, 95% CI [0.52 to 0.95], P=0.02, i^2=43.5%, n = 705). *See forest plot below:*

Analysis 1.2. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 2 Progression-free survival.



Meta-analysis bisphosphonates versus control – sub-group analysis – Progression-Free Survival

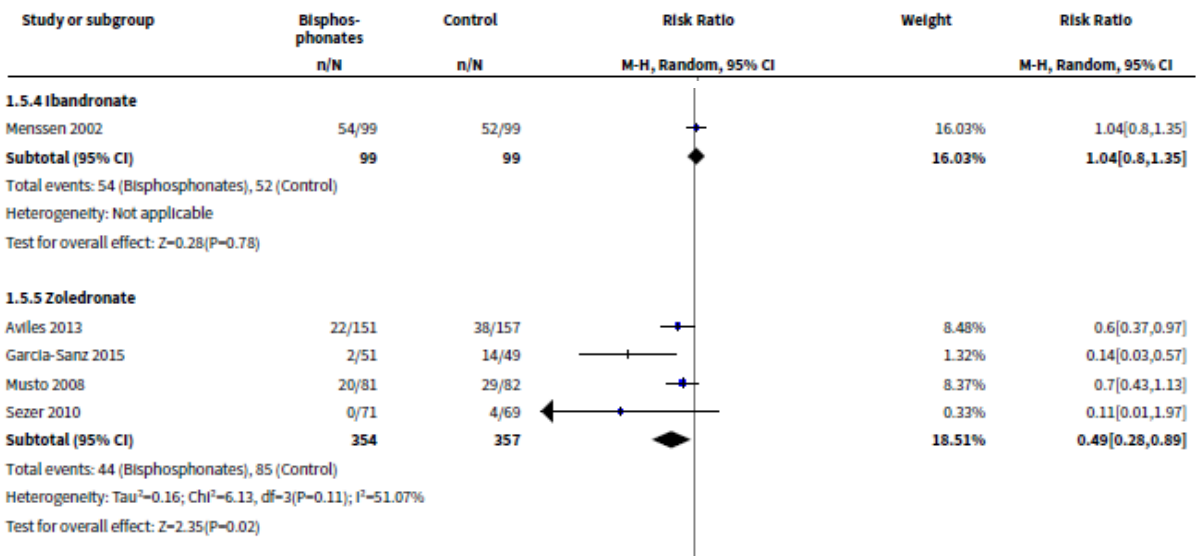
2 Progression-free survival	7	908	Hazard Ratio (Random, 95% CI)	0.75 [0.57, 1.00]
2.1 Clodronate	1	26	Hazard Ratio (Random, 95% CI)	0.63 [0.17, 2.34]
2.2 Pamidronate	1	177	Hazard Ratio (Random, 95% CI)	1.24 [0.66, 2.33]
2.3 Zoledronate	5	705	Hazard Ratio (Random, 95% CI)	0.70 [0.52, 0.95]

The network meta-analysis conducted by Mhaskar et al. did not report an estimate for an indirect comparison of zoledronate to ibandronate, since there was no data for ibandronate for this outcome.

Skeletal related events (SRE)

Ibandronate was not found to have a significant benefit compared to control (RR 1.04, 95% CI [0.8 to 1.35]; P=0.78, n = 198, 1 trial). Zoledronate showed a significant benefit compared to control (RR 0.49, 95% CI [0.28 to 0.89]; P=0.02; i^2=51%, n = 711, 4 trials). *See forest plot below.*

Analysis 1.5. Comparison 1 Bisphosphonates vs. control (efficacy), Outcome 5 Total skeletal-related events.



In the network meta-analysis conducted by Mhaskar et al for skeletal events, it was found that zoledronate is likely to be superior to ibandronate (HR 0.56 95% CI [0.26 to 0.98]; – moderate certainty of evidence).

Indirect comparison of zoledronate to ibandronate reported by Mhaskar *et al*

Outcome	Treatment 1	Treatment 2	NRCTs	Patients	HR	95% CI	95% CI	Quality of evidence (GRADE)
SRE	Zoledronate	Ibandronate	13	5727	0.56	0.26	0.98	moderate

Adverse events

The pooled results from Mhaskar *et al* showed no significant difference in frequency of either gastrointestinal symptoms or hypocalcaemia with the use of bisphosphonates compared with placebo or no treatment (Gastrointestinal symptoms: RR 1.23, 95% CI 0.95 to 1.59; seven studies; 1829 participants; P=0.85; i^2=0%; low-quality evidence; hypocalcaemia: RR 2.19, 95% CI 0.49 to 9.74; three studies; 1090 participants; P=0.88; i^2=0%; low-quality evidence). The network analysis found that participants on zoledronate may have less gastrointestinal toxicity compared to those on pamidronate 90mg however the estimate did include the null (RR 0.86 95% CI [0.24 to 2.27]; eight RCTs, n=3789 – low quality (imprecision). Network meta-analysis for hypocalcaemia not conducted.

Osteonecrosis of the jaw (ONJ)

Mhaskar *et al* reported that bisphosphonates may increase ONJ compared with placebo; however the confidence interval is very wide (RR 4.61, 95% CI 0.99 to 21.35; p = 0.05; i^2=0%; six studies; n= 1284; low-quality evidence). Test for sub-group difference found no difference between pamidronate and zoledronate compared to control (P=0.77), i^2=0%. No data was reported in the review for ibandronate for this outcome. In the network meta-analysis there were more participants in the zoledronate group with ONJ compared to the pamidronate groups (90mg and 30mg). However there was uncertainty in the evidence which was graded as very low certainty due to imprecision and that the contributing direct evidence was low quality. (Zoledronate vs pamidronate 90mg RR=6.19 95% CI [0.09 to 38.16] – very low certainty; pamidronate 30mg vs zoledronate RR 0.77 95% CI 0.00 to 5.09; eight RCTs, n=3746).

Quality of evidence

Mhaskar *et al* systematic review and network meta-analysis reported on GRADE assessments for the overall direct pooled effect of bisphosphonates against placebo/other bisphosphonates as we all as for the indirect comparisons in the network meta-analysis. The certainty of evidence for direct comparison of individual agents was not included in the report by Mhaskar *et al*. The certainty of evidence for the indirect comparisons of zoledronic acid and ibandronate ranged from very low (zoledronate vs placebo for PFS) to moderate (zoledronate vs ibandronate for SRE).

Comparison (sourced from indirect comparisons table)		**Quality of Evidence (GRADE)**		
		Overall survival	**PFS**	**SRE**
Ibandronate	**Placebo**	low	n/a	low
Ibandronate	**Zoledronate**	low	n/a	moderate
Zoledronate	**Placebo**	moderate	very low	moderate

Costing

Zoledronate has historically been on National Contract, however for the last contract cycle, ibandronate achieved the more favourable contract price and was thus awarded on the current contract. See Table 1, below comparison of pricing (SEP/Contract/Buy out).

Table 1: Comparative of pricing

**Note standard of care to give zoledronate 3 monthly rather then 3-4 weekly*

Product	**Regimen**	**Available product**	**Cost per product**		**Cost per dose**	**Cost per dose annual 4 week regimen**	**Cost per dose annual 3 months regimen**	**Annual cost**
			Contract/buy-out					
Zoledronate	4mg IVI every 3-4 weeks	Zoledronic acid 4mg/5ml injection	R164.63	*	R164.63	R164.63	-	R1975.56
Zoledronate*	4mg IVI every 3 months	Zoledronic acid 4mg/5ml injection	R164.63	*	R164.63	-	R164.63	R658.52
Ibandronate	6mg IVI every 3-4 weeks	Ibandronic acid; 6mg; injection; 6 ml	R126.00	**	R126.00	R126.00	-	R1512.00

** Zoledronate previous contract price June 2022*
*** MHPL June 2023*

Based on previous reviews of medicines used for the management of multiple myeloma, it is estimated that there are 200 such patients in the country. Assuming all patients will require bisphosphonate therapy at some time during their management, an estimated budget impact was calculated.

Table 2: Budget impact

	Available product	**Cost per product**	Cost per dose **(contract)**	Annual cost **(contract)**	Estimated annual budget impact (200 patients)
Previous Tender Price (Monthly dose)	Zoledronic acid 4mg/5ml injection	R164.63	R164.63	R1,975.56	R395,112.00
Previous Tender Price (3-monthly dose)	Zoledronic acid 4mg/5ml injection	R164.63	R164.63	R658.52	R131,704.00
Current contract price	Ibandronic acid; 6mg; injection; 6 ml	R126.00	R126.00	R1,512.00	R302,400.00

Table 3: Incremental budget impact of zoledronate compared to previous tender price at 4-weekly dosing

Incremental budget impact	
Zoledronate previous tender price	R92,712.00

Note: *A number of generic products are available for both ibandronate and zoledronate (more so for zoledronate). Thus competitive costing can be expected at the next contract interaction.*

CONCLUSION

The Tertiary and Quaternary Expert Review Committee recommends that zoledronate be specifically recommended for the management of multiple myeloma associated bone disease. For the endpoints of overall survival, progression free survival and skeletal related effects, zoledronate was associated with statistically significant approvements when compared with control. However, the evidence for use of ibandronate for this indication is lacking and on indirect comparison zoledronic acid was likely to be superior to ibandronate for skeletal related effects. Zoledronate was not found to increase the risk of osteonecrosis of the jaw when compared with other bisphosphonates.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☒ Very low: ☐	*Overall survival* For indirect comparison, certainty of evidence for overall survival was low (zoledronate vs ibandronate, ibandronate vs placebo) to moderate (zoledronate vs placebo)
	What is the certainty/quality of evidence? High: ☐ Moderate: ☐ Low: ☐ Very low: ☒	*Progression free survival* Only data for zoledronate available and on indirect comparison, certainty of evidence was GRADED as very low (zoledronate vs placebo)
	What is the certainty/quality of evidence? High: ☐ Moderate: ☒ Low: ☐ Very low: ☐	*SRE* For indirect comparison, certainty of evidence for SRE was GRADED as low (ibandronate vs placebo) to moderate (zoledronate vs ibandronate, zoledronate vs placebo)
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☒ Small: ☐ None: ☐	*Overall survival* • Ibandronate was not found to have significant benefit, hazard ratio (HR) 1.07 (95% CI 0.69 to 1.64). • Zoledronate was found to have a significant benefit in mortality over control (HR 0.57, 95% CI 0.43 to 0.75). • On network meta-analysis no significant difference was found between zoledronate and ibandronate (HR 0.67 95% CI [0.29 to 1.31]).
	What is the size of the effect for beneficial outcomes? Large: ☐ Moderate: ☒ Small: ☐ None: ☐	*Progression free survival* • Zoledronate was found to have a significant benefit in terms of progression free survival (HR 0.7, 95% CI 0.52 to 0.95). • No data for ibandronate • NMA not completed, no data for ibandronate
	What is the size of the effect for beneficial outcomes? Large: ☐ Moderate: ☒ Small: ☐ None: ☐	*SRE* • Ibandronate was not found to have a significant benefit compared to control, RR 1.04, 95% CI 0.8 to 1.35. • Zoledronate showed a significant benefit compared to control, RR 0.49, 95% CI 0.28 to 0.89. • On network meta-analysis no significant difference was found between zoledronate and ibandronate (HR 0.56 95% CI [0.26 to 0.98]).

QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☒ Very low: ☐	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☐ Moderate: ☐ Small: ☒ None: ☐	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: ☒ Favours control: ☐ Intervention = Control *or* Uncertain: ☐	Favours zoledronate
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: ☐ No: ☐ Uncertain: ☒	Currently ibandronate on contract – will need to facilitate procurement of zoledronate
RESOURCE USE	**How large are the resource requirements?** More intensive: ☐ Less intensive: ☐ Uncertain: ☒ *Currently more intensive but dependant on next tender offer.*	Cost of medicines/ month: *See cost analysis above* *Uncertain, as the zoledronate price will only be confirmed at the next tender. Based on the previous tender price, the incremental cost of zoledronate (over ibandronate) is expected to be ~R92 000*
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: ☒ Major: ☐ Uncertain: ☐ **Is the option acceptable to key stakeholders?** Yes: ☒ No: ☐ Uncertain: ☐	Motivation received for zoledronate as preferred option
EQUITY	**Would there be an impact on health inequity?** Yes: ☐ No: ☒ Uncertain: ☐	None anticipated

Appendix 2: Excluded Articles:

Reference	Reason
Comparison of denosumab and zoledronic acid for the treatment of solid tumors and multiple myeloma with bone metastasis: a systematic review and meta-analysis based on randomized controlled trials. Jiang L, Cui X, Ma H, Tang X.J Orthop Surg Res. 2021 Jun 22;16(1):400. doi: 10.1186/s13018-021-02554-8.PMID: 34158101	Incorrect comparator
Denosumab Versus Zoledronic Acid in the Prevention of Skeletal-related Events in Vulnerable Cancer Patients: A Meta-analysis of Randomized, Controlled Trials. Chen C, Li R, Yang T, Ma L, Zhou S, Li M, Zhou Y, Cui Y.Clin Ther. 2020 Aug;42(8):1494-1507.e1. doi: 10.1016/j.clinthera.2020.05.019. Epub 2020 Jul 24.PMID: 32718784	Incorrect population
Pharmacogenetics of medication-related osteonecrosis of the jaw: a systematic review and meta-analysis. Guo Z, Cui W, Que L, Li C, Tang X, Liu J.Int J Oral Maxillofac Surg. 2020 Mar;49(3):298-309. doi: 10.1016/j.ijom.2019.07.016. Epub 2019 Aug 22.PMID: 31445964	Does not meet PICO
Association between CYP2C8 (rs1934951) polymorphism and bisphosphonate-related osteonecrosis of the jaws in patients on bisphosphonate therapy: a meta-analysis. Zhong DN, Wu JZ, Li GJ.Acta Haematol. 2013;129(2):90-5. doi: 10.1159/000342120. Epub 2012 Nov 21.PMID: 23171856	Does not meet PICO
Bisphosphonates in multiple myeloma: a network meta-analysis. Mhaskar R, Redzepovic J, Wheatley K, Clark OA, Miladinovic B, Glasmacher A, Kumar A, Djulbegovic B.Cochrane Database Syst Rev. 2012 May 16;(5):CD003188. doi: 10.1002/14651858.CD003188.pub3.PMID: 22592688 **Updated.** Review.	Updated Cochrane included
Bisphosphonates in multiple myeloma. Mhaskar R, Redzepovic J, Wheatley K, Clark OA, Miladinovic B, Glasmacher A, Kumar A, Djulbegovic B.Cochrane Database Syst Rev. 2010 Mar 17;(3):CD003188. doi: 10.1002/14651858.CD003188.pub2.PMID: 20238320 **Updated.** Review.	Updated Cochrane included
Bisphosphonates in multiple myeloma. Djulbegovic B, Wheatley K, Ross J, Clark O, Bos G, Goldschmidt H, Cremer F, Alsina M, Glasmacher A.Cochrane Database Syst Rev. 2002;(3):CD003188. doi: 10.1002/14651858.CD003188.PMID: 12137679 **Updated.** Review.	Updated Cochrane included
Bisphosphonates in multiple myeloma. Djulbegovic B, Wheatley K, Ross J, Clark O, Bos G, Goldschmidt H, Cremer F, Alsina M, Glasmacher A.Cochrane Database Syst Rev. 2001;(4):CD003188. doi: 10.1002/14651858.CD003188.PMID: 11687178 **Updated.** Review.	Updated Cochrane included
Ibandronate to treat skeletal-related events and bone pain in metastatic bone disease or multiple myeloma: a meta-analysis of randomised clinical trials. Geng CJ, Liang Q, Zhong JH, Zhu M, Meng FY, Wu N, Liang R, Yuan BY. BMJ Open. 2015 Jun 2;5(6):e007258.	Only included 1 study evaluating patients with multiple myeloma, this study was included in the Cochrane review (Mhaskar *et al*)

Appendix 3:

Bisphosphonates_ MM_Review_4N_07F

References

[1] Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Bisphosphonates in multiple myeloma: an updated network meta-analysis. Cochrane Database Syst Rev. 2017 Dec 18;12(12):CD003188.