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

TITLE: Bisphosphonates for hypercalcaemia of malignancy *(limited review)*

Date: October 2023
Date of previous review: September 2007

Key findings

- In 2007 intravenous pamidronate was recommended for inclusion on the essential medicines list for hypercalcaemia of malignancy however pamidronate has not been available for several years thus there was a need to evaluate the other registered intravenous (IV) bisphosphonates in South Africa (zoledronate and ibandronate. We thus conducted a limited review and costing.
- After screening and full text review, 2 trials were selected for inclusion. Both trials were assessed as 'unclear' risk of bias (Risk of Bias 1 assessment).
- *Comparison 1: Ibandronate vs pamidronate*
  - Response rate (restoration of normocalcaemia (CSC <2.7 mmol/l) by day 4 was similar in both ibandronate and pamidronate groups after first dose (RR 0.98 95% CI [0.75 to 1.29], P=0.89, 1 trial n=782) - low quality evidence.
  - The median duration of response (time from response to increase in CSC >2.7 mmol/l) was longer in patients treated with ibandronate compared to those receiving pamidronate (mean difference 10 days, p = 0.0303) – low quality evidence.
  - There were fewer participants in the ibandronate group (19%) who reported adverse events considered to be linked to the study medication compared to the pamidronate group (35%) (RR=0.54 95% CI [0.24 to 1.2], P =0.13, 1 trial, n=71) – low quality evidence.
- *Comparison 2: Zoledronate vs pamidronate*
  - More patients on zoledronate achieved normalization of CSC (< or equal to 2.70 mmol/L (10.8mg/dL) by day 4 compared to those on pamidronate 90mg (zoledronate 4mg 45.3% vs 33.3% – not significant; 1 trial, n=275) - moderate quality evidence.
  - There were more participants in the 4mg and 8mg zoledronate groups with a complete response by day 10 (defined as normalization of CSC to ≤ 2 .70 mmol/L (10.8 mg/dL) than in the pamidronate 90mg group (zoledronate 4mg: 88.4% compared to 69.7% for pamidronate 90mg P = 0.002; 1 trial n=275) - moderate quality evidence.
  - The most common adverse events reported were fever, anaemia, nausea, constipation, and dyspnoea) and occurred with similar frequency among the zoledronate 4mg and 8mg groups (94.2% and 95.9%) and the pamidronate 90mg group (92.2%). No treatment-related deaths occurred – moderate quality evidence.
- Both zoledronate and ibandronate have been shown to achieve normocalcaemia, both of which showing longer durations of response when compared to pamidronate. Adverse events were similar in both comparisons.
- The available data showed efficacy and safety of both zoledronate or ibandronate in this indication. It is thus proposed that these agents be recommended as a class, with the most affordable product being procured for use.

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 zoledronate and ibandronate be considered a bisphosphonate class for the management of hypercalcaemia of malignancy. This recommendation is to replace the previously recommended pamidronate, which is no longer available in South Africa.					

Rationale: Although the evidence is of low to moderate quality, both agents demonstrated their ability to achieve normocalcaemia, with a trend for superiority over pamidronate. There is no evidence to show that either zoledronate or ibandronate is superior in this indication.

Level of Evidence: *II*
Review Indicator: *New evidence of efficacy/safety*

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

BACKGROUND

In 2007 intravenous pamidronate was recommended for inclusion on the essential medicines list for hypercalcaemia of malignancy. *See review document – appendix 4.*

Pamidronate was previously registered in South Africa, however this product has been discontinued and has not been available for several years. There is thus a need to evaluate the other registered intravenous (IV) bisphosphonates in South Africa (zoledronate and ibandronate), to establish the appropriate recommendation in the absence of pamidronate.

METHODS

The evaluation comprised two parts; a rapid search update of evidence published since the last review, and an updated costing. A search for randomised controlled trials was conducted in Pubmed and Cochrane Library in August 2023 by one reviewer (JR); according to the accepted PICO. The search strategy is outlined in Appendix 2. The following PICO was utilised when assessing eligible studies.

Population	Patients with hypercalcaemia of malignancy
Intervention	IV Zoledronate or ibandronate
Comparators	IV Pamidronate or other bisphosphonate
Outcomes	No. of participants achieving normocalcaemia Time to normocalcaemia Time to next dose Safety/adverse events
Studies	Systematic reviews and meta-analyses Randomised controlled trials

Data extraction was conducted by one reviewer (JR) and another reviewer checked it (KM). Included studies were assessed independently with the Cochrane Risk of Bias 1 assessment tool[1] by two reviewers (JR and KM). Due to the limited nature of this review, a formal GRADE assessment was not conducted however a discussion of overall quality of the studies and certainty in outcomes will be included.

RESULTS

Search update

The search produced 26 results, or which 10 were duplicates and removed (16 studies in total). After title and abstract screening, 11 studies were excluded (see appendix 3 for the list of excluded studies and rationale for exclusion). An additional four studies were removed after full text review (*Total exclusions: 15 – see appendix 3*). One additional title was added after reference screening. A total of 2 trials were included.

No systematic reviews that met the PICO were identified.

Description of included studies

Table 1. Summary of included studies

Study	Study design	Types of participants	Interventions	Outcomes	Outcomes reported	Notes
Pecherstorfer et.al. 2003[2]	Open-label, stratified, randomised multicentric trial in parallel groups	Patients over 18 years suffering from malignancy and presenting with an albumin-corrected serum calcium (CSC) > 2.7 mmol/L (10.8 mg/dL) (n = 72, ITT= 67)	Ibandronate (2 or 4mg) Versus pamidronate (15, 30, 60 or 90mg) on day 0	Primary efficacy outcome: change in CSC from baseline from day 0 to day 4. Secondary efficacy outcome: response rate and time to re-increase of CSC.	• CSC was significantly (P<0.0001) lowered following the IV administration of ibandronate or pamidronate. • In the ITT population, the mean change in CSC from day 0 to day 4 was 0.73±0.48 mmol/l for ibandronate and 0.57±0.33 mmol/l for pamidronate. • The mean difference between the decreases in the ibandronate and the pamidronate group was 0.09 mmol/l. • The one-sided 95% CI for the difference between ibandronate and pamidronate had a lower limit of 0.05 mmol/l. This value was within the CI of 0.2 mmol/l laid down in the study protocol. Thus, the Hypocalcemic effect of ibandronate was not inferior to that of pamidronate.	• Open-label
Major et.al. 2001[3]	Concurrent, parallel, multicentre, randomized, double-blind, double-dummy trials	Patients over 18 years with histologic or cytologic confirmation of cancer and severe HCM (baseline CSC ≥ 3 mmol/L (12 mg/dL) (n = 287)	Zoledronate (4 or 8 mg versus pamidronate (90 mg) (administered with simultaneous IV hydration) *Single dose*	• Rate of complete response by day 10 • Response duration, and • Time to relapse	• Both doses of zoledronate were superior to pamidronate in the treatment of HCM. • The complete response rates by day 10 were 88.4% (P = 0.002), 86.7% (P = 0.015), and 69.7% for zoledronate 4 mg and 8 mg and pamidronate 90 mg, respectively. • Normalization of CSC occurred by day 4 in approximately 50% of patients treated with zoledronate and in only 33.3% of the pamidronate treated patients. • The median duration of complete response favoured zoledronate 4 and 8mg over pamidronate 90 mg with response durations of 32, 43, and 18 days, respectively.	• Patients were not rehydrated prior to measurement of serum calcium

Risk of bias assessment (Internal validity)

The Pecherstorfer *et al*. [2] trial was randomised controlled trial with patients centrally randomised with minimization. The trial was open-label and neither participants nor personnel were blinded. Outcome assessors were also not blinded however the main outcomes are laboratory assessed. The main analysis was intention-to treat, with both per protocol and intention-to-treat analyses reported. Three (9%) and two (6%) participants were excluded from the ibandronate and pamidronate groups respectively due to protocol violations. All outcomes were reported for both intention-to-treat and per-protocol analyses. Source of funding was not provided. Overall, despite the open-label nature of the trial, it was considered as being at 'unclear risk' of bias. The Major et al. [3] trial was also assessed to be of 'unclear' risk of bias. The study was a double-blinded RCT however it was only specified that the participants were blinded thus it is unclear if personnel or outcome assessors were also blinded. Only a per-protocol analysis was conducted, and all outcomes were reported. Attrition was 0% in the zoledronate 4mg group, 8% in the zoledronate 8mg group and 4% in the pamidronate group. Funding was not explicit, and conflicts of interest were not described.

Table 1: Risk of bias.

	Pecherstorfer 2003	Major 2001
Random Sequence Generation (selection bias)	Low	Low
Allocation Concealment (selection bias)	Low	Low
Blinding of participants and personnel (performance bias)	Unclear	Unclear
Blinding of outcome assessment (detection bias)	Unclear	Low
Incomplete Outcome Data (attrition bias)	Low	Unclear
Selective Reporting (reporting bias)	Low	Unclear
Other Bias	Low	Low
OVERALL	Unclear	Unclear

EFFECTS OF INTERVENTIONS

Comparison 1: Ibandronate (2 or 4mg) versus pamidronate (15, 30, 60 or 90mg)

Outcome 1.1: Number of patients achieving normocalcaemia at day 4

Response rate (restoration of normocalcaemia (CSC <2.7 mmol/l) as determined by a minimum of one prescribed laboratory examination, and a decrease in CSC of at least 0.3 mmol/l compared with levels on day 0) by day 4 to ibandronate and pamidronate after first dose were similar, 76.5% (26/35 patients) and 75.8% respectively (RR 0.98 95% CI [0.75 to 1.29], P=0.89, 1 trial n=78[2]).

Outcome 1.2: Number of patients achieving normocalcaemia at day 10

The included study for this comparison did not report on this outcome.

Outcome 1.3: Duration of response in days

The median duration of response (time from response to increase in CSC >2.7 mmol/l) was 14 days in patients treated with ibandronate and 4 days in those receiving pamidronate (mean difference 10

days, p = 0.0303). However, subgroup analyses showed a dose response where CSC levels were maintained for up to 14 days with the higher dose of pamidronate (60mg and 90mg).[2]

Outcome 1.4: Safety/adverse events

Majority of patients had adverse events that are expected in a population with malignant disease with majority of severe AEs considered to be caused by progression of underlying malignancy. Percentage of participants with reported serious adverse events was lower in the ibandronate group (60%) compared to the pamidronate group (65%) (RR=0.92 95% CI [0.64 to 1.32], P=0.65, 1 trial, n=71). There were fewer participants in the ibandronate group (19%) who reported adverse events considered to be linked to the study medication compared to the pamidronate group (35%) (RR=0.54 95% CI [0.24 to 1.2], P =0.13, 1 trial, n=71).

Comparison 2: Zoledronate (4 or 8 mg or pamidronate (90 mg)

Outcome 2.1: Number of patients achieving normocalcaemia at day 4)

Onset of normalization of CSC (< or equal to 2.70 mmol/L (10.8mg/dL), occurred by day 4 in approximately one half of the patients treated with zoledronate, whereas only 33.3% of the pamidronate 90mg patients had CSC normalization by day 4 (45.3% for zoledronate 4mg – not significant and 55.6% for zoledronate 8 mg – P=0.021; 1 trial, n=275).

Outcome 2.2: Number of patients achieving normocalcaemia at day 10)

There were more participants in the 4mg and 8mg zoledronate groups with a complete response by day 10 (defined as normalization of CSC to ≤ 2 .70 mmol/L (10.8 mg/dL) than in the pamidronate 90mg group (zoledronate 4mg: 88.4% compared to 69.7% for pamidronate 90mg P = 0.002; zoledronate 8 mg: 86.7% P = 0.015; 1 trial n=275).

Outcome 2.3: Duration of response in days

In patients in whom normal serum values were achieved, the median duration of complete response in patients treated with 4 mg or 8 mg of zoledronate was 32 and 43 days, respectively, compared with 18 days in the pamidronate group (p value not reported).

Outcome 2.4: Safety/adverse events

The most common adverse events reported were fever, anaemia, nausea, constipation, and dyspnoea) and occurred with similar frequency among the zoledronate 4mg and 8mg groups (94.2% and 95.9%) and the pamidronate 90mg group (92.2%). Two patients in the zoledronate 8mg group and one patient in the pamidronate 90mg group developed grade 4 abnormal serum creatinine values. Two patients developed grade 3 creatinine changes in the zoledronate 4mg group and three patients each in the zoledronate 8mg and pamidronate 90-mg group. Two other serious adverse events were observed: one patient in the zoledronate 4mg group experienced confusion and hallucination, and one patient in the pamidronate 90-mg group developed thrombocytopenia. No treatment-related deaths occurred.

Costing

Product	Regimen	Available product	Cost per product			Cost per dose (contract)	Cost per dose (SEP)
			SEP	Contract			
Zoledronate*	4mg IV	Zoledronate 4mg/5ml injection	R815.35	R164.63	***	R164.63	R815.35
Ibandronate	4mg IV	Ibandronate; 6mg; injection; 6 ml	R529.67	R126.00	**	R126.00	R529.67

*** Previous contract price

** Current contract price

*many more zoledronate generics available, price above on agent previously available.

Quality of Evidence

Overall, the quality of the evidence for effectiveness and safety was considered low for comparison 1 (ibandronate vs pamidronate) and moderate for comparison 2 (zoledronate vs pamidronate). With regard to imprecision, the Pecherstorfer et al trial (ibandronate vs pamidronate) had a very small sample size (n=78) and confidence intervals for estimates were relatively wide. The trial was also considered to be of 'unclear' risk of bias. The Major et al. trial (zoledronate vs pamidronate) was also assessed as 'unclear' risk of bias however had a comparatively larger sample size (n=275). Heterogeneity and indirectness were not a concern for either comparison as there was only 1 trial for each outcome and the data did meet the PICO and the review question.

CONCLUSION

Both zoledronate and ibandronate have been shown to achieve normocalcaemia, both of which showing longer durations of response when compared to pamidronate.

The data comparing pamidronate and ibandronate demonstrate non-inferiority while the comparison of pamidronate and zoledronate showed that zoledronate is more effective in terms of time to normalisation of serum calcium.

The available data shows that both zoledronate and ibandronate are effective and safe in this indication. It is thus proposed that these agents be recommended as a class, with the most affordable product being procured for use.

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1. Medical Doctor/Radiation oncology, Western Cape. No conflicts declared.
2. National Department of Health. No conflicts declared.
3. SCTA technical support. No conflicts declared.

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 ☐	*Ibandronate vs pamidronate* • RoB 1 for Pecherstorfer et al. evaluated as 'unclear'. • Very small sample size (n=78)
	What is the certainty/quality of evidence? High ☐ Moderate ☒ Low ☐ Very low ☐	*Zoledronate vs pamidronate* • RoB 1 for Major et al. evaluated as 'unclear'. • Sample size (n=275)
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	*Ibandronate vs pamidronate* • **Outcome 1.1: No. of patients achieving normocalcaemia at day 4**: RR 0.98 95% CI [0.75 to 1.29] p=0.89
	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	*Ibandronate vs pamidronate* • **Outcome 1.3: Duration of response in days:** Mean difference 10 days, P=0.303 in favour of ibandronate.
	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☐ Small ☐ None ☒	Zoledronate vs pamidronate • **Outcome 2.1: No. of patients achieving normocalcaemia at day 4: 4mg** = 45.3% vs 33.3%, RR 1.4 95% CI [0.97 to 2.0], P=0.0690
	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	Zoledronate vs pamidronate • **Outcome 2.2: No. patients achieving normocalcaemia at day 10:** 4mg = 88.4% vs 69.7%, RR 1.27 95% CI [1.09 to 1.47], P=0.015 NNT 6 95% CI [4 to 15].
	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	Zoledronate vs pamidronate • **Outcome 2.3: Duration of response in days:** Mean difference 14 days – **p value not reported**
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Very low ☐	*Ibandronate vs pamidronate* • RoB 1 for Pecherstorfer et al. evaluated as 'unclear'. • Very small sample size (n=78)

QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐	*Zoledronate vs pamidronate* • RoB 1 for Major et al. evaluated as 'unclear'. • Sample size (n=275)
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Ibandronate vs pamidronate • % of patients with SAE: RR 0.92 in favour of ibandronate 95% CI 0.64 to 1.32], P=0.65 • No. patients with AEs linked to study medication: RR 0.54 in favour of ibandronate 95% CI 0.24 to 1.12 P=0.13.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Zoledronate vs pamidronate Adverse events reported occurred with similar frequency among the zoledronate 4mg and 8mg groups (94.2% and 95.9%) and the pamidronate 90mg group (92.2%).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒	No superiority observed – both intervention and control outweigh harms
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.*

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [X] Major: [ ] Uncertain: [ ] **Is the option acceptable to key stakeholders?** Yes: [X] No: [ ] Uncertain: [ ]	**Ease of administration** <u>Ibandronate vs pamidronate (pech 2003)</u> • Ibandronate had a shorter infusion time (1 hour) compared to pamidronate (not more than 1mg/min). <u>Zoledronate vs pamidronate (Major 2001)</u> • Zoledronate: 5-min IV infusion. • Pamidronate: 2 hour infusion.
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [X] Uncertain: [ ]	None anticipated

Appendix 2: Search Strategy

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Search No.	Search Details	Results
2	(("zoledronic acid"[MeSH Terms] OR "ibandronic acid"[MeSH Terms]) AND "hypercalcemia"[MeSH Terms] AND "neoplasms"[MeSH Terms]) AND (randomizedcontrolledtrial[Filter])	10
1	("zoledronic acid"[MeSH Terms] OR "ibandronic acid"[MeSH Terms]) AND "hypercalcemia"[MeSH Terms] AND "neoplasms"[MeSH Terms]	119

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search	Query	Results
#1	MeSH descriptor: [Hypercalcemia] explode all trees	**352**
#2	MeSH descriptor: [Neoplasms] explode all trees	**112129**
#3	MeSH descriptor: [Ibandronic Acid] explode all trees	**227**
#4	MeSH descriptor: [Zoledronic Acid] explode all trees	**759**
#5	(#3 OR #4) AND #1 AND #2	**16**

Appendix 3: Excluded Articles:

	Reference	Exclusion Reason
1	**Ibandronate or Zoledronate in Treating Patients With Newly Diagnosed Bone Metastases From Breast Cancer** NCT00326820 https://clinicaltrials.gov/show/NCT00326820, **2006** | added to CENTRAL: 31 January 2020 | 2020 Issue 01CT.gov	Only on clinicaltrials.gov – no published results
2	**S0308 Zoledronate or Ibandronate in Preventing Bone Problems in Women With Stage IV Breast Cancer That Has Spread to the Bone** NCT00301886 https://clinicaltrials.gov/show/NCT00301886, **2006** | added to CENTRAL: 31 May 2018 | 2018 Issue 5	Only on clinicaltrials.gov – no published results
3	**Monoclonal Antibody Compared With Zoledronate in Treating Women With Breast Cancer and Bone Metastases** NCT00060138 https://clinicaltrials.gov/show/NCT00060138, **2003** | added to CENTRAL: 31 May 2018 | 2018 Issue 5	Only on clinicaltrials.gov – no published results
4	**A prospective, randomized, placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer** MS Zaghloul, R Boutrus, H El-Hossieny, YA Kader, I El-Attar, M Nazmy International journal of clinical oncology, **2010**, 15(4), 382-389 | added to CENTRAL: 30 April 2011 | 2011 Issue 2	Not specifically looking at the outcome of hypercalcaemia
5	**Zoledronate in Treating Patients With Solid Tumors That Have Spread to the Bone** NCT00003884 https://clinicaltrials.gov/show/NCT00003884, **1999** | added to CENTRAL: 31 May 2018 | 2018 Issue 5	Only on clinicaltrials.gov – no published results

6	**Comparison of Two Schedules of Zoledronic Acid in Treating Patients With Breast Cancer That Has Spread to the Bone** NCT00458796 https://clinicaltrials.gov/show/NCT00458796, **2007** | added to CENTRAL: 31 May 2018 | 2018 Issue 5	Only on clinicaltrials.gov – no published results
7	**Clinical significance of zoledronic acid and strontium-89 in patients with asymptomatic bone metastases from non-small-cell lung cancer** Y Wang, H Tao, X Yu, Z Wang, M Wang Clinical lung cancer, **2013**, 14(3), 254-260 | added to CENTRAL: 31 December 2013 | 2013 Issue 12	Not specifically looking at the outcome of hypercalcaemia
8	**The role of denosumab in the prevention of hypercalcaemia of malignancy in cancer patients with metastatic bone disease** IJ Diel, JJ Body, AT Stopeck, S Vadhan-Raj, A Spencer, G Steger, R von Moos, F Goldwasser, A Feng, A Braun. European journal of cancer (Oxford, England : 1990), **2015**, 51(11), 1467-1475 | added to CENTRAL: 30 September 2015 | 2015 Issue 9	Wrong intervention
9	**Cost-effectiveness of zoledronic acid in the management of skeletal metastases in patients with lung cancer in France, Germany, Portugal, the Netherlands, and the United kingdom** AD Joshi, JA Carter, MF Botteman, S Kaura Clinical therapeutics, **2011**, 33(3), 291-304.e8 | added to CENTRAL: 31 December 2011 | 2011 Issue 12	Cost effectiveness analysis, not RCT
10	**Use of zoledronic acid for high risk prostate cancer patients** H Rexer. Der Urologe. Ausg. A, **2005**, 44(2), 183-184 | added to CENTRAL: 31 October 2005 | 2005 Issue 4	Not specifically looking at the outcome of hypercalcaemia
11	**Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival, and bone resorption markers in patients with advanced multiple myeloma** HD Menssen, A Sakalová, A Fontana, Z Herrmann, C Boewer, T Facon, MR Lichinitser, CR Singer, L Euller-Ziegler, M Wetterwald, D Fiere, M Hrubisko, E Thiel, PD Delmas. Journal of clinical oncology, **2002**, 20(9), 2353-2359 | added to CENTRAL: 31 January 2003 | 2003 Issue 1	Not specifically looking at the outcome of hypercalcaemia
12	**Zoledronic acid in the treatment of hypercalcaemia of malignancy: results of the international clinical development program.** Major PP, Coleman RE. Semin Oncol. 2001, 2 (6):17-24.	Discussed findings from included RCTs
13	**Serum parathyroid hormone-related protein levels and response to bisphosphonate treatment in hypercalcaemia of malignancy.** Rizzoli R, Thiébaud D, Bundred N, Pecherstorfer M, Herrmann Z, Huss J, et. al. Journal of Clinical Endocrinology and Metabolism. 1999, 84 (10): 3545-3550.	Discussed findings from included RCTs
14	**Dose-response study of ibandronate in the treatment of cancer associated hypercalcaemia.** Ralston SH, Thiébaud D, Herrmann Z, Steinhauer EU, Thürlimann B, Walls J, et. al. British Journal of Cancer. 1997, 75 (2): 295-300.	Dose finding study
15	**Randomized phase II trial comparing different doses of the bisphosphonate ibandronate in the treatment of hypercalcaemia of malignancy.** Pecherstorfer M, Herrmann Z, Body JJ, Manegold C, Degardin M, Clemens MR, et.al. Journal of Clinical Oncology. 1996, 14 (1): 268-76.	Dose finding study

Appendix 4: Previous review - pamidronate

Malignancy_Pamidronate_RN_10July200

References

[1] Higgins J P T, Altman D G, GÃ¸tzsche P C, JÃ¼ni P, Moher D, Oxman A D et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ 2011; 343 :d5928 doi:10.1136/bmj.d5928

[2] Pecherstorfer M, Steinhauer EU, Rizzoli R, Wetterwald M, Bergström. Efficacy and safety of ibandronate in the treatment of hypercalcaemia of malignancy: a randomized multicentric comparison to pamidronate. Support Care Cancer. 2003, 11: 539-547.

[3] Major P, Lortholary A, Hon J, Adbi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seaman J. Zolendronic acid is superior to pamidronate in the treatment of hypercalcaemia of malignancy: a pooled analysis of two randomised, controlled clinical trials. 2001, 19(2): 558-567.