



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

Name of medicine (INN):	Zoledronic Acid 4mg/5mL concentrate for dilution for IV Infusion
Indication:	For the prevention of skeletal related events in patients with advanced malignancies involving the bone. Also for the treatment of hypercalcemia of malignancy (HCM).
Date of deliberation:	24 July 2015 26 November 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>The Council based their recommendation on the result of the ERG evaluation, which showed that among the bisphosphonates, zoledronic acid is the most effective in reducing vertebral fractures. In a meta-analysis of 76 RCTs on men and women with low bone density or osteoporosis, zoledronic acid has the highest risk reduction for vertebral fracture by 72% compared to other bisphosphonates (OR=0.28; 95%CI: 0.19 and 0.40). Among Asians, zoledronic acid also decreased fracture and osteoporosis risk by 32% and 19% respectively (Zhang et al. Asian Pacific J Trop Med).</p> <p>Among patients with cancer and bone metastasis, zoledronic acid also decreased pathologic fractures by 40%. In terms of reduction of hypercalcemia, zoledronic acid decreased the risk by 73% (RR=0.27; 95%CI: 0.10 and 0.72). However, compared with ibandronate or pamidronate, there is no significant difference in terms of preventing skeletal related events among cancer patients.</p> <p>Zoledronic acid has no effect on the overall survival of patients with breast cancer, but among women who are already post-menopausal, the overall survival was improved by 24% (RR=0.76; 95%CI: 0.66 and 0.88)(Yan et al. Eur J Cancer 2012). It also decreased skeletal related events among breast cancer patients by 41% (RR=0.59; 95%CI: 0.42 and 0.82)(Wong et al. Cochrane 2012) as well as among those with lung cancer (RR=0.81; 95%CI: 0.67 and 0.97)(Lopez-Olivo et al. Support Care Cancer 2012).</p>

(See Attachment for the full ERG evaluation)

Cost data:

The cost of treatment with **zoledronic acid 4mg/5mL concentrate for dilution for IV infusion** will amount to Php 105,712.50 for 6 infusions (metastatic bone disease) and Php 176,187.50 for 10 infusions (adjuvant treatment). Another calculation was also done considering the use of **zoledronic acid 5mg/100mL solution for infusion**, which will amount to Php 24,897.95 per year. Given these data, it was noted that its use will be more expensive compared to alendronate (Php 19,008 per year) and ibandronate (Php 19,164 per year).

(See Attachment).

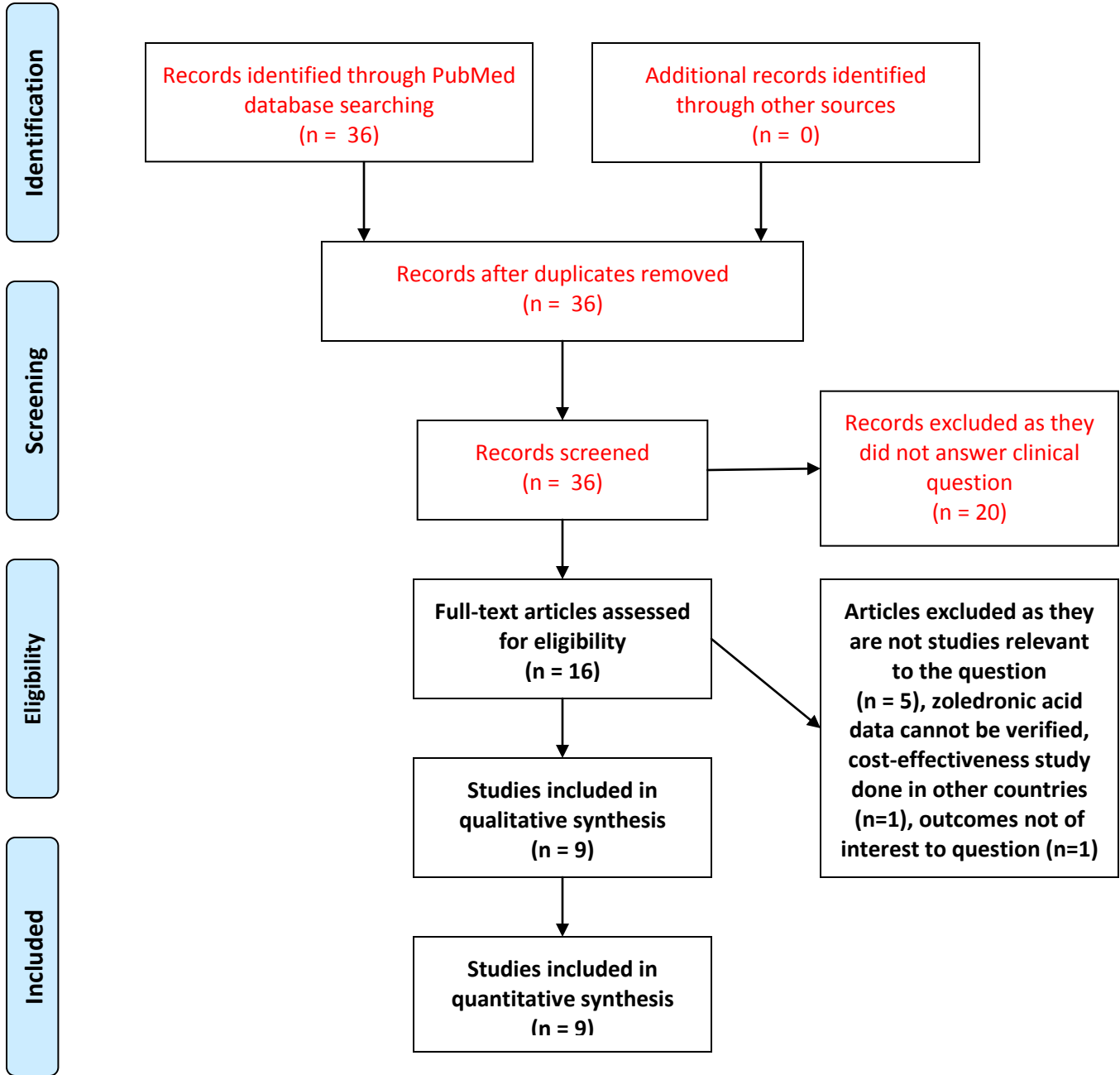
Remarks:

The ERG evaluated the documents submitted by the proponent to support their appeal and it was noted that the articles were already cited or included in the review. The subject of the new articles provided were either not the focus of the research question or of lesser quality of evidence than what was already cited or included. The additional studies submitted in the appeal also concurred with the ERG findings that zoledronic acid has some advantage over other bisphosphonates, but in terms of the research question provided and the intention of treatment to provide clinically-relevant outcomes, the ERG still maintain its findings in the review.

The Council concurred to this and given that the product has prohibitive cost and the proponent did not give a lower price offer, the initial recommendation to disapprove its inclusion still remains.

The Secretary of Health has officially disapproved the proposal to include zoledronic acid in the PNF.

PRISMA Table



1) What is the comparative clinical effectiveness of Zoledronic acid solution for IV infusion and other bisphosphonates in treating malignancy-associated hypercalcemia? 2) How effective is the absorption of Zoledronic acid being a bisphosphonate as compared with oral osteoporosis agents? 3) What is the cost-effectiveness of Zoledronic acid versus other bisphosphonates (Ibandronate, Alendronate, Risedronate in treating osteoporosis or bone resorption)?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Zoledronic acid/ bisphosphonates		Control			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
1	MacLean et al. Annn Int Med 2008	Meta-analysis	76 RCTs on men and women with low bone density or osteoporosis	Alendronate vs. placebo	Vertebral fracture	95	1,507	167	1,320		OR=0.46; 95%CI: 0.36 and 0.60
				Etidronate vs. placebo	Vertebral fracture	9	137	19	126		OR=0.39; 95%CI: 0.17 and 0.91
				Ibandronate vs. placebo	Vertebral fracture	125	2,955	137	1,964		OR=0.58; 95%CI: 0.46 and 0.76
				Pamidronate vs. placebo	Vertebral fracture	8	123	14	122		OR=0.54; 95%CI: 0.22 and 1.33
				Risedronate vs. placebo	Vertebral fracture	114	1,040	182	1,024		OR=0.57; 95%CI: 0.44 and 0.73
				Zoledronic acid vs. placebo	Vertebral fracture	40	4,865	123	4,293		OR=0.28; 95%CI: 0.19 and 0.40
2	Zhang et al. Asian Pacific J Trop Med	Meta-analysis	9 RCTs	Zoledronic acid vs. placebo	Fracture	412	8,428	570	8,399		RR=0.68; 95%CI: 0.58 and 0.80
					Osteoporosis	2,459	8,828	2,818	8,852		RR=0.81; 95%CI: 0.76 and 0.87
3	Machado et al. Clin Therapeutics 2009	Meta-analysis	18 RCTs on cancer patients with bone metastasis	Clodronate vs. placebo	All skeletal-related events		339		342		RR=0.87; 95% CI: 0.75 and 1.00
				Pamidronate vs. placebo			1,124		1,127		RR=0.81; 95% CI 0.73 and 0.91

				vs. pamidronate							
6	Huang et al. PLOS One 2012	Meta-analysis	7 RCTs on 9,518 patients with breast cancer	Zoledronic acid vs. control (non-zoledronic acid therapy)	Overall survival Disease-free survival Recurrence-free survival						RR=0.85; 95%CI: 0.73 and 1.00 RR=0.75; 95%CI: 0.52 and 1.08 RR=0.87; 95%CI: 0.74 and 1.04
7	Lopez-Olivo et al. Support Care Cancer 2012	Meta-analysis	7 RCTs on lung cancer	Zoledronic acid vs. control (other bisphosphonates) Zoledronic acid vs. ibandronate	Skeletal related events Survival days Skeletal related events	148 496 (days) 5	662 26	100 282 (days) 7	441 27		RR=0.81; 95%CI: 0.67 and 0.97 MD=72; 95%CI: -8.9 and 152.9 RR=0.74; 95%CI: 0.27 and 2.0
8	Valachis et al. Oncologist 2013	Meta-analysis	15 RCTs on patients with breast cancer	Zoledronic acid vs. control (placebo or delayed zoledronic acid)	Overall survival Disease-free survival Overall fracture rate						RR=0.81; 95%CI: 0.70 and 0.94 RR=0.86; 95%CI: 0.70 and 1.06 RR=0.78; 95%CI: 0.63 and 0.96
9	He et al. J Hematol Oncol 2013	Meta-analysis	8 RCTs on 7,730 breast cancer patients	Zoledronic acid vs. control (observation or delayed zoledronic acid)	Overall survival Recurrence-free survival Fracture rate	334 156 98	3,771 3,676 1,995	379 193 118	3,769 3,678 2,000		RR=0.88; 95%CI: 0.77 and 1.01 RR=0.81; 95%CI: 0.66 and 0.99 RR=0.77; 95%CI: 0.60 and 1.00

EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				Over-all Quality	Importance
							No. of patients		Effect			
No. of Studies	Design	Limitation	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute MD		
Outcome: Vertebral fracture among patients with osteoporosis (indirect comparison)												
1	Meta-analysis	None	None	None	None		Zoledronic acid	Placebo	0.28; 95%CI: 0.19 and 0.40		Moderate	Critical
1	Meta-analysis	None	None	None	None		Alendronate	Placebo	0.46; 95%CI: 0.36 and 0.60		Moderate	Critical
1	Meta-analysis	None	None	None	None		Residronate	Placebo	0.57; 95%CI: 0.44 and 0.73		Moderate	Critical
1	Meta-analysis	None	None	None	None		Ibandronate	Placebo	0.58; 95%CI: 0.46 and 0.76		Moderate	Critical
Outcome: Fracture among cancer patients												
1	Meta-analysis	None	None	None	None		Zoledronic acid	Placebo	0.60; 95%CI: 0.47 and 0.76		High	Critical
Outcome: Hypercalcemia among cancer patients												
1	Meta-analysis	None	None	None	None		Zoledronic acid	Placebo	0.27; 95%CI: 0.10 and 0.72		High	Critical
Outcome: Skeletal related events												
1	Meta-analysis	None	None	None	None		Zoledronic acid	Ibandronate	0.74;95%CI: 0.27 and 2.0		High	Critical

DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS

<p>PARAMETER (Indicate information for intended recipient) * <u>INTENDED RECIPIENT:</u></p>	<p>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</p>	<p>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</p>	<p>REFERENCES</p>
<p>COST PER DOSAGE UNIT (in PhP) a. Proposed list price to the government b. Current prevailing market price</p>	<p>¹Zoledronic acid 4mg/5mL (Zometa) Php 17,618.75 ²Zoledronic acid 5 mg/100 mL (Aclasta) Php 24,897.95</p>	<p>Alendronate 70mg (Fosavance) P 396 Ibandronate 150mg (Bonviva) P 1,597</p>	<p>¹company submission (Zometa) ²MIMS</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>Zoledronic acid 4mg/5mL: • given every 4 months (metastatic bone disease) at least 6 infusions • given every 6 months (adjuvant treatment) at least 10 infusions Zoledronic acid 5 mg/100 mL: 5mg infusion once a year</p>	<p>1 every week for alendronate (52 doses for 1 year) 1 monthly for ibandronate (12 doses for 1 year)</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Zoledronic acid 4mg/5mL: • metastatic bone disease: Php 105,712.50 for 6 infusions • adjuvant treatment: Php 176,187.50 for</p>	<p>Php 19,008 per year (alendronate) Php 19,164 per year (ibandornate)</p>	

	10 infusions Zoledronic acid 5 mg/100 mL: Php 24,897.95		
ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n Php) a. Implementation costs: (cost of drug administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.)			
TOTAL COST PER PATIENT PER TREATMENT COURSE (in Php) Total Direct + Additional Costs	Zoledronic acid 4mg/5mL: • metastatic bone disease: Php 105,712.50 for 6 infusions • adjuvant treatment: Php 176,187.50 for 10 infusions Zoledronic acid 5 mg/100 mL: Php 24,897.95	Php 19,008 per year (alendronate) Php 19,164 per year (ibandornate)	
ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE			
QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)			
DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)			

REVIEWERS' RECOMMENDATIONS

Literature Search

- We searched Pubmed last February 2015 using the term “zoledronic acid” and limit the article type to meta-analysis. The yield was 36 articles. We reviewed the 36 articles and considered 22 articles for full text review.
- There were 16 available full text articles. We reviewed the 16 and included 9 in this review.
 - He M, Fan W, Zhang X(1). Adjuvant zoledronic acid therapy for patients with early stage breast cancer: an updated systematic review and meta-analysis. *J Hematol Oncol*. 2013 Oct 23;6(1):80. doi: 10.1186/1756-8722-6-80.
 - Valachis A(1), Polyzos NP, Coleman RE, Gnant M, Eidtmann H, Brufsky AM, Aft R, Tevaarwerk AJ, Swenson K, Lind P, Mauri D. Adjuvant therapy with zoledronic acid in patients with breast cancer: a systematic review and meta-analysis. *Oncologist*. 2013;18(4):353-61. doi: 10.1634/theoncologist.2012-0261. Epub 2013 Feb 12.
 - Lopez-Olivo MA(1), Shah NA, Pratt G, Risser JM, Symanski E, Suarez-Almazor ME. Bisphosphonates in the treatment of patients with lung cancer and metastatic bone disease: a systematic review and meta-analysis. *Support Care Cancer*. 2012 Nov;20(11):2985-98. doi: 10.1007/s00520-012-1563-z. Epub 2012 Sep 7.
 - Huang WW(1), Huang C, Liu J, Zheng HY, Lin L. Zoledronic acid as an adjuvant therapy in patients with breast cancer: a systematic review and meta-analysis. *PLoS One*. 2012;7(7):e40783. doi: 10.1371/journal.pone.0040783. Epub 2012 Jul 26.
 - Zhang J(1), Wang R, Zhao YL, Sun XH, Zhao HX, Tan L, Chen DC, Hai-Bin X. Efficacy of intravenous zoledronic acid in the prevention and treatment of osteoporosis: a meta-analysis. *Asian Pac J Trop Med*. 2012 Sep;5(9):743-8. doi: 10.1016/S1995-7645(12)60118-7.
 - Wong MH(1), Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev*. 2012 Feb 15;2:CD003474. doi: 10.1002/14651858.CD003474.pub3.
 - Yan T(1), Yin W, Zhou Q, Zhou L, Jiang Y, Du Y, Shao Z, Lu J. The efficacy of zoledronic acid in breast cancer adjuvant therapy: a meta-analysis of randomised controlled trials. *Eur J Cancer*. 2012 Jan;48(2):187-95. doi: 10.1016/j.ejca.2011.10.021. Epub 2011 Nov 17.
 - Machado M(1), Cruz LS, Tannus G, Fonseca M. Efficacy of clodronate, pamidronate, and zoledronate in reducing morbidity and mortality in cancer patients with bone metastasis: a meta-analysis of randomized clinical trials. *Clin Ther*. 2009 May;31(5):962-79. doi: 10.1016/j.clinthera.2009.05.009.
 - MacLean C(1), Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, Mojica W, Timmer M, Alexander A, McNamara M, Desai SB, Zhou A, Chen S, Carter J, Tringale C, Valentine D, Johnsen B, Grossman J. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med*. 2008 Feb 5;148(3):197-213. Epub 2007 Dec 17.

Results of the Review

Effectiveness

- Included in this review are 9 meta-analysis of randomized controlled trials classified as “high quality” body of evidence based on GRADE.
- There are no direct comparisons between bisphosphonates for the treatment of osteoporosis. The available data are indirect comparison of placebo-controlled trials. In a meta-analysis of 76 RCTs on men and women with low bone density or osteoporosis, zoledronic acid has the highest risk reduction for vertebral fracture by 72% compared to other bisphosphonates (OR=0.28; 95%CI: 0.19 and 0.40). Risedronate and alendronate decreased the risk by 43% and 54% respectively (MacLean et al. *Annn Int Med* 2008). Among Asians, zoledronic acid also decreased fracture and osteoporosis risk by 32% and 19% respectively (Zhang et al. *Asian Pacific J Trop Med*).
- Among patients with cancer and bone metastasis, zoledronic acid also decreased pathologic fractures by 40%. Zoledronic acid is better than clodronate and pamidronate. In terms of reduction of hypercalcemia, zoledronic acid decreased the risk by 73% (RR=0.27; 95%CI: 0.10 and 0.72). It is also better than clodronate or pamidronate which reduced the risk by only 27% and 40% respectively (Machado et al. *Clin Therapeutics* 2009). Compared with ibandronate or pamindronate, there is no significant difference in terms of preventing skeletal related events among cancer patients.
- Zoledronic acid has no effect on the overall survival of patients with breast cancer, However, among women who are already post-menopausal, overall survival was improved by 24% (RR=0.76; 95%CI: 0.66 and 0.88)(Yan et al. *Eur J Cancer* 2012). It also decreased skeletal related events among breast cancer patients by 41% (RR=0.59; 95%CI: 0.42 and 0.82)(Wong et al. *Cochrane* 2012) as well as among those with lung cancer (RR=0.81; 95%CI: 0.67 and 0.97)(Lopez-Olivo et al. *Support Care Cancer* 2012).

Summary of Review

- It was found that zoledronic acid is most effective in reducing vertebral fractures among the bisphosphonates. It is also effective than other bisphosphonates as adjuvant treatment for cancer in terms of survival, prevention of fractures or control of hypercalcemia. However, compared with other bisphosphonates (ibandronate and pamindronate) the effectiveness was similar.

Cost Data

- In terms of cost, the annual infusion of zoledronic acid is Php 24,897 to Php 176,187.50 compared to the annual cost of alendronate and ibandronate at Php 19,008 and Php 19,164, respectively.

Overall Recommendation

- For the treatment of osteoporosis, zoledronic acid is more effective than alendronate or ibandronate by around 20% but more expensive by 30%. For patients with cancer, there is no significant difference between zoledronic acid and ibandronate or pamindronate in terms of skeletal events.
- There is not enough evidence or justification to include zoledronic acid in the formulary. It may offer advantage in terms of compliance but the initial cost is high. The FEC may need to decide based on the government’s capacity and willingness to pay.

References

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Response to appeal on the reviewers' recommendation on Zoledronic Acid

The articles submitted to support the appeal were already cited or included in the review. There are some additional articles but the subject of the new articles were either not the focus of the research question or of lesser quality of evidence than what was already cited or included. Prior to the review, the ERG considered clinically relevant outcomes like skeletal events or survival. The additional studies submitted in the appeal also concurred with the ERG findings that zoledronic acid has some advantage over other bisphosphonates. But in terms of the research question provided and the intention of treatment to provide clinically-relevant outcomes, the ERG still maintain its findings in the review:

“For patients with cancer, there is no significant difference between zoledronic acid and ibandronate or pamidronate in terms of skeletal events. There is not enough evidence or justification to include zoledronic acid in the formulary. It may offer advantage in terms of compliance but the initial cost is high. The FEC may need to decide based on the government's capacity and willingness to pay.”

Because cost is the issue, we strongly recommend to the manufacturer to make the cost of zoledronic acid more comparable to the comparator drugs in the review for it to be included in the PNF.