Evidence Summary on Zoledronic Acid for Individuals with Malignancy-Related Bone Disease

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Context of the Assessment

The Health Technology Assessment Council (HTAC) reviewed the clinical and cost-effectiveness evidence and recommendations of the World Health Organization (WHO) Expert Committee on the Selection and Use of Essential Medicines considering the inclusion of zoledronic acid in the Core List of the WHO Essential Medicines List (EML) in 2017.

In addition, the HTAC considered available local and/or international Clinical Practice Guidelines (CPG) and conducted a costing and budget impact analysis to determine the cost to the government for financing these drugs.

The comparator to be used for zoledronic acid for the costing and budget impact analysis is "***other bisphosphonates***." Per HTAC and HTAD resolution, appropriate comparator drugs to be used must have:

- ❏ Philippine Food and Drug (FDA)-registered Certificate of Product Registration (CPR)
- ❏ Source National Regulatory Agency (NRA)-registered indication for Malignancy-related Bone Disease (MRBD)

Among all of the bisphosphonates included in the FDA verification portal, those with MRBD indications from their source NRAs were ***alendronate and pamidronic acid.*** Upon expert consultation, ***alendronate is not used*** in practice, and is not found in the CPGs. Hence, pamidronic acid was used for the costing analysis comparator.

No other drug indicated for MRBD is listed in the PNF.

On **07 September 2022**, the HTAC posted its preliminary recommendation for the government financing of zoledronic acid through its inclusion in the Philippine National Formulary (PNF), which was posted for appeals until **21 September 2022**.

Policy Question

Should zoledronic acid be included in the Philippine National Formulary for the treatment of patients with malignancy-related bone disease?

Research Questions

Clinical Assessment

1. Among patients with cancer who are at risk of bone loss, fracture or with established osteoporosis, including those with advanced malignancies and bone metastases, what is the efficacy or effectiveness of zoledronic acid compared with other bisphosphonates or placebo in terms of:
   a. Reduction of skeletal-related events (e.g., *pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia*)
   b. Bone mineral density
   c. Reduction of pain related to bone lesions/metastases
2. What is the safety of zoledronic acid compared with other bisphosphonates or placebo in terms of adverse events among patients with cancer who are at risk of bone loss, fracture or with established osteoporosis, including those with advanced malignancies and bone metastases?

Economic Assessment

1. What is the associated medication cost per patient of using zoledronic acid compared with other bisphosphonates for individuals with malignancy-related bone disease?
2. What is the total medication cost for the expected number of individuals using zoledronic acid compared with other bisphosphonates?

Budget Impact Analysis

1. What is the total medication cost for the expected number of individuals with MRBD using zoledronic acid compared to other bisphosphonates?

Key Findings

The HTAC concluded with the following findings based on its decision framework as stipulated in Republic Act 11223 or the *Universal Healthcare Act*:

Criteria	Malignancy-Related Bone Disease
Clinical Efficacy, Effectiveness, and Safety	The use of zoledronic acid has ***comparable to better efficacy*** compared to other bisphosphonates in terms of reducing the overall risk of skeletal-related events and attaining better pain relief among individuals with bone disease related to any primary cancer.
	Zoledronic acid has ***comparable to better safety profile*** compared to other bisphosphonates among individuals with malignancy-related bone disease in terms of any adverse event. However, there is no evidence on the odds of experiencing osteonecrosis of the jaw among zoledronic acid over other bisphosphonates.
Affordability and Viability	The total cost of treatment which includes the drug regimen and administration per patient per year for zoledronic acid and pamidronic acid are ₱38,161.50 and ₱148,921.50, respectively. From this, the computed total incurred costs for the government are as follows: ₱0.31 B for zoledronic acid, and ₱1.22 B for pamidronic acid. The cost savings for using zoledronic acid over pamidronic acid is ₱0.91 B. ***Zoledronic acid has cheaper associated medical costs*** than pamidronic acid in treating individuals with malignancy-related bone disease.
	The estimated budget impact (i.e. cost of drug regimen and administration, AE management) with zoledronic acid and pamidronic acid for 3 years is ₱0.97 B and ₱3.79 B respectively. The cost savings for using zoledronic acid over pamidronic acid among all users for 3 years is ₱2.82 B. Overall, the total cost of treatment for ***zoledronic acid is cheaper*** than pamidronic acid.
Cost-effectiveness	There is ***insufficient evidence*** to measure the cost-effectiveness of zoledronic acid compared to pamidronic acid. The current available evidence are all from upper-middle income to high-income countries and therefore not applicable to the Philippine setting. Of note, zoledronic acid is cheaper than pamidronic acid, has similar efficacy, and thus is likely to be more cost-effective over the comparator.

I. Summary of clinical efficacy and safety evidence and recommendations of the WHO and CPGs

WHO approved indication in the EML	Clinical Evidence from WHO EML	Supporting Clinical Practice Guidelines
Treatment of malignancy-related bone disease	*Clinical research question:* ● Among patients with cancer who are at risk of bone loss, fracture or with established osteoporosis, including those with advanced malignancies and bone metastases, what is the efficacy or effectiveness of zoledronic acid compared with other bisphosphonates or placebo in terms of: ○ Reduction of skeletal-related events (e.g., *pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia*) ○ Bone mineral density ○ Reduction of pain related to bone lesions/metastases ● What is the safety of zoledronic acid compared with other bisphosphonates or placebo in terms of adverse events among patients with cancer who are at risk of bone loss, fracture or with established osteoporosis, including those with advanced malignancies and bone metastases? The WHO EML Expert Committee recommended zoledronic acid be added to the Complementary List of the EML for this indication. The Committee also considered the evidence presented in the application for alternative bisphosphonates to support the inclusion of zoledronic acid on the Complementary List of EML but the evidence for other bisphosphonates was not adequate to include them in the Complementary List. However, the Expert Committee noted that the proponent of the listing did not	***In an official correspondence, the local society, Philippine Society for Medical Oncology, stated that the clinical practice guidelines they are currently using for zoledronic acid are the following:*** **NCCN CPG: Breast Cancer (2022)** Recommended ***zoledronic acid*** in addition to chemotherapy or endocrine therapy for the management of recurrent, unresectable (local or regional) or stage IV (M1) breast cancer where bone metastasis is present, expected survival is ≥ 3 months, and renal function is adequate. *Grade of recommendation (pp. CAT-1):* ● **Category 1:** *Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.* **NCCN CPG: Prostate Cancer (2022)** *Other recommended treatment for the prevention of Skeletal-Related Events*

	follow the standard template, and some important elements of the evaluation were missing or inadequately addressed. These important elements include the *actual outcome statistic, p-values, and quality of evidence*. As such, most of the values cited here were extracted by the HTAD internal assessment team as deemed relevant from the citation in the WHO EML summary. **General Findings** ● *Efficacy:* The use of zoledronic acid has ***comparable to better efficacy*** compared to other bisphosphonates in terms of reducing the overall risk of skeletal-related events and attaining better pain relief among individuals with bone disease related to breast cancer, multiple myeloma and/or any primary cancer. ● *Safety:* zoledronic acid has ***comparable to better safety profile*** compared to other bisphosphonates among individuals with malignancy-related bone disease in terms of any adverse event. However, the evidence on the odds of experiencing osteonecrosis of the jaw among zoledronic acid over other bisphosphonates is inconclusive. **Evidence considered by the WHO** ***Efficacy Outcomes*** **A. Systematic Reviews** Palmieri et al (2013) *[Mixed-treatment meta-analysis of 17 RCTs]* *Population: Metastatic breast and prostate cancer and multiple myeloma* *Interventions: Zoledronic acid (4mg)* *Comparator: Other bisphosphonates and placebo* *Quality of evidence: Not performed* ● **Reduction in the Risk of Skeletal-Related Events (SRE):** Zoledronic acid seems to be the most efficacious bisphosphonate for reducing the risk of skeletal-related events (SREs) in patients with cancer of the breast or prostate and those with multiple myeloma.	*(PROS-14; PROS-I 2 of 3)*: In patients with castration-resistant prostate cancer who have bone metastases, denosumab and ***zoledronic acid*** have been shown to prevent disease-related skeletal complications, which include fracture, spinal cord compression, or the need for surgery or RT to bone. ● When compared to Zoledronic acid, denosumab was shown to be superior in the prevention of skeletal-related events ● Zoledronic acid is NOT recommended for patients with creatinine clearance of <20 mL/min. *Grade of Recommendation (PROS-14; PROS-I 2 of 3):* ● **Category 2A**: *based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate* ***Note: No local CPG found for zoledronic acid**

	○ **Breast Cancer:** ■ Oral ibandronate was deemed inferior to zoledronic acid in reducing the overall risk of skeletal events (rate ratio for SREs 1.148, 95% CI 0.967–1.362). ■ Zoledronic acid was associated with the lowest annual incidence rate of SREs (1.60) among the bisphosphonates included in the analysis, followed by ibandronate (oral, 1.67; i.v., 1.70), pamidronic acid (2.07), and clodronate (2.29). ○ **Prostate Cancer:** Zoledronic acid was associated with the lowest annual incidence rate of SREs (1.60; excess SRE rate: none specified) among the bisphosphonates included in the analysis, followed by 1.11 for clodronate (excess SRE rate: 35%), and 1.41 for pamidronic acid (excess SRE rate: 71%). ○ **Multiple Myeloma:** Zoledronic acid was associated with the lowest annual incidence rate of SREs (1.60; excess SRE rate: none specified) among the bisphosphonates included in the analysis, followed by 1.64 for pamidronic acid (excess SRE rate: 15%), 1.90 for clodronate (excess SRE rate: 33%), and 2.49 for i.v. ibandronate (excess SRE rate: 75%). Wong & Wiffen (2002) *[Systematic review of 30 RCTs]* *Interventions: Bisphosphonates* *Comparator: Placebo* *Quality of evidence: Not performed* ● **Best pain response in 12 weeks** ○ The odds of having the best pain response in 12 weeks were significantly higher (OR: 2.37, 95% CI 1.61 to 3.5) among those in the bisphosphonates group than those in the placebo group. ● **Proportion of patients with reduction in analgesics:** The odds of reducing the use of analgesics is significantly higher among those in the	

	bisphosphonates groups than those in the placebo group. ○ At week 4: OR 2.81 (95% CI: 1.24 to 6.38) ○ At week 12: OR 2.37 (95% CI: 1.1 to 5.12]) ● **Other pain and analgesic outcome measures** ○ Pain relief by primary disease site ■ Among patients with ***breast cancer,*** the odds of attaining pain relief is 1.83 times higher [95% CI 1.11 to 3.04] among those in the bisphosphonates arm than those in the placebo arm ■ Among patients with ***prostate cancer,*** there is no significant association of attaining pain relief between the bisphosphonates arm and the placebo arm (OR: 1.81, 95% CI: 0.82 to 4.02) ■ Among patients with ***any primary site cancer***, the odds of attaining pain relief is 8.47 times higher [95% CI 2.69 to 27] among those in the bisphosphonates arm than those in the placebo arm. ■ Among patients with ***multiple myeloma***, the odds of attaining pain relief is 3.51 times higher [95% CI 1.08 to 11.4] among those in the bisphosphonates arm than those in the placebo arm, based on only one (1) RCT. Wong et al (2012) *[Systematic review]* *Population: Breast cancer patients with bone metastases* *Interventions: Bisphosphonates* *Comparator: No bisphosphonates/placebo* *Quality of evidence: Not performed* ● **Global quality of life** ○ Among breast cancer individuals with bone metastases, no significant difference in global quality of life was found between zoledronic acid and IV pamidronic acid (***no statistical measure provided in the SR***) in one non-inferiority study.	

	○ The risk of SRE was significantly reduced by 10% - 40% among those in the bisphosphonate group than in the control group in 8 out of 8 studies *(2 studies did not report the test of significance*; RR 0.6 to 0.9). (*Note: zoledronic acid was analyzed together with the other bisphosphonates for this outcome*). Mhaskar et al (2012) *[Network meta-analysis]* *Population: patients with multiple myeloma* *Interventions: Bisphosphonates - zoledronic acid, 4 mg (15-minute infusion), pamidronic acid Disodium, 90 mg (2–3 hours), Ibandronate* *Comparator: Control arm - no therapy, placebo, or other bisphosphonates* ● **Reduction in Vertebral Fractures:** Based on moderate quality of evidence, bisphosphonates significantly reduced the risk of vertebral fracture by 26% (RR 0.74, 95% CI 0.62 to 0.89; I^2 = 7%) compared to the control arm ● **Reduction of Non-vertebral Fractures:** Based on moderate quality of evidence, bisphosphonates had no statistically significant difference with the control arm in terms of the risk of non-vertebral fractures (Risk ratio [RR] = 1.03, 95% CI: 0.68 to 1.56) ● **Proportion of SRE:** Based on moderate quality evidence, bisphosphonates significantly reduced the risk of SREs by 20% (RR 0.80, 95% CI 0.72 to 0.89) compared to the control arm. **B. Randomized Clinical Trials** Barrett et al (2014) *[Phase III RCT]* *Population: Breast cancer patients with bone metastases (N=1404)* *Intervention: Ibandronate (n=705)* *Comparator: zoledronic acid (n=699)* ● **Reduction in risk of SRE** ○ There is no significant association of skeletal-related events (Annual Rate Ratio: 1.148 ,95% CI 0.967–1.362) between ibandronic acid (annual rate: 0.499[95% CI: 45.4–54.9] per person-year) and zoledronic acid (annual rate: 0.435 [95% CI:	

	0·393–0·480] per person year). Kohno et al (2005) *[Phase III RCT]* *Population: breast cancer patients with bone metastases (N=228)* *Interventions: Zoledronic acid (n=114)* *Comparator: No bisphosphonates / placebo (n=114)* ● **Time to First SRE:** Zoledronic acid significantly delayed time-to-first SRE (median not reached in 364 days; Cox regression; P = .007) ● **Reduction in the Risk of SRE:** Zoledronic acid reduced the risk of SREs by 41% (risk ratio = 0.59; P = .019) compared with placebo. Body et al (2007) *[Phase III RCT]* *Population: breast cancer patients with bone metastases (N = 275)* *Intervention: Ibandronate (n = 137)* *Comparator: Zoledronic acid (n = 138)* ● **Reduction in cross-linked C-terminal telopeptide of type I collagen (CTX) leading to Skeletal-Related Events:** The reductions in CTX caused by ibandronate and zoledronic acid were *considered statistically equivalent* for either serum or urinary levels of this bone marker (P < 0.001 for all one-sided noninferiority Wilcoxon tests; the 90% Hodges–Lehman CIs for the difference were -1.7% to 3.0%, and were completely within the noninferiority margin of 15%). Saad et al (2002) *[RCT]* *Population: prostate cancer patients with bone metastases (N = 422)* *Intervention: Zoledronic acid (n = 214)* *Comparator: Placebo (n = 208)* ● **Proportion of SRE:** At least one skeletal-related event occurred in 44.2%of patients who received placebo and 33.2% of patients with prostate cancer who received zoledronic acid at 4 mg (difference = −11.0%, 95% CI = −20.3% to −1.8%; P = .021) and zoledronic acid at 8/4 mg (38.5%; difference versus placebo = −5.8%, 95% CI = −15.1% to 3.6%; *P* = .222).	

	• **Time to First SRE:** Median time to first SRE was 321 days for patients who received placebo, but was not reached for patients who received zoledronic acid at 4 mg (*P* = .011 versus placebo), and was 363 days for those who received zoledronic acid at 8/4 mg (*P* = 0.491 versus placebo). Rosen et al (2004) *[Phase III RCT]* *Population: patients with bone metastases secondary to lung carcinoma and other solid tumors (except carcinomas of the breast and prostate) (N=773)* *Interventions: Zoledronic acid (n=257)* *Comparator: No bisphosphonates / placebo (n=250)* • **Overall Risk for SREs:** The hazard of developing an SRE is 31.7% lower in the 4-mg zoledronic acid group (HR= 0.693; *P* = 0.003) as compared with the placebo group. Rosen et al (2001) [RCT] Rosen et al (2003) *[Phase III RCT]* *Population: patients with bone lesions secondary to advanced breast carcinoma or multiple myeloma (N=1,648)* *Interventions: zoledronic acid (4 mg) (n=564)* *Comparator: pamidronic acid (90 mg) (n=558)* • **Incidence of skeletal complications:** Zoledronic acid (4mg) reduced the mean annual incidence of skeletal complications (skeletal morbidity rate) by 25% compared with pamidronic acid (1.04 events per year for 4 mg zoledronic acid vs. 1.39 events per year for pamidronic acid; P=0.084). • **Risk of developing any skeletal complications:** Zoledronic acid (4 mg) significantly reduced the risk of developing skeletal complications by 15.9% as compared to pamidronic acid in the overall population(risk ratio, 0.841; P=0.030). ○ **for patients with breast carcinoma:** Zoledronic acid significantly reduced the risk of developing any skeletal complications by 20.1% (RR=0.799; 95% CI, 0.657–0.972, P=0.025) as compared to pamidronic acid among patients with breast carcinoma.	

	■ For breast cancer patients receiving chemotherapy: The risk of developing skeletal complications was comparable between the zoledronic arm and pamidronic acid arm (RR=0.955; *P* = 0.749) ■ For breast cancer patients receiving hormonal therapy: Zoledronic acid significantly reduced the risk of developing skeletal complications by 30.7% (RR=0.693; 95% CI, 0.527–0.911; *P* = 0.009) as compared to the pamidronic acid arm. ○ **for patients with multiple myeloma:** The risk of developing skeletal complications was comparable between the zoledronic arm and pamidronic acid arm. (RR=0.932; *P* = 0.593). Morgan et al (2010) *[RCT]* *Population: Multiple myeloma patients (N = 1,960)* *Intervention: Zoledronic acid (n = 981)* *Comparator: Oral clodronic acid (n = 979)* ● **Overall Survival:** Zoledronic acid extended median overall survival by ***5.5 months*** (50 months, IQR 21.0 to not reached vs 44.5 months, IQR 16.5 to not reached; p=0.04). **C. Observational Studies** ***No observational studies cited for efficacy outcomes*** ***Safety Outcomes:*** **A. Systematic Reviews** ***No SRs cited for safety outcomes*** **B. Randomized Clinical Trials** ***No RCTs cited for safety outcomes***	

	C. Observational Studies Saad et al (2012) *[prospective analysis]* *Population: Cancer patients with bone metastasis and osteonecrosis of the jaw (N = 89)* *Interventions: I.V. zoledronic acid (4 mg) (n = 37)* *Comparator: S.C. Denosumab (120 mg) (n = 52)* ● **Osteonecrosis of the Jaw (ONJ):** Among patients with positively adjudicated ONJ, 37 (1.3%) were in the zoledronic acid group and 52 (1.8%) were in the denosumab group. There is ***no significant difference*** between treatment groups (p = 0.13). Edwards et al (2016) *[retrospective analysis]* *Population: Cancer patients with atypical femur fractures (N=74)* *Interventions: Bisphosphonate therapy (zoledronic acid or ibandronate) in cancer patients (n = 23)* *Comparator: alendronate pamidronic acid (PAM) among other bisphosphonates, oncology, and cancer therapy (n = 51)* ● **Osteonecrosis of the jaw (ONJ):** There is ***no significant difference*** in the odds of experiencing ONJ between the bisphosphonates arm than the control arm (OR 1.32, 95% CI 0.12 to 14.41).	

II. Costing analysis

For the costing analysis, the direct medical cost items included were the: (1) cost of the drug regimen; and the (2) cost of other direct medical cost items *[cost of serology and supplies]* at the third-party payer/government perspective for one year. As for the comparators, the HTAC agreed to use bisphosphonates with FDA-released CPRs related to malignancy-related bone diseases; hence the use of pamidronic acid. From these, the final costing outputs were the total cost of treatment regimen per patient and for all expected users. Regimens and resource utilization were consulted with the Philippine Society on Medical Oncology (PSMO). With regard to the duration of treatment, PSMO provided the time of administration while the treatment duration was based on MIMS (2022). For purposes of costing, we assumed one (1) year of treatment using each drug.

The total cost of treatment which includes the drug regimen and administration per patient per year for zoledronic acid and pamidronic acid are **₱38,161.50** and **₱148,921.50**, respectively.

The total number of users were given by the PSMO, using the projected new cases of individuals with bone metastases based on the GLOBOCAN data for the Philippines. From this, the computed total incurred costs for the government are as follows: ₱0.31 B for zoledronic acid and ₱1.22 B for pamidronic acid. The cost savings accrued when zoledronic acid is used over pamidronic acid is ₱0.91 B.

The unit costs of zoledronic acid and pamidronic acid were derived from the price offered by local distributors (*as mentioned by PSMO, United Laboratories Inc. for zoledronic acid; and Ambica International for pamidronic acid*). The table below indicates the unit costs and assumptions used in the analysis. ***Zoledronic acid has cheaper associated medical costs*** than pamidronic acid in treating individuals with malignancy-related bone disease.

Parameter	INTERVENTION Zoledronic Acid	COMPARATOR Pamidronic Acid	Remarks / Assumptions	Reference
Part 1: Cost of drug regimen				
A=Unit cost of drug	₱2,400.00	₱10,920		PSMO Letter
B=Frequency of use per cycle	1	1		PSMO Letter; MIMS (2022)
C=Duration of drug regimen	13	13	For one year of treatment	
A*B*C=Total cost of drug regimen (D)	₱31,200.00	₱141,960.00		
Part 2: Other costs (e.g., cost of monitoring, cost of AE management)				
Other cost item 1: Serum Creatinine				
Unit Cost of serum creatinine	₱250.00	₱250.00	Used only once, prior to the initiation of treatment	PGH Schedule of Fees (2020)
Number of tests needed per year	1	1		Official PSMO Correspondence
Sub-Total	₱250.00	₱250.00		
Other cost item 2: Ionized Calcium				
Unit Cost of Ionized Calcium	₱545.00	₱545.00	Used only once, prior to the initiation of treatment	PGH Schedule of Fees (2020)
Number of tests needed per year	1	1		Official PSMO Correspondence
Sub-Total	₱545.00	₱545.00		
Other cost item 3: Serum Albumin				
Unit Cost of Serum Albumin	₱310.00	₱310.00	Used only once, prior to the initiation of treatment	PGH Schedule of Fees (2020)
Number of tests needed per year	1	1		Official PSMO Correspondence
Sub-Total	₱310.00	₱310.00		

Other cost item 4: Cost of Supplies				
Unit Cost of Macroset	₱36.00	₱36.00	Zoledronic acid and pamidronic acid are administered via the IV route. Supplies are used once per cycle	Corazon Locsin Montelibano Memorial Regional Hospital (n.d.)
Unit Cost of IV Cannula	₱45.50	₱45.50		
Unit Cost of IV Starter Pack	₱70.00	₱70.00		
Unit Cost of Volumetric Chamber	₱250.00	₱250.00		
Unit Cost of NSS 100 mL	₱49.00	₱49.00		DPRI (2021)
Sub-Total for ONE Cycle	₱450.50	₱450.50		
No. of cycles	13	13	For one year of treatment	
Sub-Total for ALL Cycles	₱5,856.50	₱5,856.50		
Total Associated Costs per Individual				
TOTAL (E)	₱6,961.50	₱6,961.50	For one year of treatment	
Total Cost of Treatment Regimen for all users per year				
Total Cost of Treatment Regimen per patient (F=D+E)	₱38,161.50	₱148,921.50	For one year of treatment	
Incremental cost of treatment		-₱96,507.50		
Total Cost of Treatment Regimen for all users per year				
Expected number of patients who will use the drug (G)	8,214	8,214		
Total Cost of Treatment Regimen for all users (H=F*G)	₱313,458,561.00	₱1,223,241,201.00	For one year of treatment	
in billions	₱0.31	₱1.22		
Incremental cost of treatment (in billions)		-₱0.91		

III. Budget Impact Analysis

Zoledronic Acid as Treatment for Malignancy-Related Bone Disease

The budget impact analysis over a 3-year horizon for zoledronic acid compared to pamidronic acid was performed using data from reputable sources. The prevalence and incidence of malignancy-related bone disease in the Philippines for 2022 to 2024 were provided by the PSMO (*as they derived from WHO GLOBOCAN estimates*). The time horizon used for this BIA is for a treatment of one (1) year. The estimated total cost of treatment with zoledronic acid and pamidronic acid for 3 years is ₱0.97 B and ₱3.79 B respectively. The cost savings accrued when zoledronic acid is used over pamidronic acid is ₱2.82. Overall, ***zoledronic acid is cheaper*** than pamidronic acid.

Table XX. Budget impact of zoledronic acid and pamidronic acid (in billions)

Parameter/Year	Projected No. of Individuals Taking zoledronic acid, or pamidronic acid	INTERVENTION	COMPARATOR	Remarks	References
		Zoledronic Acid	Pamidronic Acid		
Cost per patient per year		₱38,161.50	₱148,921.50	Projected new cases of individuals with bone metastases based on GLOBOCAN data for the Philippines	N/A
2022	8,214	₱0.31	₱1.22		Official PSMO Correspondence
2023	8,485	₱0.32	₱1.26		
2024	8,765	₱0.33	₱1.31		
TOTAL COST FOR 3 YEARS		₱0.97	₱3.79		N/A
Incremental Cost of Treatment for all users for 3 years			-₱2.82		

IV. Summary of cost-effectiveness evidence and recommendations of the WHO

WHO approved indication in the EML	Remarks on Cost-effectiveness from WHO Review for Essential Medicines listing
Malignancy-related bone disease	In 2015, the MSF International Medical Products Price Guide reported a median buyer price for zoledronic acid 4 mg/5 mL vial of US$ 23.45 in 2015. ***No studies were cited by the WHO for the cost-effectiveness of zoledronic acid.***

Using clinical outcomes from Wong et al, (2012)	***Zoledronic Acid***	***Pamidronic Acid***
Number Needed to Treat	11	11
Cost per Patient	₱419,776.50	₱1,638,136.50
Interpretation	**₱419,776.50** would be needed to administer ZA to **11** individuals with MRBD to prevent 1 SRE	**₱1,638,136.50** would be needed to administer PA to **11** individuals with MRBD to prevent 1 SRE

Using clinical outcomes from Rosen et al, (2004) and Mhaskar et al (2012)	***Zoledronic Acid***	***Pamidronic Acid***
Number Needed to Treat	12	12
Cost per Patient	₱457,938.00	₱1,787,058.00
Interpretation	**₱457,938.00** would be needed to administer ZA to **12** individuals with MRBD to prevent 1 SRE	**₱1,787,058.00** would be needed to administer PA to **12** individuals with MRBD to prevent 1 SRE

V. Recommendations

The **HTAC recommends the government financing of zoledronic acid** (4mg/5mL concentrated solution for IV infusion) for the treatment of patients with malignancy-related bone disease **through its inclusion in the Philippine National Formulary (PNF)**. Currently, there are no PNF-listed drugs indicated for malignancy-related bone diseases. The basis for the HTAC recommendations are as follows:

1. Zoledronic acid has comparable to better efficacy and safety profile compared to other bisphosphonates in terms of reducing the overall risk of skeletal-related events, pain, and any adverse event.

2. Based on the costing analysis, the total cost of treatment for zoledronic acid is cheaper than pamidronic acid. The government will need ₱0.31 billion to implement zoledronic acid among its potential total users.

Drug	Total cost of treatment	Total incurred costs for the government	3-year estimated budget impact
Zoledronic Acid	₱38,161.50	₱0.31 billion	₱0.97 billion
Pamidronic Acid	₱148,921.50	₱1.22 billion	₱3.79 billion

3. Using the clinical outcomes from previous studies (e.g., Wong et al [2012], Rosen et al [2004] and Mhaskar et al [2012]), about ₱419,776.50 to ₱457,938.00 would be needed to administer zoledronic acid to 11-12 individuals with malignancy-related bone disease for the prevention of one incidence of skeletal-related event.

   However, there is ***insufficient evidence*** to compare the cost-effectiveness of zoledronic acid with pamidronic acid as the current available evidence is not applicable to the Philippine setting. Of note, zoledronic acid is cheaper than pamidronic acid, has similar efficacy, and is thus likely to be more cost-effective over the comparator.