Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

MEDICINES RECOMMENDED FOR INCLUSION IN THE PHILIPPINE NATIONAL FORMULARY (PNF)

As of 21 December 2021, the Health Technology Assessment Council (HTAC) has finished the assessment and deliberation for the minor inclusion (i.e., additional strength, immediate packaging, net content) of **sambong 250mg tablets as anti-urolithiasis** in the Philippine National Formulary (PNF).

The HTAC hereby makes public the **preliminary recommendation for the inclusion of sambong 250mg tablets** in the PNF. The evidentiary basis used for the said recommendation is shown in the annex of this advisory.

All comments, inputs and/or appeals may be submitted until **04 January 2022** for consideration of the HTAC through email at hta@doh.gov.ph.

Should you wish to submit hard copies of your submissions, you may drop them off at the 4th floor, Philippine Blood Disease and Transfusion Center, Lung Center Compound, Quezon Avenue, Quezon Avenue, Quezon City. Appeals shall no longer be entertained after the prescribed deadline.

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Annex A. General Information on the Proponent and Proposed Inclusion

GENERIC NAME	Blumea balsamifera L. (Sambong Leaf)
BRAND NAME (if any)	PITAHC Sambong
THERAPEUTIC CLASSIFICATION	Herbal Medicine (Anti-urolithiasis/Diuretic)
FOR LISTED MEDICINES:	
• **Current Dosage Strength**	500 mg tablet
• **Proposed Dosage Strength**	250 mg tablet
• **Current Net Content**	Strip Foil x 10's (box of 60's)
• **Proposed Net Content**	Strip Foil x 10's (box of 100's)
• **Current Immediate Packaging**	N/A
• **Proposed Immediate Packaging**	N/A
MANUFACTURER	PITAHC Tacloban Herbal Processing Plant
IMPORTER/TRADER	N/A
DISTRIBUTOR	PITAHC

Annex B. Summary of Evidence Reviewed

The **new dosage and net content** of the medicine:	**Yes**	**No**	**Remarks/Evidence**
1. Has good quality	✓		Sambong 250mg tablet has a Certificate of Product Registration with the Philippine Food and Drug Administration (FDA) valid until 12 July 2026, assuring the public of its quality.
2. Has proven safety based on sound evidence	✓		1. The active FDA CPR valid until July 2026 certifies for the safety of the product. (see CPR below) 2. The *Sambong* 500mg tablet is currently included in the

			Philippine National Drug Formulary (8th edition) which establishes the recognition of the product's safety by the Department of Health. An equivalent dosing is employed for this product. 3. Based on a recent systematic review of Tolosa et al., 2020, there were no serious adverse events associated with the use of the product. Mild epigastric pain and tinnitus were the adverse events reported in the included studies. (*see clinical evidence below*)
3. Has proven efficacy for the stated indication based on sound evidence	✓		1. The active FDA CPR valid until July 2026 certifies for the efficacy of the product. (see CPR below) 2. The *Sambong* 500mg tablet is currently included in the Philippine National Drug Formulary (8th edition) which establishes the recognition of the product's efficacy as a diuretic and an anti-urolithiasis by the Department of Health. An equivalent dosing is employed for this product. 3. Based on the systematic review of Tolosa et al2020, this drug is effective in treating patients with urolithiasis by radiographic evidence of a decrease in size and/or the number of stones, the passage of stone/s and/or disappearance or reduction of signs and symptoms. (*see clinical evidence below*)
4. Has favorable cost-effectiveness analysis	✓		For the same dosing regimen, using 250 mg tablets incurs a lower cost than using the 500 mg tablet as an anti-urolithiasis. Please see the costing table (*Annex D*) below.
5. Other considerations	✓		Using 250 mg tablets is a more practical and affordable option for pediatric patients (7-12 years old) or patients with urinary stones less than 5 mm.

Annex C. Clinical Evidence

One systematic review examining the efficacy and safety of Blumea balsamifera (L.) DC (NIRPROMP Tablet) for the treatment of urinary tract stones was reviewed for this minor inclusion (Tolosa et al., 2020). The review concluded that sambong is an effective treatment for patients with urolithiasis. Results show that there was a decrease in the size and number of stones, increased passage/disappearance of stones, and a reduction of signs and symptoms with no serious adverse events in the intervention arm compared to placebo.

The following tables summarize the key findings from the review and the characteristics of included studies.

Table 1. Summary of Findings from the Systematic Review of Tolosa, et al., 2020

	No. of studies	No. of events over total population [n/N]		Effect Measure	Quality of Evidence
		Sambong tablet	Placebo		
Efficacy outcomes					
Radiographic evidence of decrease in size or number of stone	2 studies *(De Leon, 1990 and NIRPROMP, 1994)*	14 / 22 (63.64%)	1 / 19 (5.26%)	Odds Ratio: 23.45 (95%CI: 3.37 to 163.19)	⨁⨁⨀⨀ Low
Increase or complete passage of stone/s	2 studies *(De Leon, 1990 and NIRPROMP, 1994)*	17 / 23 (73.91%)	1 / 19 (5.26%)	Odds Ratio: 38.04 (95%CI: 5.11 to 283.40)	⨁⨁⨀⨀ Low
Disappearance or reduction of signs and symptoms	2 studies *(De Leon, 1990 and NIRPROMP, 1994)*	18 / 23 (78.26%)	7 / 19 (36.84%)	Odds Ratio: 7.48 (95%CI: 1.67 to 33.48)	⨁⨁⨀⨀ Low
Safety outcomes					
Epigastric pain	1 study *(De Leon, 1990)*	2 / 23 (8.33%)	0 / 23 (0.00%)	*not reported*	⨁⨀⨀⨀ Very Low
Tinnitus	1 study *(De Leon, 1990)*	0 / 23 (0.00%)	2 / 23 (9.09%)	*not reported*	⨁⨀⨀⨀ Very Low

Table 2. Characteristics of Included Studies by Tolosa et al, 2020

Author, Year	Study Design	Population	Intervention	Comparator	Outcome	Overall Risk of Bias (RoB) *Note: The overall ROB Rating of the study was based on the reported ROB per domain by Tolosa et al*
Bernaldo, 2009	RCT (Open label)	(N=31) >19 years old with non obstructing stones regardless of size Exclusion: Patients with Chromium chloride <30 ml/min, on thiazide diuretics, hyperkalemia >5.6, hypocalcemia	● Sambong (500 mg 2x/day for at least 2 days) ● Potassium Citrate 20% solution 10 mL 3x/day for 2 months Follow-up: at 1 month, 2 months and 3 months.	Placebo	Disappearance of stone Decrease in size of stone	*Random sequence generation (selection bias):* Low risk *Allocation concealment (selection bias):* High risk *Blinding of participants and personnel (performance bias):* Low risk *Blinding of outcome assessment (detection bias):* Low risk *Incomplete outcome data (attrition bias):* Low risk *Selective reporting (reporting bias):* Low risk *Other bias:* Unclear risk *Overall:* **High risk**

De Leon, 1990	RCT (Double-blinded)	(N=25) 15-60 y/o with radiographic evidence of urinary tract stones with good renal function Exclusion: Patients with chronic renal disease, gout, asthma, CHF class III, uncontrolled DM, blood dyscrasia, no diuretics, allopurinol, acetazolamide or diuretics within 2 weeks	Sambong tablet (dosing not indicated) Baseline labs- CBC, FBS, BUN, creatinine, electrolytes, Uric Acid, Calcium, 24-h urine collection	Placebo	Decrease in size or number of stones Complete passage of stone and disappearance of signs and symptoms Increased passage of stones and disappearance or reduction of signs and symptoms Complete cure / partial cure Epigastric pain episode Tinnitus.	*Random sequence generation (selection bias):* Low risk *Allocation concealment (selection bias):* High risk *Blinding of participants and personnel (performance bias):* Low risk *Blinding of outcome assessment (detection bias):* Low risk *Incomplete outcome data (attrition bias):* Unclear risk *Selective reporting (reporting bias):* Low risk *Other bias:* Unclear risk *Overall:* **High risk**
NIRPROMP, 1994	RCT (Double-blinded)	(N=19) 15-60 y/o with urinary tract stones >5 mm on excretory urogram or renal ultrasound with good renal function. Exclusion: nephrocalcinosis, staghorn calculi, and bladder outlet obstruction,	Sambong tablet 40 mg/kg/day Baseline labs- CBC, FBS, BUN, Creatinine, electrolytes, UA, Calcium, 24-h urine collection instructed to eat their usual diet, increase liquids to 3 liters per day	Placebo	radiographic evidence of decrease in size or number of stones Complete passage of stone and disappearance of signs and symptoms Increased passage of stones and disappearance	*Random sequence generation (selection bias):* Low risk *Allocation concealment (selection bias):* High risk *Blinding of participants and personnel (performance bias):* High risk *Blinding of outcome assessment (detection bias):* High risk *Incomplete outcome data (attrition bias):* Low risk *Selective reporting (reporting bias):* Low risk *Other bias:* Unclear risk *Overall:* **High risk**

		chronic renal disease, gout, asthma, CHF class III, uncontrolled DM, blood dyscrasias; no diuretics, allopurinol, acetazolamide, or diuretics within 2 weeks	Follow-up: day 4, day 7, week 2 and week 4		or reduction of signs and symptoms Complete cure / partial cure	
Vergara, (Unpublished)	RCT (Open label)	(N= 50 patients in the intervention) (N=50 patients in the control) Adults with distal 3rd ureterolithiasis with calculi measuring 6-10 mm; normal serum creatinine	Sambong + Hydration: 2 500 mg tablets 3x/day with Hydration of 2.5 L/day Follow up: 16 weeks	Hydration Only: 2.5 L/day	Average and spontaneous stone passage	*Random sequence generation (selection bias):* Low risk *Allocation concealment (selection bias):* High risk *Blinding of participants and personnel (performance bias):* High risk *Blinding of outcome assessment (detection bias):* Unclear risk *Incomplete outcome data (attrition bias):* Low risk *Selective reporting (reporting bias):* Low risk *Other bias:* Unclear risk *Overall:* **High risk**

Annex D. Costing table for Sambong 250mg Tablet vs Sambong 500mg Tablet as an *Anti-urolithiasis*

PARAMETER*	PROPOSED INCLUSION *Sambong 250mg Tablet*	CURRENTLY LISTED IN THE PNF *Sambong 500mg Tablet*	References
COST PER DOSAGE UNIT (in PhP) [A]	PHP 1.80 *[Market Survey, PITAHC]*	PHP 5.25 *[Drug Price Reference Index, 2021]*	Market Survey, PITAHC DPRI, 2021
NUMBER OF DOSAGE UNITS PER UNIT COURSE [B]	**40mg/kg/day in 3 divided doses for 2 weeks then decrease to 20mg/kg/day in 2-3 divided doses until 6 weeks of treatment (week 3-6)** *Calculation for 60-kg body weight:* For 2 weeks: 2,400 mg/day in 3 divided doses per day - 2,400 mg/day / 250mg = 9.6 tabs per day - 10 tablets per day: 4 tablets in the morning (qam) + 4 tablets at noon + 2 tablets at night (qpm) - 10 tablets/day x 14 days = **140 tablets** For the next 4 weeks: 1,200 mg/day in 2-3 divided doses per day - 1,200 mg/day / 250mg = 4.8 tabs per day - 5 tablets per day: 2 tablets in the morning (qam) + 2 tablets at noon + 1 tablets at night (qpm)	**40mg/kg/day in3 divided doses for 2 weeks then decrease to 20mg/kg/day in 2-3 divided doses until 6 weeks of treatment (week 3-6)** *Calculation for 60-kg body weight:* For 2 weeks: 2,400 mg/day in 3 divided doses per day - 2,400 mg/day / 500mg = 4.8 tabs per day - 5 tablets per day: 2 tablets in the morning (qam) + 2 tablets at noon + 1 tablets at night (qpm) - 5 tablets/day x 14 days = **70 tablets** For the next 4 weeks: 1200 mg/day in 2-3 divided doses per day - 1,200 mg/day / 500mg = 2.4 tabs per day - 1 tablet x 3 times a day - 3 tablets per day: 1 tablets in the morning (qam) + 1 tablets at noon + 1 tablets at night (qpm)	*Philippine National Formulary 8th edition, 2019 (PNF)* *Manufacturer's Literature* *MIMS, 2021* *UP- NIRPROMP, 1994 (Extracted Phase III trial for Urinary tract Stones- Sambong Technology Transfer Document)* *NKTI, 2021* *UP- NIRPROMP, 1994 (Sambong Technology Transfer Document)* Philippines Dietary Reference Index, 2018

	- 5 tablets/day x 28 days = **140 tablets** **TOTAL number of 250-mg tablets per treatment regimen: 280 tablets** <u>*Calculation for 30-kg body weight:*</u> For 2 weeks: 1,200 mg/day in 3 divided doses per day - 1,200 mg/day / 250mg = 4.8 tabs per day - 5 tablets per day: 2 tablets in the morning (qam) + 2 tablets at noon + 1 tablets at night (qpm) - 5 tablets/day x 14 days = **70 tablets** For the next 4 weeks: 600 mg/day in 2-3 divided doses per day - 600 mg/day / 250mg = 2.4 tabs per day - 3 tablets per day: 1 tablet in the morning (qam) + 1 tablet at noon + 1 tablet at night (qpm) - 3 tablets/day x 28 days = **84 tablets** **TOTAL number of 250-mg tablets per treatment regimen: 154 tablets**	- 3 tablets/day x 28 days = **84 tablets** **TOTAL number of 500-mg tablets per treatment regimen: 154 tablets** <u>*Calculation for 30-kg body weight:*</u> For 2 weeks: 1,200 mg/day in 3 divided doses per day - 1,200 mg/day / 500mg = 2.4 tabs per day - 1 tablet x 3 times a day - 3 tablets/day x 14 days = **42 tablets** For the next 4 weeks: 600 mg/day in 2-3 divided doses per day - 600 mg/day / 500mg = 1.2 tabs per day - 2 tablets per day: 1 tablet in the morning (qam) + 1 tablet at noon - 2 tablets/day x 28 days = **56 tablets** *Note: Equivalent to **33.33 mg/kg/day** and has exceeded the recommended daily dose (20-25 mg/kg/day); hence the value of the 250mg tablet for more accurate dosing for smaller body weight patients* **TOTAL number of 500-mg tablets per treatment regimen: 98 tablets**	

TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP) [C=AxB]	*Calculation for 60-kg body weight:* 280 tablets x PHP 1.80= **PHP 504.00** *Calculation for 30-kg body weight:* 154 tablets x PHP 1.80= **PHP 277.20**	*Calculation for 60-kg body weight:* 154 tablets x PHP 5.25= **PHP 808.50** *Calculation for 30-kg body weight:* 98 tablets x PHP 5.25= **PHP 514.50**	Drug Price Reference Index, 2021
ADDITIONAL COST PER PATIENT PER TREATMENT COSTS: (in PhP) **a. Implementation costs: (cost of drug administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.)** **b. Intervention costs:**	a. Patients must also drink an additional 3 liters of water per 24 hours to prevent dehydration related to diuretic intake. Normal daily intake of water is 6-8 glasses/day. Reported adverse events include epigastric pain, constipation and flatulence. Support management only. Treatment for epigastric pain: *Aluminum Hydroxide, Magnesium Hydroxide tablet (assuming maximum dose for 6 weeks)* PHP 1.10 per tablet *[DOH Drug Price Reference Index 2021]* x 2 tablets a day x 42 days = PHP 92.40 b. Ultrasound at baseline and every 2 weeks (up to 6 weeks of treatment) on Sambong treatment until complete expulsion of kidney stones. ● KUB (Kidney, Ureters, Bladder) Ultrasound: PHP 230.00 *[PGH Charity rate, 2021]*	a. Patients must also drink an additional 3 liters of water per 24 hours to prevent dehydration related to diuretic intake. Normal daily intake of water is 6-8 glasses/day. Reported adverse events include epigastric pain, constipation and flatulence. Support management only. Treatment for epigastric pain: *Aluminum Hydroxide, Magnesium Hydroxide tablet (assuming maximum dose for 6 weeks)* PHP 1.10 per tablet *[DOH Drug Price Reference Index 2021]* x 2 tablets a day x 42 days = PHP 92.40 b. Ultrasound at baseline and every 2 weeks (up to 6 weeks of treatment) on Sambong treatment until complete expulsion of kidney stones. ● KUB (Kidney, Ureters, Bladder) Ultrasound: PHP 230 *[PGH Charity rate, 2021]*	Tolosa et al., 2020 UP- NIRPROMP, 1994 (Sambong Technology Transfer Document) MIMS, 2021 https://www.mims.com/philippines/drug/info/kremil-s Drug Price Reference Index, 2021 PGH Charity Rates as of June 2021

(management of adverse drug reactions) [D]	• PHP 230.00 x 4 = PHP 920.00 *Calculation for 60-kg body weight:* **TOTAL:** PHP 92.40 + PHP 920.00 = **PHP 1,012.40** *Calculation for 30-kg body weight:* No management needed for epigastric pain in pediatric patients. **TOTAL: PHP 920.00**	• PHP 230.00 X 4 = PHP 920.00 *Calculation for 60-kg body weight:* **TOTAL:** PHP 92.40 + PHP 920.00 = **PHP 1,012.40** *Calculation for 30-kg body weight:* No management needed for epigastric pain in pediatric patients. **TOTAL: PHP 920.00**	
TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) [E=C+D]	*Calculation for 60-kg body weight:* Direct Medication Cost = **PHP 504.00** Other direct medical costs = **PHP 1,012.40** **TOTAL: PHP 1,516.40** *Calculation for 30-kg body weight:* Direct Medication Cost = **PHP 277.20** Other direct medical costs (i.e. ultrasound) = **PHP 920.00** **TOTAL: PHP 1,197.20**	*Calculation for 60-kg body weight:* Direct Medication Cost = **PHP 808.50** Other direct medical costs = **PHP 1,012.40** **TOTAL: PHP 1,820.90** *Calculation for 30-kg body weight:* Direct Medication Cost = **PHP 514.50** Other direct medical costs (i.e. ultrasound) = **PHP 920.00** **TOTAL: PHP 1434.50**	

Price difference on total cost per patient (in Php) (Total cost per patient of currently listed product - Total cost per patient of proposed inclusion)	*For 60-kg body weight:* **Php 304.50** *(Cost savings in using the 250mg tablet)* *For 30-kg body weight:* **Php 237.30** *(Cost savings in using the 250mg tablet)*	