



Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

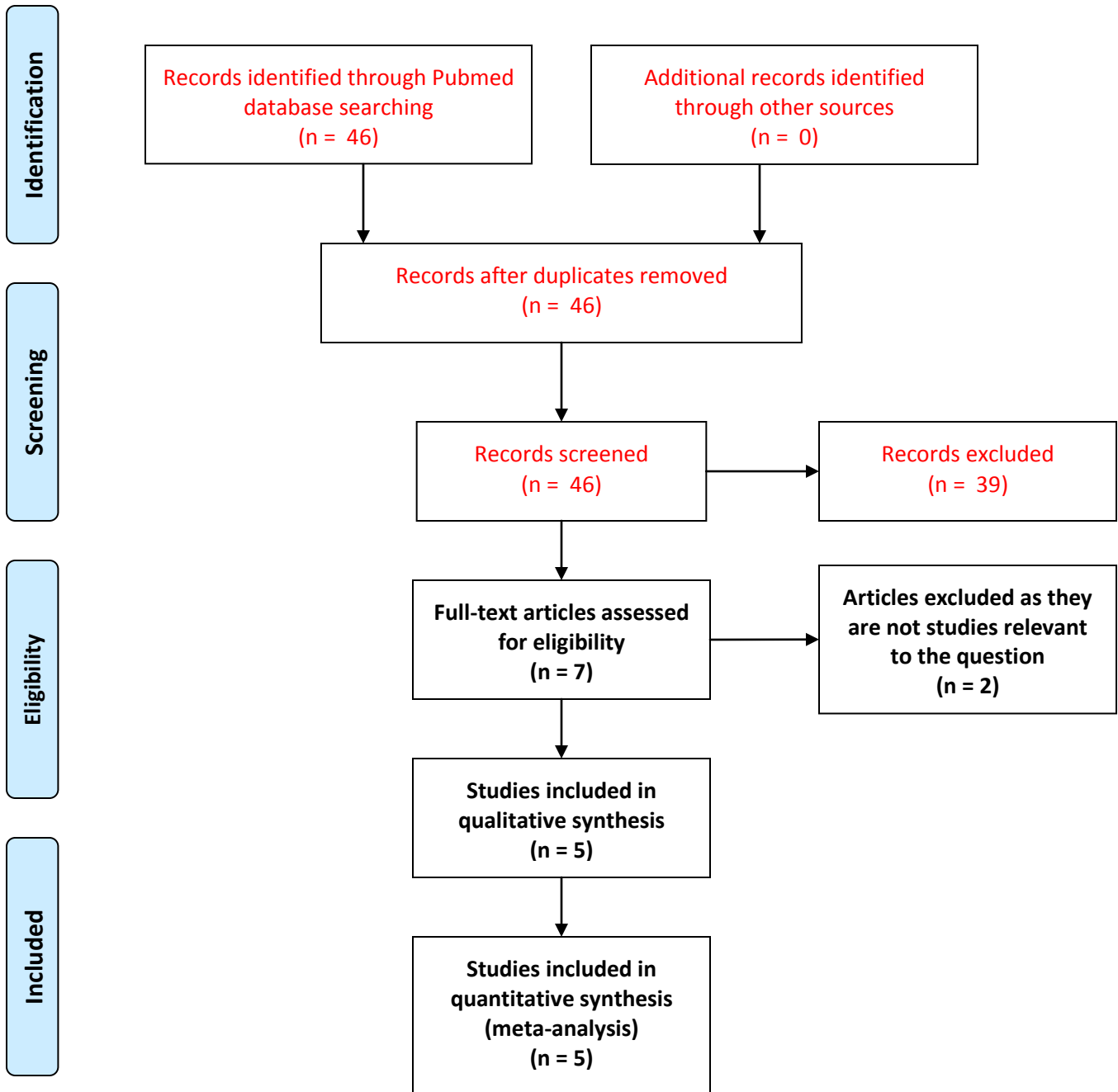
Name of medicine (INN):	Rebamipide 100 mg tablet
Indication:	For the treatment of gastric mucosal lesions (erosion, bleeding, redness and edema) in the following conditions : acute gastritis and acute exacerbation of chronic gastritis ; for the treatment of gastric ulcers.
Date of deliberation:	26 November 2015
Recommendation:	DISAPPROVAL
Clinical evidence:	<p>Among patients with erosive gastritis, rebamipide was shown to be slightly better than sucralfate in terms of improvement in symptoms and endoscopy score finding (0.6 vs 1.05, $p < 0.01$). For patients with iatrogenic and NSAID induced ulcers, rebamipide has similar efficacy compared with H2 blocker (famotidine). Same result was also seen when compared with omeprazole among patients with iatrogenic or <i>H. pylori</i> positive gastric ulcer.</p> <p>In terms of adverse event, there was no significant difference between rebamipide compared to sucralfate, famotidine or omeprazole.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
Cost data:	The total weekly cost of rebamipide is Php 267.12 compared to Php 1,000.16 for sucralfate and Php 72.66 for omeprazole.
Remarks:	Although the evidence review group recommended the inclusion of rebamipide, the Council questioned the use of sucralfate as the basis for the conclusion given that the standard treatment for gastric ulcer are the proton pump inhibitors. It was also noted that if rebamipide will be compared with sucralfate, the former will indeed have favourable results because sucralfate given alone is not effective in the management of gastric ulcer. It was likewise stressed that rebamipide is not considered as first line agent for gastric ulcer and is more expensive that the currently

listed omeprazole. In view of these findings, the Council recommended its disapproval for inclusion.

No appeal for reconsideration was received within the set deadline, thus the recommendation of the Council to disapprove the medicine still remains.

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

PRISMA Table



1) How effective is Rebamipide against other cytoprotective agents (Sucralfae, antacids, etc.) in managing patients with gastric ulcers? 2) How is Rebamipide compared with other cytoprotective agents in terms of safety? 3) What is the cost-effectiveness of Rebamipide versus other cytoprotective agents?

EVIDENCE TABLE 1

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES				GRADE OF EVIDENCE	REMARKS	
					EVENTS	Rebamipide/ experimental		Control			
					(including adverse events)	No. of events *	Total # of patients	No. of events *			Total # of patients
	Du et al. Dig Dis Sci, 2007	RCT	453 patients with chronic erosive gastritis	Rebamipide vs. sucralfate	Improvement in symptom score	3.05		2.84		Computed value from text. Improvement from baseline was significant	
					End of treatment endoscopy score	0.6	SD 0.10	1.05	SD 0.19	p<0.01	
					Adverse event	2 (0.62%)	342	1 (1.03%)	110	NS	
	Yamamoto et al. J Gastroenterol 2006	Clinical trial (match-control)	261 patients with chronic NSAID use	Rebamipide vs. famotidine	Change in Lanza score (H pylori neg)	-0.5		-1.1		Moderate	Higher Lanza score suggested worse clinical findings by endoscopy
					Change in Lanza score (H pylori pos)	0.1		-1.2			
					Adverse drug reaction	10 (15.9%)	63	10 (15.2%)	66		
	Kim et al, J Korean Med Sci, 2010	RCT	63 patients with iatrogenic gastric ulcers	Rebamipide vs. famotidine	No pain during treatment period	17 (65.4%)	26	15 (60.0%)	25		NS
	Takayama et al. World J Gastroenterol, 2013	RCT	90 patients with iatrogenic gastric ulcers	Rebamipide vs. lansoprazole	Healing rates	93.3%	45	90.9%	44		NS
	Song et al. Digestion, 2011	RCT	132 patients with H pylori gastric ulcer	Rebamipide vs. omeprazole	Healing rates (12 wks)	53 (81.5%)	65	52 (82.5%)	63		NS
					Adverse event	26.2%		23.9%			NS

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>Rebamipide 100 mg (Mucoprotec) P 12.72 per tab</p>	<p>¹Sucralfate 1 g tab: P 35.72 ²Omeprazole 40 mg capsule: Php 10.38</p>	<p>*company submission: P 23.04 per 100 mg tab (Mucosta)</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>21 tabs/week</p>	<p>Sucralfate: 28 tabs/week Omeprazole: 7 capsules/week</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>Php 267.12</p>	<p>Sucralfate: Php 1,000.16 Omeprazole: Php 72.66</p>	
<p>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.)</p>			
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p>Php 267.12</p>	<p>Sucralfate: Php 1,000.16 Omeprazole: Php 72.66</p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE</p>			
<p>QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			
<p>DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			

REVIEWERS' RECOMMENDATIONS

Literature Search

- We searched Pubmed last April 2015 using the terms “rebamipide” and limit articles to meta-analysis. The yield was only 2 articles. We repeated the search “rebamipide” and limit to randomized controlled trials. The yield was 44. We reviewed the 46 abstracts and considered 7 for full text retrieval.
- We reviewed the 7 full text and included 5 articles in this review. The following were included:
 - Takayama M(1), Matsui S, Kawasaki M, Asakuma Y, Sakurai T, Kashida H, Kudo M. Efficacy of treatment with rebamipide for endoscopic submucosal dissection-induced ulcers. *World J Gastroenterol.* 2013 Sep 14;19(34):5706-12. doi: 10.3748/wjg.v19.i34.5706.
 - Song KH(1), Lee YC, Fan DM, Ge ZZ, Ji F, Chen MH, Jung HC, Bo J, Lee SW, Kim JH. Healing effects of rebamipide and omeprazole in *Helicobacter pylori*-positive gastric ulcer patients after eradication therapy: a randomized double-blind, multinational, multi-institutional comparative study. *Digestion.* 2011;84(3):221-9. doi: 10.1159/000329353. Epub 2011 Jul 8.
 - Kim YJ(1), Cheon JH, Lee SK, Kim JH, Lee YC. Rebamipide may be comparable to H2 receptor antagonist in healing iatrogenic gastric ulcers created by endoscopic mucosal resection: a prospective randomized pilot study. *J Korean Med Sci.* 2010 Apr;25(4):583-8. doi: 10.3346/jkms.2010.25.4.583. Epub 2010 Mar 19.
 - Du Y(1), Li Z, Zhan X, Chen J, Gao J, Gong Y, Ren J, He L, Zhang Z, Guo X, Wu J, Tian Z, Shi R, Jiang B, Fang D, Li Y. Anti-inflammatory effects of rebamipide according to *Helicobacter pylori* status in patients with chronic erosive gastritis: a randomized sucralfate-controlled multicenter trial in China-STARS study. *Dig Dis Sci.* 2008 Nov;53(11):2886-95. doi: 10.1007/s10620-007-0180-z. Epub 2008 Feb 21.
 - Yamao J(1), Kikuchi E, Matsumoto M, Nakayama M, Ann T, Kojima H, Mitoro A, Yoshida M, Yoshikawa M, Yajima H, Miyauchi Y, Ono H, Akiyama K, Sakurai G, Kinoshita Y, Haruma K, Takakura Y, Fukui H. Assessing the efficacy of famotidine and rebamipide in the treatment of gastric mucosal lesions in patients receiving long-term NSAID therapy (FORCE--famotidine or rebamipide in comparison by endoscopy). *J Gastroenterol.* 2006 Dec;41(12):1178-85. Epub 2007 Feb 6.

Effectiveness/Efficacy

- Among patients with erosive gastritis, rebamipide was shown to be slightly better than sucralfate in terms of improvement in symptoms and endoscopy score finding (0.6 vs 1.05: lower score better).
- Among patients with iatrogenic and NSAID induced ulcers, rebamipide has similar efficacy compared with H2 blocker (famotidine).
- Rebamipide was also shown to have similar efficacy with omeprazole among patients with iatrogenic or H pylori positive gastric ulcer.

Safety

- In terms of adverse event, there was no significant difference between rebamipide compared to sucralfate, famotidine or omeprazole.

Summary of Review

- In summary, we found rebamipide to be slightly better than sucralfate and equally effective with famotidine or omeprazole.

Cost Data (Cost-comparison table)

- In terms of cost, the total weekly cost of rebamipide is Php 267.12 compared to Php 1,000.16 for sucralfate and Php 72.66 for omeprazole.

Final Recommendation of FEC

- Overall we found rebamipide to be more effective than sucralfate and more affordable. We recommend rebamipide to be included in the formulary.

References

1. Xiong J(1), Lai S, Zhang P, Li Q, Wei Y, Yang Y, Wang T, Liu L, Ma X, Chen D. Rebamipide plus proton pump inhibitor versus proton pump inhibitor alone in the treatment of endoscopic submucosal dissection-induced gastric ulcer: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2014 Sep;93(12):e64. doi: 10.1097/MD.000000000000064.
2. Zhang S(1), Qing Q, Bai Y, Mao H, Zhu W, Chen Q, Zhang Y, Chen Y. Rebamipide helps defend against nonsteroidal anti-inflammatory drugs induced gastroenteropathy: a systematic review and meta-analysis. *Dig Dis Sci*. 2013 Jul;58(7):1991-2000. doi: 10.1007/s10620-013-2606-0. Epub 2013 Feb 28.
3. Takayama M(1), Matsui S, Kawasaki M, Asakuma Y, Sakurai T, Kashida H, Kudo M. Efficacy of treatment with rebamipide for endoscopic submucosal dissection-induced ulcers. *World J Gastroenterol*. 2013 Sep 14;19(34):5706-12. doi: 10.3748/wjg.v19.i34.5706.
4. Song KH(1), Lee YC, Fan DM, Ge ZZ, Ji F, Chen MH, Jung HC, Bo J, Lee SW, Kim JH. Healing effects of rebamipide and omeprazole in *Helicobacter pylori*-positive gastric ulcer patients after eradication therapy: a randomized double-blind, multinational, multi-institutional comparative study. *Digestion*. 2011;84(3):221-9. doi: 10.1159/000329353. Epub 2011 Jul 8.
5. Kim YJ(1), Cheon JH, Lee SK, Kim JH, Lee YC. Rebamipide may be comparable to H2 receptor antagonist in healing iatrogenic gastric ulcers created by endoscopic mucosal resection: a prospective randomized pilot study. *J Korean Med Sci*. 2010 Apr;25(4):583-8. doi: 10.3346/jkms.2010.25.4.583. Epub 2010 Mar 19.
6. Du Y(1), Li Z, Zhan X, Chen J, Gao J, Gong Y, Ren J, He L, Zhang Z, Guo X, Wu J, Tian Z, Shi R, Jiang B, Fang D, Li Y. Anti-inflammatory effects of rebamipide according to *Helicobacter pylori* status in patients with chronic erosive gastritis: a randomized sucralfate-controlled multicenter trial in China-STARS study. *Dig Dis Sci*. 2008 Nov;53(11):2886-95. doi: 10.1007/s10620-007-0180-z. Epub 2008 Feb 21.
7. Yamao J(1), Kikuchi E, Matsumoto M, Nakayama M, Ann T, Kojima H, Mitoro A, Yoshida M, Yoshikawa M, Yajima H, Miyauchi Y, Ono H, Akiyama K, Sakurai G, Kinoshita Y, Haruma K, Takakura Y, Fukui H. Assessing the efficacy of famotidine and rebamipide in the treatment of gastric mucosal lesions in patients receiving long-term NSAID therapy (FORCE--famotidine or rebamipide in comparison by endoscopy). *J Gastroenterol*. 2006 Dec;41(12):1178-85. Epub 2007 Feb 6.