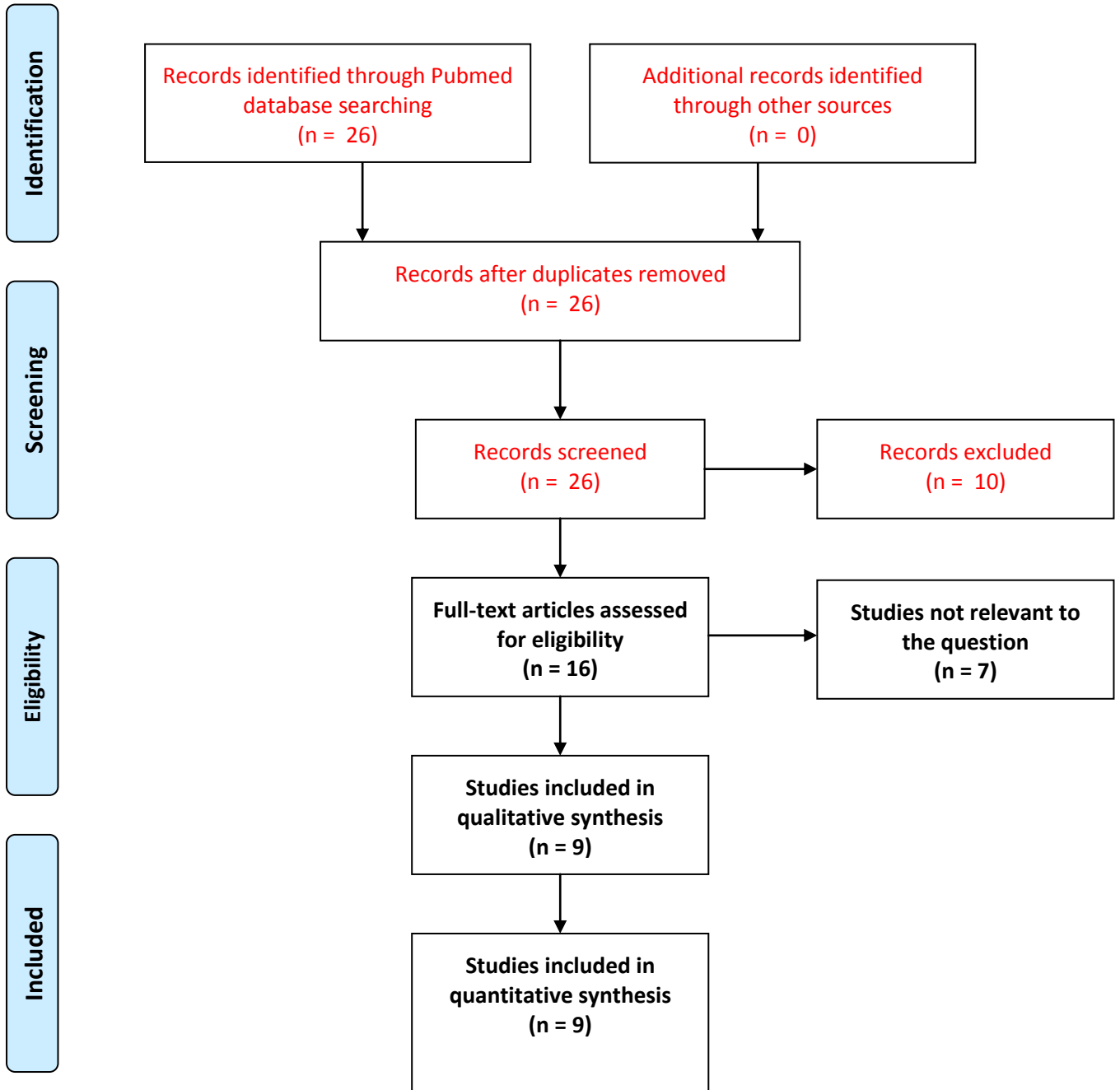




Republic of the Philippines  
Department of Health  
**OFFICE OF THE SECRETARY**

<b>Name of medicine (INN):</b>	<b>Prucalopride (as succinate) 1 mg and 2 mg film coated tablet</b>
<b>Indication:</b>	Used for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.
<b>Date of deliberation:</b>	24 July 2015
<b>Recommendation:</b>	<b>DISAPPROVAL</b>
<b>Clinical evidence:</b>	<p>The review involved 11 randomized controlled trials among patients with chronic constipation. Among those uncontrolled by laxatives, prucalopride 2 mg had more spontaneous complete bowel movement (BM) (19.5% vs. 9.6%; <math>p &lt; 0.01</math>) than placebo. It also had better patient rating as effective (34.6% vs. 18.7%; <math>p &lt; 0.01</math>) (Tack et al., 2008). Even among patients with severe chronic constipation, prucalopride 2mg was shown to have more spontaneous complete bowel movement than placebo (30.9% vs. 12.0%; <math>p &lt; 0.01</math>) (Camilleri et al, 2008). This was also confirmed by another study of Quigley et al in 2008. Among the elderly with chronic constipation, prucalopride 2 mg was shown to be more effective than placebo (1.9 vs 0.6; <math>p &lt; 0.05</math>) in terms of a change in BM from baseline. Similar effectiveness findings were observed among Asians. The efficacy of prucalopride however has not been seen in children.</p> <p>In terms of safety, prucalopride 2 mg had similar incidence of side effect like nausea and headache than placebo (71.4% vs. 67.1%; NS) (Tuck et al, 2008).</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
<b>Cost data:</b>	<p>The direct cost comparison showed that prucalopride is more expensive by at least 3 times than bisacodyl treatment. The FEC noted this and agreed that there are other cheaper alternatives listed in the current Formulary such as Senna and bisacodyl.</p> <p><i>(See Attachment).</i></p>
<b>Remarks:</b>	The Secretary of Health has officially disapproved the proposal to include prucalopride in the PNF. There was no appeal received within the set deadline, thus the recommendation of the Council still remains.

PRISMA Table



1. Among adult patients 30 – 60 year old with chronic constipation, would the use of prucalopride improve signs and symptoms better than domperidone in a randomized clinical trial?

**EVIDENCE TABLE 1**

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS	Prucalopride		Control			
					(including adverse events)	No. of events *	Total # of patients	No. of events *	Total # of patients		
1	Tack et al. Gut 2008	RCT	720 patients with constipation not totally controlled by laxatives	Prucalopride vs. placebo	Spontaneous complete bowel movement	Prucalo 2 mg 46 (19.5%)	236	23 (9.6%)	240		p<0.01
						Prucalo 4 mg 56 (23.6%)	237	23 (9.6%)	240		p<0.01
					Patient rating as effective	Prucalo 2 mg 71 (34.6%)	205	39 (18.7%)	209		p<0.01
						Prucalo 4 mg 85 (36.1%)	180	39 (18.7%)	209		p<0.01
					Overall quality of life change (negative reflect 3improvement)	Prucalo 2 mg -0.65	SD 0.05	-0.38	SD 0.05		p<0.01
						Prucalo 4 mg -0.66	SD 0.05	-0.38	SD 0.05		p<0.01
					Adverse event (headache, nausea, abdominal pain)	Prucalo 2 mg 170 (71.4%)	238	161 (67.1%)			NS
						Prucalo 4 mg 178 (74.8%)	238	161 (67.1%)			NS
2	Coremans et al. Digestion, 2003	RCT	55 patients with constipation not totally controlled by	Prucalopride vs. placebo	Clinical visual analogue score-end of treatment (higher score is better)	54.3		25.4			p<0.01

			laxatives		Adverse event (headache, nausea)	24 (88.9%)	27	12 (46.2%)	26		
3	Sloots et al. Aliment Pharmacol Ther, 2002	RCT	49 patients with chronic constipation	Prucalopride vs. placebo	Mean colonic total transit time	42.8 hrs		54.8 hrs			NS
					Adverse event	25	27	10	25		
4	Emmanuel et al. Aliment Pharmacol Ther, 2002	RCT	74 women with chronic constipation	Prucalopride vs. placebo	Change in whole gut transit time	-11.2	SD 21.8	-1.1	SD 21.3		p=0.03
5	Camilleri et al. NEJM, 2008	RCT	620 patient with severe chronic constipation	Prucalopride 2 mg vs. placebo	>3 spontaneous complete bowel movement	64 (30.9%)	207	25 (12.0%)	209		p<0.01
					Percent BM with normal consistency (change from baseline)	22.9%		13.5%			p<0.01
					Percent of patient with severe straining (change from baseline)	-13.7%		-5.1%			p<0.01
				Prucalopride 4 mg vs. placebo	>3 spontaneous complete bowel movement	58 (28.4%)		25 (12.0%)	209		p<0.01
					Percent BM with normal consistency (change from baseline)	21.6%		13.5%			p<0.01
					Percent of patient with severe straining (change from baseline)	-13.5%		-5.1%			p<0.01

6	Quigley et al. Alimant Pharmacol Ther, 2008	RCT	641 patients with severe chronic constipation	Prucalopride 2 mg vs. placebo	Overall Patient Assessment of Constipation-QOL (change from baseline)	-0.85	214	-0.47	212		p<0.01
				Prucalopride 4 mg vs. placebo	Overall Patient Assessment of Constipation-QOL (change from baseline)	-0.86	215	-0.47	212		p<0.01
				Prucalopride 2 mg vs. placebo	Prolonged QT	1 (0.6%)	165	2 (1.2%)	164		NS
				Prucalopride 4 mg vs. placebo	Prolonged QT	1 (0.6%)	165	2 (1.2%)	164		NS
7	Muller-Lissner et al. Neurogastroen terol Motil	RCT	300 elderly patients with chronic constipation	Prucalopride 1 mg vs. placebo	Spontaneous complete BM per wk (change from baseline)	1.9	76	0.6	70		p<0.05
				Prucalopride 2 mg vs. placebo		1.7	75	0.6	70		p<0.05
				Prucalopride 4 mg vs. placebo		1.8	79	0.6	70		p<0.05
				Prucalopride 1 mg vs. placebo	Patients with adverse event (abdominal pain, nausea, headache)	48.7%	76	44.4%	72		NS
				Prucalopride 2 mg vs. placebo		38.7%	75	44.4%	72		NS
				Prucalopride 4 mg vs. placebo		47.5%	80	44.4%	72		NS
8	Ke et al. Neurogastroen terol Motil, 2012	RCT	501 patients with chronic constipation (Asia-Pacific Region)	Prucalopride mg vs. placebo	>3 spontaneous complete bowel movement	83 (33.3%)	249	26 (10.3%)	252		p<0.01
					Patient Assessment	-0.7	249	-0.4	252		p<0.01

					of Constipation-symptoms score (change from baseline)						
					Patient Assessment of Constipation-QOL (change from baseline)	-0.8	249	-0.4	252		p<0.01
					Any adverse event (diarrhea, headache, nausea)	142 (57.0%)	249	92 (36.5%)	252		
9	Mugie et al. Gastroenterol, 2014	RCT	213 children with functional constipation	Prucalopride vs. placebo	Spontaneous BM per wk (change from baseline)	1.5	SD 2.35	1.0	SD 1.78		NS
					Treatment-related AE	74 (69.8%)	106	65 (60.7%)	107		

**DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS**

<p><b>PARAMETER</b> (Indicate information for intended recipient)*  <b><u>INTENDED RECIPIENT:</u></b></p>	<p><b>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</b></p>	<p><b>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</b></p>	<p><b>REFERENCES</b></p>
<p>COST PER DOSAGE UNIT (in PhP)                      a. Proposed list price to the government                      b. Current prevailing market price</p>	<p><sup>1</sup>Prucalopride 2mg PhP 46.79 per tab</p>	<p><sup>2</sup>Bisacodyl 5mg PhP 1.49 per tab</p>	<p><sup>1</sup>Company submission  <sup>2</sup>Bisacodyl DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p>30 per month</p>	<p>30 per month</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p>P 1,403.70 per month</p>	<p>P 44.70 per month</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><b>P 1,403.70 per month</b></p>	<p><b>P 44.70 per month</b></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 “prucalopride” limited to randomized controlled trial. The yield was 26 articles. We reviewed the 26 articles and considered 16 for full text retrieval.
- We reviewed the 16 articles and considered 9 for inclusion in this review. The following articles were included in this review:
  - Mugie SM(1), Korczowski B(2), Bodi P(3), Green A(4), Kerstens R(5), Ausma J(5), Ruth M(5), Levine A(6), Benninga MA(7). Prucalopride is no more effective than placebo for children with functional constipation. *Gastroenterology*. 2014 Dec;147(6):1285-95.e1. doi: 10.1053/j.gastro.2014.09.005. Epub 2014 Sep 16.
  - Ke M(1), Zou D, Yuan Y, Li Y, Lin L, Hao J, Hou X, Kim HJ. Prucalopride in the treatment of chronic constipation in patients from the Asia-Pacific region: a randomized, double-blind, placebo-controlled study. *Neurogastroenterol Motil*. 2012 Nov;24(11):999-e541. doi: 10.1111/j.1365-2982.2012.01983.x. Epub 2012 Aug 8.
  - Müller-Lissner S(1), Rykx A, Kerstens R, Vandeplassche L. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. *Neurogastroenterol Motil*. 2010 Sep;22(9):991-8, e255. doi: 10.1111/j.1365-2982.2010.01533.x. Epub 2010 Jun 7.
  - Quigley EM(1), Vandeplassche L, Kerstens R, Ausma J. Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation--a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*. 2009 Feb 1;29(3):315-28. doi: 10.1111/j.1365-2036.2008.03884.x. Epub 2008 Nov 8.
  - Tack J(1), van Outryve M, Beyens G, Kerstens R, Vandeplassche L. Prucalopride (Resolor) in the treatment of severe chronic constipation in patients dissatisfied with laxatives. *Gut*. 2009 Mar;58(3):357-65. doi: 10.1136/gut.2008.162404. Epub 2008 Nov 5.
  - Camilleri M(1), Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med*. 2008 May 29;358(22):2344-54. doi: 10.1056/NEJMoa0800670.
  - Coremans G(1), Kerstens R, De Pauw M, Stevens M. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial. *Digestion*. 2003;67(1-2):82-9.
  - Emmanuel AV(1), Roy AJ, Nicholls TJ, Kamm MA. Prucalopride, a systemic enterokinetic, for the treatment of constipation. *Aliment Pharmacol Ther*. 2002 Jul;16(7):1347-56.
  - Sloots CE(1), Poen AC, Kerstens R, Stevens M, De Pauw M, Van Oene JC, Meuwissen SG, Felt-Bersma RJ. Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation. *Aliment Pharmacol Ther*. 2002 Apr;16(4):759-67.



### **Effectiveness/Efficacy**

- There are no randomized controlled trials or indirect comparison between prucalopride and domperidone for patients with chronic constipation.
- Our review however covered 11 randomized controlled trials among patients with chronic constipation. Among patients with chronic constipation uncontrolled by laxatives, prucalopride 2mg had more spontaneous complete bowel movement (19.5% vs. 9.6%;  $p < 0.01$ ) than placebo. It also had better patient rating as effective (34.6% vs. 18.7%;  $p < 0.01$ ) (Tuck et al., 2008).
- Even among patients with severe chronic constipation, prucalopride 2mg was shown to have more spontaneous complete bowel movement than placebo (30.9% vs. 12.0%;  $p < 0.01$ ) (Camilleri et al, 2008). This also confirmed by another study of Quigley et al in 2008.
- Among the elderly with chronic constipation, prucalopride 2 mg was shown to be more effective than placebo (1.9 vs 0.6;  $p < 0.05$ ) in terms of change in BM from baseline. Similar effectiveness findings for Asians.
- The efficacy of prucalopride however has not been shown in children.

### **Safety**

- In terms of adverse event, prucalopride 2 mg had similar incidence of side effect like nausea and headache than placebo (71.4% vs. 67.1%; NS) (Tuck et al, 2008).

### **Summary of Review**

- Our review showed prucalopride to be more effective than placebo or laxatives for the treatment of chronic constipation.

### **Cost Data**

- Our direct cost comparison showed that prucalopride is more expensive by at least 3 times than bisacodyl treatment.

### **Overall Recommendation**

- Because prucalopride has been shown to be effective and safe among patients with chronic constipation who are not responsive to laxatives like bisacodyl, we recommend prucalopride to be included in the formulary despite its higher cost than laxatives.

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