South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Alimentary tract conditions

1) Executive Summary

Date: 5 April 2018
Medicine (INN): Proton pump inhibitors
Medicine (ATC): A02BC
Indication (ICD10 code): Symptomatic oesophageal reflux disease (GORD) or peptic ulcer disease (K21.0/K21.9/K22.7/ K25.0-7/K25.9/K26.1-7/K26.9/K27.0-/K27.9)
Patient population: Adults
Level of Care: Secondary level
Prescriber Level: Doctors, medical officers
NNT: n/a
Current standard of Care: Lansoprazole, oral
Motivator/reviewer name(s): Dr R Coetzee, Ms TD Leong, Dr R de Waal
PTC affiliation: Dr R Coetzee: WC PTC

2) Name of author(s)/motivator(s)

Primary reviewer(s): Dr R Coetzee, Ms TD Leong
Secondary reviewer: Dr R de Waal

3) Author affiliation and conflict of interest details

- *Dr R Coetzee:* University of the Western Cape; Adult Hospital Level Committee (2017-2020); no conflicts declared.
- *Ms TD Leong:* National Department of Health, Essential Drugs Programme; Secretariat to the Adult Hospital Level Committee (2017-2020); no conflicts declared.
- Dr R de Waal: University of Cape Town; PHC Expert Review Committee and National Essential Medicines List Committee; no conflicts declared.

4) Introduction/Background

Proton pump inhibitors (PPIs) decrease secretion of gastric acid, blocking the last enzyme in the system that actively transports acid from gastric parietal cells into the gastrointestinal lumen, hydrogen–potassium adenosine triphosphatase, also known as the proton pump. Proton pump inhibitors are mainly used to treat symptoms of gastroesophageal reflux disease and gastritis. Proton pump inhibitors also are used to treat peptic ulcers (duodenal and gastric) and drug induced ulcers, such as those associated with nonsteroidal anti-inflammatory drugs; the bacterium that causes ulcers, *Helicobacter pylori,* is eradicated by treatment with a proton pump inhibitor and antibiotics. Proton pump inhibitors also are used to promote healing of erosive esophagitis. Oesophagitis can lead to scarring and narrowing of the oesophagus (stricture) or to Barrett oesophagus, which is a risk factor for oesophageal cancer.[i]

Cochrane review suggests that PPI therapy is more effective than H2RAs in relieving heartburn in patients with GORD who are treated empirically and in those with endoscopy negative reflux disease.[ii]

Currently, the PPI, lansoprazole is recommended in the Adult Hospital Level STGs and EML, 2015[iii] for gastro-oesophageal reflux disease (GORD), Barrets oesophagitis, peptic ulcer disease and eradication of *Helicobacter pylori.*

The purpose of the review is to evaluate the comparative efficacy of proton pump inhibitors for use in specific indications, and therefore classify them as therapeutic alternatives.

5) Clinical Question

P Adults with symptomatic oesophageal reflux disease (GORD) or peptic ulcer disease
I Lansoprazole
C Alternative proton pump inhibitor(s) – including omeprazole, pantoprazole, rabeprazole, esomeprazole
O Relief/resolution of symptoms

What is the comparative effectiveness and safety of proton pump inhibitors in adult patients, with symptomatic gastro oesophageal reflux disease or peptic ulcer disease for relief/resolution of symptoms (heartburn, acid regurgitation, epigastric pain)?

6) Method

A. Databases

1. Cochrane library
2. PUBMED
3. Google scholar

B. Search strategies:

1. Cochrane library

Search terms: 'proton pump inhibitors' AND 'oesophageal reflux' AND 'peptic ulcer' restricted to Cochrane reviews.

2. PUBMED

((((((("proton pump inhibitors"[All Fields] OR "proton pump inhibitors"[MeSH Terms] OR ("proton"[All Fields] AND "pump"[All Fields] AND "inhibitors"[All Fields]) OR "proton pump inhibitors"[All Fields]) AND ("gastroesophageal reflux"[MeSH Terms] OR ("gastroesophageal"[All Fields] AND "reflux"[All Fields]) OR "gastroesophageal reflux"[All Fields] OR "gerd"[All Fields])) AND ("peptic ulcer"[MeSH Terms] OR ("peptic"[All Fields] AND "ulcer"[All Fields]) OR "peptic ulcer"[All Fields])) AND (symptomatic[All Fields] AND relief[All Fields])) AND ("review"[All Fields] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields])) AND ("adult"[MeSH Terms] OR "adult"[All Fields])) AND class[All Fields]

3. Google scholar:

Search terms:
i) proton pump inhibitors AND efficacy AND comparatives AND review OR meta-analysis
ii) proton pump inhibitors AND therapeutic class AND review OR meta-analysis

Searches were performed on 1 September 2018 and were restricted to systematic reviews or meta-analyses of RCTs, English language and peer reviewed journal publications.

Six reviews were retrieved from the Cochrane library, 56 articles from PUBMED and three publications from Google scholar.

C. Excluded studies

See Appendix A

D. Evidence synthesis

The following three systematic reviews/meta-analyses met the PICO criteria:

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes (95% CI)	Comments
I. Li et al, 2017[iv]	Network meta-analysis	25 RCTs	Adults with endoscopically confirmed erosive oesophagitis, followed up for 4 to 8 weeks.	Pantoprazole 40mg, lansoprazole 30mg, rabeprazole 20mg, esomeprazole 20mg, esomeprazole 40mg, dexlansoprazole 60mg	Endoscopic healing rates at 4 and 8 weeks.	• ***Healing rates at 4 weeks: vs lansoprazole 30 mg:*** - esomeprazole 20mg 1.07 (0.76 to 1.50) - esomeprazole 40mg 1.30 (1.10 to 1.53) - rabeprazole 20mg 0.79 (0.53 to 1.19) • ***Healing rates at 4 weeks: vs omeprazole 20 mg:*** - pantoprazole 40mg 1.11 (0.89 to 1.37) - lansoprazole 30mg 1.12 (0.93 to 1.35) - rabeprazole 20mg 0.89 (0.62 to 1.28) - esomeprazole 20mg 1.20 (0.88 to 1.64) - esomeprazole 40mg 1.46 (1.24 to 1.71) - rabeprazole 20 mg 0.89 (0.62 to 1.28) • ***Healing rates at 8 weeks: vs lansoprazole 30 mg:*** - esomeprazole 20mg 1.09 (0.76 to 1.50) - esomeprazole 40mg 1.37 (1.13 to 1.67) - rabeprazole 20mg 0.768 (0.42 to 1.11) • ***Healing rates at 8 weeks: vs omeprazole 20 mg:*** - pantoprazole 40mg 1.31 (1.02 to 1.69) - lansoprazole 30mg 1.15 (0.92 to 1.43) - rabeprazole 20mg 0.78 (0.50 to 1.21) - esomeprazole 20mg 1.25 (0.92 to 1.69) - esomeprazole 40mg 1.58 (1.29 to 1.92) • ***Healing rates at 8 weeks: vs lansoprazole 30 mg:*** - esomeprazole 20mg 1.09 (0.76 to 1.56) - esomeprazole 40mg 1.37 (1.13 to 1.67) - rabeprazole 20mg 0.68 (0.42 to 1.11)	Research question was clear and 3 databases searched. Study design was given, but not the search terms or search strategy. Data selection and analysis done in duplicate and disagreements resolved with two additional reviewers. Study quality assessed using the Cochrane Collaboration Risk of Bias Tool, and funnel plots showed no apparent publication bias as it appeared symmetrical. However, there is a degree of uncertainty regarding publication bias as language of searches was not provided and whether grey literature was included was not indicated. Statistical heterogeneity was investigated; and individual RCTs was described and reported to be heterogeneous in terms of baseline disease severity with 'endoscopic healing effect sizes decreased with increasing severity'. Results should be interpreted with caution as: *- Only 7 RCTs reported healing rates at 4 weeks, and 10 RCTs reported healing rates at 10 weeks. The follow-up period of 4 to 8 weeks requires results of this study to be interpreted with caution to determine long-term*

						[See figures 1, 2, 3, below]	*safety and effectiveness. (All RCTS used ITT analysis).* *- Only RCTs investigating standard- and low-dose PPIs were considered.* **A major limitation of this analysis is that doses of the various PPIs were not always comparable.**
II. McDonagh et al, 2009	Meta-analysis	68 studies - 40 RCTs, 6 SRs, 15 observational studies, 16 other (RCTS reviewed to evaluate efficacy; observational studies for adverse effects).			- symptomatic relief of GORD - PUD (treatment & prevention of NSAID-induced PUD) -eradication of *H. pylori* -long-term safety & effectiveness in GORD (beyond 8 weeks) - comparative safety of PPIs -factors affecting safety & effectiveness of PPIs	• **GORD:** - Limited indirect evidence from placebo-controlled and active-control trials shows similar efficacy for all 5 PPIs. *[See tables 1,2,3,4 below]* • **PUD:** <u>- duodenal ulcer (10 RCTS)</u> i) L30 vs O20 (5RCTS) Risk diff -0.2 (-3.0 to 2.6) ii) P40 vs O20 (1RCT) Risk did 4.84 (-0.96 to 11.70) iii) E40 vs O40 (1RCT) Risk diff -0.97 (-6.4 to 4.35) *No evidence of a difference in healing rate among PPIs.* **- gastric ulcer (3 RCTS)** i) R20 vs O20 (1RCT) No significant difference in healing rate. ii) R10 vs O20 (1RCT) No significant difference in healing rate. iii) L30 vs O20 (1RCT) healing rate at 8 weeks: 93% vs 82%, p=0.04 – *but poor quality RCT with selection bias and high attrition rate in the omeprazole arm.* - <u>NSAID-induced ulcer (treatment)</u> No comparative PPI RCTs. -<u>NSAID-induced ulcer (prevention)</u>	There were a number of review questions that were clearly defined in terms of PICO criteria. Study design of studies for the various questions were adequately described. Four databases were searched and pharmaceutical manufacturers were also invited to submit dossiers. Evidence selection and data abstraction was done in duplicate and disagreements resolved through consensus. Validity assessment of studies using various tools and statistical heterogeneity was assessed. Individual RCTs were described and quality assessed. The review concludes that there is no evidence of significant difference between PPIs. However, evidence is limited and of poor to moderate quality with high heterogeneity (dissimilar patient populations, outcomes, dose comparisons of interventions, etc.). Also, the authors mention the controversy regarding the appropriateness of dose comparisons in head-to-head trials comparing esomeprazole with omeprazole - The US Food and Drug Administration's

						- No difference between P20, P40, O20 daily in rates of therapeutic or endoscopic failure at 6 months (regular NSAIDs for arthritic conditions). - A good-quality systematic review and 7 subsequent RCTs showed no difference between omeprazole, lansoprazole, and pantoprazole – but RCTs very heterogeneous. • ***H. pylori eradication:*** - 5 SRs and 29 RCTs: pooled analysis showed no significant difference in eradication rates amongst PPIs; but significant heterogeneity amongst studies. • ***Long-term use in GORD (beyond 8 weeks):*** - time in remission, rate of endoscopically verified remission & rates of relapse was greater for higher vs lower dose PPI. • ***Comparative safety of PPIs:*** - Paucity of head-to-head long-term trials specifically measuring ADRs. - Available evidence shows no difference between PPIs. - Evidence suggests associated *C difficle* diarrhoea (though, not hospitalization); risk of osteoporotic bone fractures with PPIs. - Evidence is mixed regarding association of PPIs with community acquired pneumonia. • ***Factors affecting safety & effectiveness of PPIs:*** - Age, gender, and race: no difference found among groups. - Clopidogrel: Concomitant PPI, following ACS shown to increase risk of death or re-hospitalisation for ACS – adjusted OR 1.25 (1.11 to 1.41).	clinical review of esomeprazole indicates that esomeprazole 40mg is "pharmacodynamically thrice that of the s-isomer" in omeprazole 20mg.
III. Klok et al, 2003[v]	Meta-analysis	45 RCTs	GORD(16 RCTs), PUD(9),	Omeprazole 20mg (O20),	Endoscopic healing of GORD and	<u>*Endoscopic healing of GORD:*</u> - E40 vs O20 (2 RCTs, n=3,729): RR 1.18 (95% CI: 1.14, 1.23).	Review question clear and study design of interest clearly stated. Three databases searched and search

			H. pylori eradication(9)	pantoprazole 40mg (P40), 80mg (P80); lansoprazole 30mg (L30), 60mg (L60); rabeprazole 20mg (R0), 40mg (R40); esomeprazole 40mg (E40)	PUD; eradication of *H. pylori*	- No significant differences shown with other comparisons: P40 vs O20 (4 RCTs, n=604), L30 vs O20 (6 RCTs, n=1,881) and R20 vs O20 (2 RCTs, n=409). - Results of individual RCTs of other dosages could not be pooled as only single RCTs identified. <u>*Endoscopic healing of PUD:*</u> - P40 vs O20 (3 RCTs, n=760); the RR was 1.07 (95% CI: 1.02, 1.13). - No significant differences with other comparisons: L30 vs O20 (3 RCTs, n=504) and R20 vs O20 (2 RCTs, n=432). <u>*H. pylori eradication:*</u> - No significant differences for following: L60 vs O40 (5 RCTs, n=860), L30 vs O40 (2 RCTs, n=196), R40 vs L60 (2 RCTs, n=354), R20 vs O40 (2 RCTs, n=314), R40 vs O40 (2 RCTs, n=311), P40 vs O40 (2 RCTs, n=213), P80 vs O40 (2 RCTs, n=349), E40 vs O40 (2 RCTs, n=833). The significant differences above were shown with the highest dose of PPI. Thus, difference may be dose dependent and not PPI specific. **PPIs appeared comparable, thus choice may be price/cost dependant.**	strategy provided. Publication bias possible as grey literature not included and searches done in only four languages. Two reviewers selected and analysed the evidence; but process to minimise bias and error not described. Assessment of study validity and quality not discussed. Details of individual studies was not provided and thus it was not possible to determine heterogeneity amongst RCTs. Pooled studies were also not reviewed for statistical heterogeneity. This results should be interpreted with caution, as individual RCTs were not described and information regarding heterogeneity and quality of RCTs are lacking.

Despite esomeprazole 40 mg being more efficacious than lansoprazole 30 mg and omeprazole 20 mg for healing of erosive esophagitis, the difference in benefit is small and insufficient in recommending esomeprazole over other PPIs (Of note is that esomeprazole 40 mg is similar to a double dose of omeprazole). Overall, PPIs have been shown to be relatively comparable for initial treatment of endoscopy-negative reflux disease, erosive esophagitis, peptic ulcer disease (and prevention of NSAID-associated ulcer disease) and *H. pylori* eradication.

I: Li et al, 2017: Healing rates of endoscopically confirmed erosive oesophagitis- *figures 1,2,3*

Figure 1: Network meta-analysis results: healing rates at 4 weeks

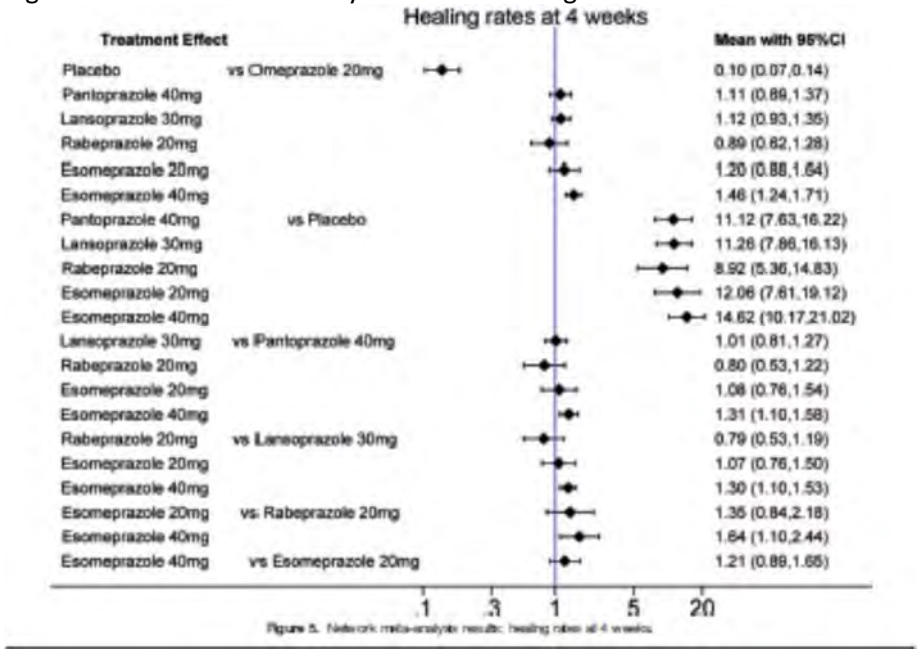


Figure 2: Network meta-analysis results: healing rates at 8 weeks

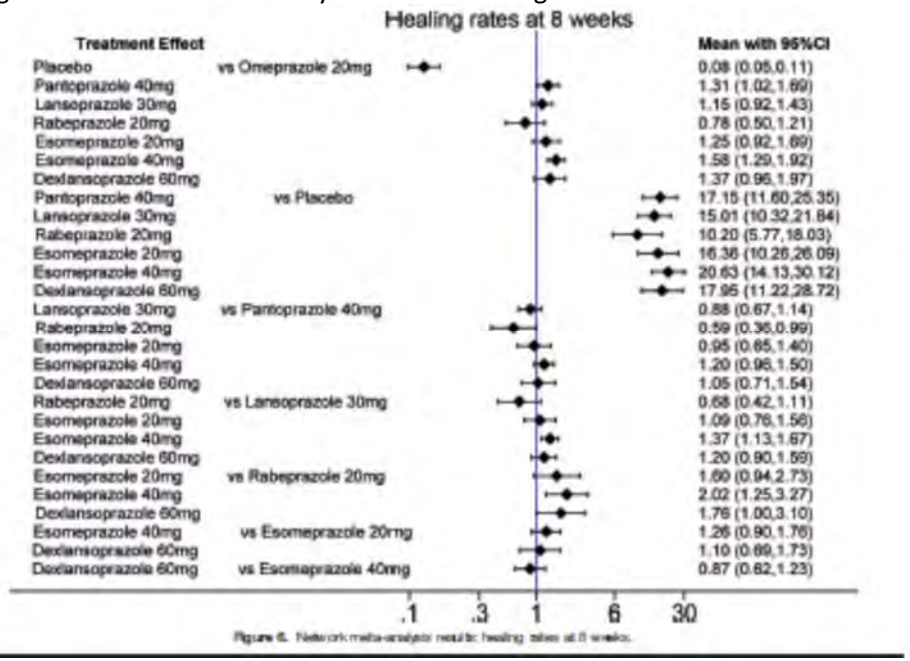
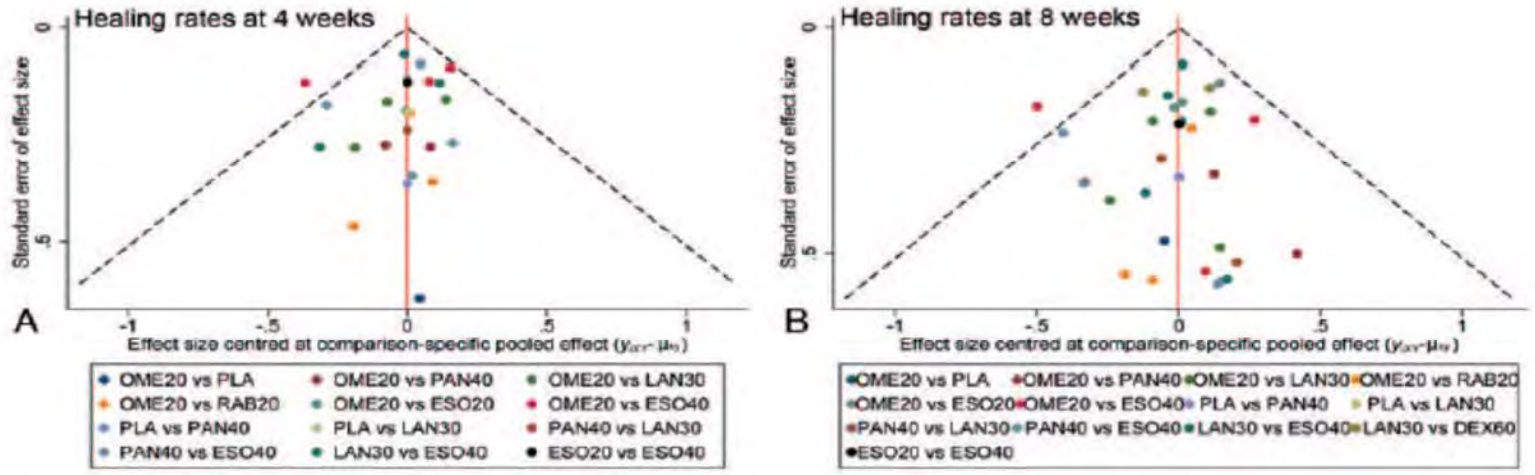


Figure 3: Funnel plots for primary efficacy outcome healing rates at 4 and 8 weeks (A and B), different colours represent different comparisons



II. McDonagh et al, 2009: Symptomatic relief of GORD – *tables 1,2,3,4*

Table 1: Symptom resolution in erosive GORD (McDonagh et al, 2009)

Proton pump inhibitor and daily dose	Resolution of symptoms at 4 weeks (95% CI)
Esomeprazole 40 mg	73% (65 to 82)
Lansoprazole 30 mg	70% (61 to 80)
Omeprazole 20 mg	65% (54 to 76)
Omeprazole 40 mg	76% (65 to 87)
Pantoprazole 20 mg	77% (70 to 84)
Pantoprazole 40 mg	72% (62 to 83)
Rabeprazole 20 mg	69% (52 to 86)

Table 2: Resolution of heartburn (% of patients) at 4 weeks (McDonagh et al, 2009 – derived from Cochrane review[i])

	Endoscopically verified nonerosive gastroesophageal reflux disease		Presumptive treatment of symptoms	
Drug, dose	Number of trials	%, range	Number of trials	%, range
Esomeprazole 20 mg	2	61% to 62%		
Esomeprazole 40 mg	2	57% to 71%		
Esomeprazole 40 mg			1	84%
Omeprazole 10 mg or 20 mg			1	75%
Omeprazole 10 mg or 20 mg	4	56% to 95%		
Omeprazole 20 mg	5	58% to 84%	4	60% to 70%
Omeprazole 40 mg	1	95%		
Pantoprazole 20 mg			1	81%
Pantoprazole 40 mg	1	57%	1	66%
Rabeprazole 10 mg or 20 mg	1	98%		

Table 3: Pooled estimates of healing rates for GORD

Drug	Proportion of group whose esophagitis has healed at 4 weeks (95% CI)	Proportion of group whose esophagitis has healed at 8 weeks (95% CI)
Esomeprazole 20 mg	73% (66-79)[5, 6]	87% (84-91)[5, 6]
Esomeprazole 40 mg	78% (73-83)[4, 5, 12, 20, 29, 30, 36, 38]	90% (88-92)[4, 5, 12, 18, 20, 29-31, 38]
Lansoprazole 15 mg	63% (52-73)[25]	73% (63-82)[25]
Lansoprazole 30 mg	73% (67-79)[4, 14, 15, 21, 23, 25, 29]	86% (83-90)[4, 14, 15, 18, 21, 23, 25, 29]
Omeprazole 20 mg	70% (64-76)[5, 6, 12, 15, 21, 22, 25-27, 38]	85% (81-88)[5, 6, 12, 15, 21, 22, 25-27, 31, 38]
Omeprazole 40 mg	68% (59-78)[14, 17]	87% (76-99)[14]
Pantoprazole 20 mg	67% (54-81)[27]	77% (65-88)[27]
Pantoprazole 40 mg	71% (65-78)[17, 20, 23, 26, 30]	89% (86-92)[20, 23, 26, 30]
Rabeprazole 10 mg	65% (47-83)[22]	84% (71-96)[22]
Rabeprazole 20 mg	69% (59-79)[22, 40]	82% (76-89)[22, 40]

Data from the cited studies were pooled using a random-effect model.

Table 4: Risk differences in healing of oesophagitis in RCTs of PPIs vs omeprazole 20 mg

Drug, daily dose	Risk difference[a] at 4 weeks in comparison with omeprazole (95% CI)	Risk difference[a] at 8 weeks in comparison with omeprazole (95% CI)
Esomeprazole 20 mg	3% (–1 to 7)[5, 6]	3% (0 to 6)[5, 6]
Esomeprazole 40 mg	7% (1 to 12), pooled[5, 12, 36, 38 36] **number needed to treat = 14**	5% (1 to 9), pooled[5, 12, 31, 36, 38] **number needed to treat = 20**
Lansoprazole 30 mg	2% (–3 to 6), pooled [15, 21, 25]	1% (–2 to –5), pooled [15, 21, 25]
Pantoprazole 20 mg	–4% (–12 to 5)[27]	–7% (–15 to 0)[27]
Pantoprazole 40 mg	–1% (–13 to 11)[26]	3% (–3 to 10)[26]
Rabeprazole 10 mg	–6% (–15 to 3)[22]	–3% (–10 to 4)[22]
Rabeprazole 20 mg	–2% (–8 to 3)[22, 32]	–3% (–8 to 2)[22, 32]

[a] Risk difference was calculated as the difference between the percent of the group on the test proton pump inhibitor in which esophagitis healed and the percent of the group on omeprazole 20 mg daily in which esophagitis healed.

E. Evidence quality

Systematic reviews were of low to moderate quality, as the RCTs reviewed were generally heterogeneous and there may be a degree of uncertainty with regards to the results.

F. Dosage recommendations

NICE[vi] considered that a class effect could be assumed for all PPIs and the choice of agent should be based on patient preferences and clinical circumstances.

Table 5. PPI doses relating to evidence synthesis and recommendation (NICE 2014).

PPI	Full/standard dose	Low dose (on-demand dose)	Double dose
Esomeprazole	20 mg[1] once a day	Not available	40 mg[3] once a day
Lansoprazole	30 mg once a day	15 mg once a day	30 mg[2] twice a day
Omeprazole	20 mg once a day	10 mg[2] once a day	40 mg once a day
Pantoprazole	40 mg once a day	20 mg once a day	40 mg[2] twice a day
Rabeprazole	20 mg once a day	10 mg once a day	20 mg[2] twice a day

[1] Lower than the licensed starting dose for esomeprazole in GORD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg.

[2] Off-label dose for GORD.

[3] 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.

AGREE II assessment of the NICE Clinical guideline: GORD and dyspepsia in adults: investigation and management, 3 September 2014; see Appendix B.

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?
Confident [X] Not confident [ ] Uncertain [ ]</td><td>See evidence synthesis table above.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td>See evidence synthesis table above.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [X] No [ ]

List the members of the group.

List specific exclusion from the group:
Esomeprazole</td><td>Rationale for therapeutic alternatives included:

References:
See above NICE (2014); Mcdonagh et al, 2017

Rationale for exclusion from the group:
Low dose esomeprazole not available, and rational prescribing warrants use of PPIs in dose series.

References: SAMF,2016[vii]</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [X] Uncertain [ ]</td><td>Cost of medicines/ month (30 days):
A: Full/standard dose
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Lansoprazole, 30 mg caps</td><td>10.69*</td></tr><tr><td>Omeprazole, 20 mg caps</td><td>8.98*</td></tr><tr><td>Pantoprazole, 40 mg</td><td>64.23 to 128.47**</td></tr><tr><td>Rabeprazole, 20 mg</td><td>100.40 to 200.80**</td></tr></table>B: Low dose
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Lansoprazole, 15 mg</td><td>61.52 to 123.03**</td></tr><tr><td>Omeprazole, 10 mg tabs</td><td>17.83*</td></tr><tr><td>Pantoprazole, 20 mg</td><td>42.12 to 84.25**</td></tr><tr><td>Rabeprazole, 10 mg</td><td>50.13 to 100.26**</td></tr></table>* Contract circular HP09-2016SD
**SEP Database 5 June 2018 – 30% to 60% of average SEP (these items are not listed on the MSH Drug Price indicator database).
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
</table>

FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☒	☐

Recommendation: Based on this evidence review the Adult ERC recommends PPIs as a therapeutic class with preference to using the dose-equivalent cheapest option.
Uncertainty exits around the safety of long-term use of PPIs (i.e. *C difficile* infection; decrease in BMD; pneumonia).
Rationale: Overall, PPIs have been shown to be relatively comparable for initial treatment of endoscopy-negative reflux disease, erosive esophagitis, peptic ulcer disease (and prevention of NSAID-associated ulcer disease) and *H. pylori* eradication.

Level of Evidence: II Systematic review of moderate to low evidence, Guidelines

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[X]	[ ]

VEN status:

Vital	Essentia	Necessary
[ ]	[X]	[ ]

NEMLC MEETING OF 27 SEPTEMBER 2018:
NEMLC accepted the evidence review and the recommendation(s) as proposed by the Adult Hospital Level Committee.

Monitoring and evaluation considerations
Duration of PPI use in practice

Research priorities
Long-term safety of PPIs

APPENDIX A

Excluded studies:

Author, date	*Type of study*	*Reason for exclusion*
Sigterman et al, 2013	Cochrane review	Duplicate – included in McDonagh et al, 2009
Pinto-Sanchez et al, 2017	Cochrane review	Comparison of different PPIs not reviewed
Tighe et al, 2014	Cochrane review	Review of GORD in children– not relevant to PICO
Song et al, 2014	Cochrane review	Safety of long-term PPI therapy – not relevant to PICO
Wang et al, 2009	Cochrane review	H2RA add-on therapy to PPI for nocturnal gastric acid breakthrough – not relevant to PICO
Deva S et al, 2012	Cochrane review	Dual therapy (H2RA and PPI) for resected colorectal cancer – not relevant to PICO
Scarpignato et al, 2016	Position paper	Search criteria not met
Johnson et al, 2017	Narrative review	Search criteria not met
UEG Week 2013 Poster Presentation	Conference poster	Search criteria not met
UEG Week 2015 Poster Presentation	Conference poster	Search criteria not met
UEG Week 2014 Poster Presentation	Conference poster	Search criteria not met
Tang et al, 2013	Narrative review	Search criteria not met
Rouby et al, 2018	Narrative review	Search criteria not met
Cheng et al, 2014	Narrative review	Search criteria not met
Savarino et al, 2017	RCT	Search criteria not met – not relevant to PICO
Kahrilas, 2008	Narrative review	Search criteria not met
Ward et al, 2011	RCT	Search criteria not met (Children and adolescents)
Maradey-Romero et al, 2014	Review	Search criteria not met
Mejia et al, 2009	Review	Search criteria not met
Skrzydło-Radomańska et al, 2015	Pharmacokinetic study	Search criteria not met
Mouly et al, 2009	Observational study	Search criteria not met
Oshima et al, 2018	Pharmacology study	Search criteria not met
Calabrese et al, 2007	Narrative review	Search criteria not met
Thomson, 2018	Narrative review	Search criteria not met
Esposito et al, 2015	Systematic review	Search criteria not met (Paediatrics)
Talley, 2016	Narrative review	Search criteria not met
UEG Week 2015 Oral Presentations	Conference abstract	Search criteria not met
Ming Yeh et al, 2014	Systematic review	Search criteria not met (Paediatrics)
Talley, 2017	Narrative review	Search criteria not met
UEG Week 2014 Oral Presentations	Conference abstract	Search criteria not met
Ortiz-Guerrero et al, 2018	Pharmacodynamic study	Search criteria not met
UEG Week 2013 Oral Presentations	Conference abstract	Search criteria not met
Ohkuma et al, 2018	Pharmacodynamic study	Search criteria not met
Flook et al, 2007	Observational study	Search criteria not met
Abstracts from the 2017 Society of General Internal Medicine Annual Meeting	Conference abstract	Search criteria not met
Abstracts from the 37th Annual Meeting of the Society of General Internal Medicine	Conference abstract	Search criteria not met
Craig et al, 2011	Narrative review	Search criteria not met
Abstracts from the 38th Annual Meeting of the Society of General Internal Medicine	Conference abstract	Search criteria not met
Abstracts from the 36th Annual Meeting of the Society of General Internal Medicine	Conference abstract	Search criteria not met
Wong et al, 2010	Case study	Search criteria not met
Barkhun et al, 2010	Economic evaluation	Search criteria not met

Not provided, 2007 (Gut)	Retraction/correction	Not relevant
Not provided, 2006 (Gut)	Retraction/correction	Not relevant
Liang et al, 2008	RCT	Search criteria not met (esomeprazole formulation comparisons)
Gastroenterology services in the UK, 2007	Observational study	Search criteria not met
American Association for the Study of the Liver, 2013	Conference abstracts	Search criteria not met
Scientific Abstracts, 2009	Conference abstracts	Search criteria not met
Lim et al, 2010	Narrative review	Search criteria not met
Loyd et al, 2007	Economic evaluation	Search criteria not met
Arents et al, 2002	Observational study	Search criteria not met
Singh et al, 2015	Observational study	Search criteria not met
Abstracts from the 30th Annual Meeting of the Society of General Internal Medicine	Conference abstracts	Search criteria not met
Abstracts (Gut), 2005	Conference abstracts	Search criteria not met
Abstracts (HPB – Oxford), 2006	Conference abstracts	Search criteria not met
Calderón-Larrañaga et al, 2013	Observational study	Search criteria not met
Prakash et al, 2008	Narrative review	Search criteria not met
Makris et al, 2011	Systematic review	Not relevant to PICO
Clinical vignettes, 2004	Clinical teaching cases	Search criteria not met
The British Society of Gastroenterology, 1989	Guidelines	Search criteria not met
ECR 2012 Book of Abstracts	Educational programme	Search criteria not met

APPENDIX B

Review of clinical practice guideline:

AGREE II assessment of the NICE Clinical guideline: GORD and dyspepsia in adults: investigation and management, 3 September 2014. Refer to the attached AGREE II assessment report.

General agreement on most domains was reached between the two appraisers of these guidelines.

AGREE_Appraisal_NICE_GORD_CPG_201

AGREE_Appraisal_NICE_GORD_CPG_201

REFERENCES

[i] McDonagh MS, Carson S & Thakurta S. 2009. Drug Class Review. Proton Pump Inhibitors. Final Report Update 5. Oregan, Portland. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0008769/

[ii] Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2013 May 31;(5):CD002095. https://www.ncbi.nlm.nih.gov/pubmed/23728637

[iii] Adult Hospital Level STGs and EML, 2015

[iv] Li MJ, Li Q, Sun M, Liu LQ. Comparative effectiveness and acceptability of the FDA-licensed proton pump inhibitors for erosive esophagitis: A PRISMA-compliant network meta-analysis. Medicine (Baltimore). 2017 Sep;96(39):e8120. https://www.ncbi.nlm.nih.gov/pubmed/28953640

[v] Klok RM, Postma MJ, van Hout BA, Brouwers JR. Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use. Aliment Pharmacol Ther. 2003 May 15;17(10):1237-45. https://www.ncbi.nlm.nih.gov/pubmed/12755837

[vi] NICE. Clinical guideline: Gastro-oesophageal reflflux disease and dyspepsia in adults: investigation and management, 3 September 2014. http://nice.org.uk/guidance/cg184

[vii] SAMF, 2016.