National Prescribing Service Limited

Drug Utilisation Briefing

for

Enhanced Divisional Quality Use of Medicine Program

October 2002

Target drug group: Ulcer healing drugs

NPS related programs:
(date of delivery)

Dyspepsia (2001)
Peptic ulcers and *H. pylori* (1998)

Contents

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National Prescribing Service. Drug utilisation briefing for enhanced divisional quality use of medicine program: ulcer healing drugs. October 2002.

1. Clinical practice guidelines

- Therapeutic Guidelines: Gastrointestinal 2002 version 3.
  print version available October 2002, electronic version available to subscribers early 2003 via http://etg.hcn.net.au/
  (major changes in therapy have been incorporated for *Helicobacter pylori* eradication and gastro-oesophageal reflux disease).

- Digestive Health Foundation. Gastro-oesophageal reflux disease in adults - Guidelines for Clinicians. *Gastroenterological Society of Australia (GESA)* 2001 3rd Edition.
  http://www.gesa.org.au/members_guidelines/goreflux/index.htm

  GESA Professional Guidelines are only available to GESA Members and Health Professionals registered with Med-E-Serv InTouch (available via
  http://www.medeserv.com.au/intouch/registration/index.cfm

- Australian Medicines Handbook (AMH) 2002, 3rd Edition.

2. NPS resources available

(Caution: The guidelines above have been updated since the publication of these resources).

- NPS News 14 (February 2001).
- Prescribing Practice Review (PPR) 11 & PBS prescribing data feedback (April 2001).
- Case studies including results and expert commentaries:
  - CS1 Management of Peptic Ulcer (1998).
  - CS13 Management of Dyspepsia (2001).

(Available via the NPS website at www.nps.org.au . Print copies available on request).

3. What's what: H_2 antagonists and proton pump inhibitors (PPIs)

The definition of 'ulcer healing drugs' in this document has been taken to be: H_2 antagonists and proton pump inhibitors (PPIs).

The Australian Medicines Handbook 2002 classifies H_2 antagonists and PPIs in section12.1: Drugs for peptic ulcer disease and reflux disease. Other drugs in this classification include antibiotics (as part of regimens for *H. pylori* eradication), sucralfate, misoprostol and antacids.

- H_2 antagonists

Generic name	Strengths available*	Brand names	PBS codes
Cimetidine	200mg, 400mg, 800mg	Cimehexal®, Magicul®, SBPA Cimetidine®, Sigmetadine®, Tagamet® GenRx Cimetidine®, Cimetidine-BC®	8150Y, 8151B, 8152C, 8153D, 1157X, 1158Y, 1159B, 1156W, 8900K, 8901L
Famotidine	20mg, 40mg	Amfamox®, Pepcid®, Pepcidine®	8154E, 8155F, 2487X, 2488Y, 8906R, 8908W, 8907T, 8909X
nizatidine	150mg, 300mg	Tazac®	8156G, 8157H, 1505F, 1504E, 8930B, 8932D, 8931C, 8933E
ranitidine	150mg, 300mg	Ausran®, DBLRanitidine®, Rani 2®, Ranihexal®, Ranoxyl®, Zantac®, Zantac relief®, GenRx Ranitidine®, SBPA Ranitidine®, Ranitidine-BC®	8158J, 8159K, 8160L, 8161M, 1978D, 1927Y, 1977C, 8162N, 8902M, 8904P, 8903N, 8905Q

Note: Ranitidine and famotidine are Pharmacy medicines available from community pharmacies without a prescription.

- Proton pump inhibitors (PPIs).

Generic name	Strengths available*	Brand names	PBS codes.
esomeprazole	20mg, 40mg	Nexium®	8601Q, 8600P
lansoprazole	15mg, 30mg	Zoton®	8198L, 2240X, 2241Y, 8528W, 8529X
omeprazole	10mg, 20mg	Acimax®, Losec®, Probitor®, Maxor®	8332M, 1326T, 1327W, 8331L, 8333N
pantoprazole	20mg, 40mg	Somac®	8399C, 8007K, 8008L
rabeprazole	10mg, 20mg	Pariet®	8507R, 8509W, 8508T

* Not all brands are available in all strengths.

Refer to the 'Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners' for PBS Authority requirements and restricted benefit listings
http://www.health.gov.au/pbs/general/schedule.htm

4. What do we currently know about prescribing of H_2 antagonists and PPIs?

The two main indications for the use of H_2 antagonists and proton pump inhibitors[1] are as acid suppressants in:

- the treatment of peptic ulcer disease- in combination with antibiotics for the eradication of *H. pylori.*
- Gastro-oesophageal reflux disease (GORD).

Upper gastrointestinal problems and dyspepsia are very common.

- Approximately 25% of the adult population in Western Society experience dyspeptic symptoms at least monthly while 5% experience daily symptoms.[2]
- The BEACH survey (1998-9) showed that upper gastrointestinal (GI) problems were managed at a rate of 4.0 per 100 encounters and that new episodes of upper GI problems arose at a rate of 1.2 per 100 patient contacts.[3]
- The national SAND (Supplementary Analysis of Nominated Data) program within BEACH,[3] found that:
    - The prevalence of upper GI problems increased with age, to peak in patients aged 45-64 years (37.1%) and then decreased slightly in the older age groups;
    - More than half of patients (55.0%) who reported upper GI problems, were taking prescribed medication: 39.2% of those with dyspepsia, 68.8% of those with reflux and 94.9% of those with an ulcer;
    - Information on medication type (antacid, H_2 antagonist or PPI) was also collected, however due to recent changes in PBS listing for PPIs (see below), the findings are unlikely to represent the current pattern of medication use.

There were significant changes to the PBS listing of PPIs in mid 2001.

- Prior to May 2001, PPIs were an authority required listing on the PBS. In May 2001, pantoprazole was transferred to a restricted benefit listing for the initial treatment of peptic ulcer, GORD, scleroderma oesophagus and Zollinger-Ellinson syndrome on the basis of acceptable cost-effectiveness in GORD at the proposed price.
- Over the next six months, lansoprazole, omeprazole and rabeprazole also transferred to a restricted benefit listing for peptic ulcer, GORD, and scleroderma oesophagus. Omeprazole also gained a restricted benefit listing for Zollinger-Ellinson syndrome.
- Since May 2001, there has been a significant national increase in both PPI use and overall ulcer healing drug use (i.e. the increase in PPI use was not matched to the same extent by a fall in use of H_2 antagonists).[4]

Data suggests that prescribing of H_2 antagonists and PPIs is not always in line with best practice guidelines.

- Current guidelines recommend the use of antacids or H2 antagonists in mild to moderate oesophagitis.[5,6] However, an Australian survey showed that 40% of patients prescribed a proton pump inhibitor (PPI) for mild to moderate oesophagitis had not previously used a H_2 antagonist.[7]
- Following symptom control of GORD, current guidelines recommend a step-down approach to a H_2 antagonist, a lower strength of PPI or trial of intermittent symptom-driven therapy with PPIs.[5,6] For the year to June 2002 the low strength formulation of the PPIs accounted for only 2% of all PPI prescriptions issued nationally on the PBS.[8] This suggests that there is currently minimal step down of PPIs and there is potential for some patients to be managed on a lower dose of a PPI.

5. Principles of quality prescribing: H_2 antagonists and PPIs.

Judicious selection of management options

- Factors that could precipitate or aggravate dyspeptic symptoms should be reviewed and addressed where appropriate (e.g. diet, lifestyle and medications including NSAIDs, calcium channel blockers and theophylline).[1,2]
- Regular use of a PPI is not considered appropriate for patients with mild-intermittent GORD.[1]
- Minimise the need for prophylaxis with H_2 antagonists or PPIs against NSAID-induced ulcer. This can be achieved by avoiding unnecessary NSAID therapy, or if a NSAID is necessary, using a low-risk, shorter-acting NSAID (e.g. ibuprofen, diclofenac) or COX-2 selective NSAIDs at the minimum effective dose.[1]
- Reserve prophylaxis against NSAID-induced ulcers for high-risk patients (e.g. the elderly, those with a prior ulcer, those with a serious concomitant disease who would poorly tolerate an ulcer bleed and those taking high-dose NSAIDs, longer-acting NSAIDS or corticosteroids).[1]

Appropriate choice of medicines, where a medicine is considered necessary.

The latest edition of the Therapeutic Guidelines: Gastrointestinal and the Australian Medicines Handbook should be referred to for up to date recommendations on the use of ulcer healing drugs.

- H_2 antagonists and PPIs should be used within a planned management strategy including regular review of continued efficacy and need.
- For GORD, the choice of drug and prescribed dose should be tailored to the underlying pathological cause and symptom severity using a step down approach.[1]
- Use antacids as required or a H_2 antagonist once or twice daily as required, for patients with mild or intermittent symptoms of GORD who require drug treatment.[1]
- An initial 4-8 week course of a PPI at treatment dose is appropriate for GORD patients who have symptoms on most days.[1]
- Following symptom control of GORD, a step down approach to a H_2 antagonist or lower dose of PPI or intermittent symptom-driven therapy is recommended (with the exception of patients shown at endoscopy to have severe oesophagitis and patients with scleroderma, strictures or Barrett's oesophagus).[1,2]
- The maintenance dose of esomeprazole is 20mg daily. The 40mg dose should not be prescribed for longer than 8 weeks,[2] (see section 8).
- In patients with peptic ulcer who are *H. pylori* positive, eradicate the *H. pylori* with a one week course of an approved *H. pylori* eradication regimen followed by either a 4-6 week course of a H_2 antagonist or a 2-4 week course of a PPI. (The follow-up course of H_2 antagonist or PPI may be omitted in fit patients with small uncomplicated ulcers).[1]
- Maintenance therapy for peptic ulcers after *H. pylori* eradication is generally considered unnecessary. However if *H. pylori* eradication is not successful or not practicable recurrence of ulcers can be markedly reduced by treatment with a H_2 antagonist (note: PPIs are not available on PBS for this indication).[1]
- The generic prescribing of H_2 antagonists and PPIs (or allowing brand substitution) will generally reduce the cost of the medicine to the patient as there will be no brand premium (as is the case with Tagamet®, Zantac®, Losec®).[3]
- The prescribing of base-priced H_2 antagonists (cimetidine and ranitidine) will reduce the cost of the medicine to the patient due to the therapeutic group premium on other H_2 antagonists (unless the prescriber has sought an exemption from the HIC on clinical grounds).[3]

Safe and effective use of medicines

- The safety of long-term (10-20 years or longer) H_2 antagonist and PPI drug use remains to be established; the risks of long-term drug therapy should be considered in the context of achievable benefit.
- In the presence of alarm symptoms (e.g. pain on swallowing, dysphagia, weight loss or anaemia) drug treatment should not be used until the diagnosis is confirmed as it may mask symptoms and delay diagnosis.[1,2]
- All H_2 antagonists are mainly excreted renally so dosage reductions may be required in patients with significant renal impairment.[1,2]
- Patients who are taking warfarin or phenytoin should not be prescribed omeprazole as it has been shown to significantly enhance the action of these drugs. An alternative PPI is preferred or there should be increased monitoring of phenytoin and warfarin. As esomeprazole has also been shown to interact with phenytoin the same recommendation applies for the use of esomeprazole and phenytoin.[1,2]

6. Assisting prescribers to identify 'Quality Prescribing questions'.

Data suggests that:

- PPIs are inappropriately prescribed first-line for patients with mild to moderate GORD when a H_2 antagonist or antacid may be effective.
- 98% of PPI prescriptions on the PBS are for the highest strength formulation suggesting minimal step down of therapy to the minimum effective dose of a PPI.

Decision-making steps

Step 1: What are the core principles of Quality Prescribing?

Is current prescribing judicious, appropriate, safe and effective as outlined on the previous page?

Step 2: What are the related Quality Prescribing questions?

Step 3: What are the related data questions?

How do we measure and assess current usage against the Quality Prescribing questions?

Putting decision-making steps into practice

1. Quality Prescribing principles	2. Quality prescribing questions:	3. * Data questions:
Is current prescribing judicious?	▪ Are lifestyle factors addressed in patients presenting with dyspepsia?	▪ Nil routine data source.
	▪ Are PPIs prescribed inappropriately for patients with mild-intermittent GORD who have not had a trial of antacids or H_2 antagonists?	▪ Proportion of PPI prescribing for GORD patients (should be less than 100%). ▪ Patients switching between H_2 antagonists and PPIs as a result of step up/step down therapy.
	▪ Are PPIs prescribed inappropriately for the prophylaxis of NSAID-induced ulcers in low risk patients?	▪ Only a small proportion of patients on NSAIDs should be co-administered PPIs. ▪ Use of NSAID plus PPI in low risk patients (e.g. patients under 50 years with no prior history of ulcer and no cardiovascular disease).
Is current prescribing appropriate?	▪ Is reason for use of a H_2 antagonist or PPI recorded?	▪ Proportion of patients prescribed H_2 antagonist or PPI who do NOT have a reason for use recorded.
	▪ Do prescribers appropriately use a mix of antacids, H_2 antagonists and PPIs at varying doses? (i.e. match treatment choice to symptom severity).	▪ Proportion antacids : H_2 antagonists : PPIs. ▪ Proportion high strength PPI : low strength PPI preparation (both strengths should be prescribed).
	▪ Are PPIs used for maintenance treatment of peptic ulcers after *H. pylori* eradication? (maintenance therapy generally considered unnecessary and PPIs are not available on PBS for this indication).	▪ Proportion of PPI use for peptic ulcer which is for longer duration than 6 weeks.
	▪ Is *H. pylori* eradication therapy prescribed to all patients with peptic ulcer disease who are *H. pylori* positive?	▪ Proportion of patients with peptic ulcer disease who are *H. pylori* positive NOT prescribed a course of *H. pylori* eradication therapy.

Is current prescribing safe and effective?	▪ Are patients prescribed omeprazole also taking phenytoin or warfarin?	▪ Proportion of omeprazole users prescribed warfarin or phenytoin (should be very low and those that are, should have frequent monitoring of their phenytoin or warfarin).

*** Data questions**: *This 'step' is for further development by the Data consultancy in consultation with NPS but initial questions are included here as examples. The accessibility, interpretation and limitations of obtaining data to answer these questions all require further investigation.*

7. Limitations of the PBS dataset as a data source to review prescribing of H_2 antagonists and PPIs

- Indication for prescribing cannot be determined from PBS dataset.
- Items below co-payment are not collected for general patients, this includes antacids and ranitidine.
- Antacids and two H_2 antagonists (ranitidine and famotidine), are available 'over the counter' (i.e. without a prescription) from community pharmacies. This data is not captured by the PBS dataset.
- Knowledge of drug prices over time is required to interpret the PBS dataset. For example the cost to Government of one months supply of PPIs fell by nearly 50% between 1998 to 2000. Nationally there was an increase in volume of PPI use over this period but due to the price decrease this was accompanied by a dip in expenditure.
- Knowledge of drug prices relative to the level of co-payment over time is required to interpret the PBS dataset. If the level of co-payment is increased, drugs that were previously captured for general patients by the PBS dataset, may fall below the level of co-payment and therefore no longer be captured for general patients. For example the price of ranitidine fell below co-payment in early 2001.
- Knowledge of changes to the PBS authority requirements and restricted benefits is required to interpret the PBS dataset. For example from May 2001 onwards there was a significant increase in PPI use due to the removal of the requirement for authority prior to prescribing.
- The possible contribution of hospital prescribing should be considered e.g. are *H. pylori* eradication regimens supplied by the local hospital in your Division rather than from PBS prescriptions?

8. Future developments

- New drugs

Esomeprazole (Nexium®) gained a restricted benefit listing on the PBS in August 2002 for the healing of GORD at a dose of 40 mg daily for a maximum of 8 weeks followed by a reduction to 20 mg daily for the maintenance of healed GORD. This listing is more restrictive than for other PPIs on the PBS.
The place of esomeprazole in therapy relative to other PPIs remains to be established. Its availability extends the range of PPIs available but would not be expected to result in an increase in overall PPI use. The 40 mg dose is significantly more expensive than the treatment dose of all of the other PPIs ($75 per 30 days vs. $46-$49 per 30 days for other PPIs). PBS data is not yet available to confirm if a step down of dose is occurring but anecdotal reports suggest not. Continued long-term use of the 40 mg dose would result in a significant increase in expenditure compared with the other PPIs.

- Potential changes in clinical practice guidelines.

No information available but current edition of Therapeutic Guideline: Gastrointestinal was published October 2002 so no update expected.

9. Indicators of quality prescribing under development

Yes- will include a link to an indication for therapy.

10. Potential changes in prescribing if principles of good prescribing are followed

To follow.

11. Practice based Quality Prescribing Cycle Kit

To be developed.

12. Cost comparisons for H_2 antagonists and PPIs and pharmacoeconomic considerations

To follow.

13. References

What do we currently know about the prescribing of H_2 antagonists and PPIs?

1. Australian Medicines Handbook (AMH) 2002, 3rd edition. Adelaide, Australian Medicines Handbook Pty Ltd, 2002.
2. van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H_2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease (Cochrane Review). In*: The Cochrane Library*, Issue 3, 2002. Oxford: Update Software.
3. Sayer GP, Britt H, Horn F, et al. Measures of health and health care delivery in general practice in Australia. AIHW Cat. No. GEP3. Canberra: Australian Institute of Health and Welfare (General Practice Series no. 3).
4. Australian Doctor Health Communication Weekly, Issue 31 - 10th December 2001. http://www.australiandoctor.com.au/healthcomms_archive.asp?archive=20011210#01
5. Therapeutic Guidelines: Gastrointestinal, Version 3, 2002 North Melbourne: Therapeutic Guidelines Ltd 2002.
6. Digestive Health Foundation. Gastro-oesophageal reflux disease in adults - Guidelines for Clinicians. Gastroenterological Society of Australia *(GESA)* 2001 3rd Edition. http://www.gesa.org.au/members_guidelines/goreflux/index.htm
7. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. Journ of Clin Pharm and Ther 2000;25:333-340.
8. Health Insurance Commission, PBS claims database.

Principles of quality prescribing: H_2 antagonists and PPIs.

1. Therapeutic Guidelines: Gastrointestinal, Version 3, 2002. North Melbourne: Therapeutic Guidelines Ltd, 2002.
2. Australian Medicines Handbook (AMH) 2002, 3rd edition. Adelaide, Australian Medicines Handbook Pty Ltd, 2002.
3. Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners, 1 November 2002, Commonwealth Department of Health and Ageing.

Appendix 1 Pharmaceutical Benefits Pricing Authority. Therapeutic Relativity Sheets.

(available on line at http://www.health.gov.au/pbs/pricing/therelativity.pdf)

Relativity Sheets show specific relativities and pricing comparisons between drugs within a therapeutic group. The relativities are usually based on PBAC advice but may also be historically based.

PHARMACEUTICAL BENEFITS PRICING AUTHORITY

Therapeutic Relativity Sheets

ATC A02 - ANTACIDS, DRUGS FOR TREATMENT OF PEPTIC ULCER AND FLATULENCE	**Effective Date:** 10/02	PAGE **1** OF **1**

1. The listed antacids, both tablets and liquids, have historically been listed at the same price.
2. The sodium alginate-calcium carbonate-sodium bicarbonate product was accepted for listing as having a small advantage over the plain antacid liquids.
3. From listing up until the removal of the authority on H2 receptor antagonists, misoprostol was priced the same, or very near to, ranitidine. From October 1995 it has been reviewed as a standalone item.
4. Omeprazole is recognised by the PBAC as having advantages over the H2-receptor antagonists.
5. Lansoprazole was listed on the basis of equivalence to omeprazole, 30mg = 20mg.
6. Pantoprazole was listed on the basis that 40mg is of similar safety and efficacy to 20mg omeprazole and 20mg is of similar safety and efficacy to 10mg omeprazole and 15mg lansoprazole.
7. Omeprazole magnesium was recommended for listing on the basis of equivalence with omeprazole base.
8. Rabeprazole sodium was recommended for listing on a cost minimisation basis compared to omeprazole/omeprazole magnesium, 10mg = 10mg and 20mg = 20mg.
9. Esomeprazole magnesium trihydrate was recommended for listing on the basis that 20mg esomeprazole was equivalent to 20mg omeprazole in terms of effectiveness and safety in the maintenance of healed severe refractory ulcerating oesophagitis and that 40mg was more effective than 20mg omeprazole in healing of severe refractory ulcerating oesophagitis.