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April 17, 2006

Mr. Denis Bélanger, B.Sc.PhM  
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Re: Canadian Association of Gastroenterology Feedback on the March 6<sup>th</sup> COMPUS Summary of Findings on Proton Pump Inhibitors – Interim Report, GERD

Dear Mr. Bélanger,

I am pleased to provide comments (appended to this letter) from the Canadian Association of Gastroenterology (CAG) in regards to the COMPUS interim report on the *Summary of Findings on Proton Pump Inhibitors*, specifically regarding the GERD portion of your report.

As noted in our letter to you March 14<sup>th</sup> 2006, the CAG raised concern regarding this process. Excellent systematic reviews on this particular area have been recently published (Cochrane, 2005 CAG GERD Consensus Guidelines). Many of our comments relate to evidence that has not been included in your report. The CAG, once again, strongly recommends that much time and effort could be saved by utilizing the existing systematic reviews, at the very least as a basis with which to move forward.

In general, the document is rather cumbersome, for examples, Section 8.1 could be eliminated completely because it is reiterated in Section 8.2., and Table 2 could be streamlined to indicate only the unit cost per drug and usual daily dose range. There are substantial errors regarding terminology, i.e. it is written that PPI's increase gastric levels and this appears in several areas of your document. This is incorrect, it should be stated that they increase *gastrin* levels.

The report appears to have been conducted and written with little guidance by a clinician with expertise in the area. Ideally a "content expert" should be intimately involved in the process if the report is going to be useful for the clinician. **If substantial changes are not made to this document we must insist that it is made clear that the Canadian Association of Gastroenterology does not support this report.**

Regards,

Paul Sinclair  
Executive Director, CAG

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Our detailed comments are as follows:

1. The method of dealing with meta-analyses and RCTs are transparent but the approach to guidelines is not. These should also be assessed for quality. For example the UK NICE guidelines were sponsored by the UK government, a number of Cochrane systematic reviews were commissioned for the guideline and the process took over one year to complete with a multi-disciplinary team using the modified Delphi approach. This is likely to have a lot more rigor than a provincial guideline that involved a few pharmacists who simply gave their opinion after a cursory look at the literature. The report should give the reader an idea of the quality of the guideline in the same way that is done for meta-analyses and RCTs.
2. The report often states that there is no general agreement. Sometimes this statement is plainly ridiculous and seems to arise if one guideline says something slightly different from the others. Again there should be explicit criteria for what general agreement means. If 30 good guidelines all state one thing and one poor guideline disagrees then a sensible report would state there is generally good agreement.
3. In section 3.2 page 16 it is stated that GERD rarely causes mortality. This is correct but this section should highlight that four observational studies have suggested a strong association between GERD symptoms and esophageal adenocarcinoma
  - a) Lagergren J, Bergstrom R, Lindgren A, et al Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *New England Journal of Medicine* 1999, 340: 825-831
  - b) Chow W-H, Finkle WD, McLaughlin JK et al. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA* 1995, 274: 474-477
  - c) Farrow DC, Vaughan TL, Sweeney C et al. Gastro-oesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. *Cancer Causes and Control* 2000; 11: 231-8.
  - d) Ye W, Chow W-H, Lagergren J et al. Risk of adenocarcinomas and gastric cardia in patients with gastroesophageal reflux disease and after antireflux surgery. *Gastroenterology* 2001; 121: 1286-1293).
4. In Section 3.2.1. it is important to note that heartburn may or may not be the dominant or sole symptom, and that in most cases patients present with heartburn in association with other dyspeptic symptoms (Thomson AB, Barkun AN, Armstrong D, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian Adult Dyspepsia Empiric Treatment - Prompt Endoscopy (CADET-PE) study. *Aliment Pharmacol Ther.* 2003 Jun 15;17(12):1481-91).
5. In relation to reflux esophagitis (Section 3.2.2.), and arising from the same reference as above, Canadian data suggested that up to 43% of primary care patients with dyspeptic symptoms have erosive esophagitis – an important point regarding management.
6. In Section 3.2.4. it is important to note that the presented definition considers reflux symptoms to be part of the dyspepsia – this is not clear in your document.

7. G5 page 30 discusses attempting to reduce PPI at 3 months. It is not clear on what basis this duration was chosen. Why not 1 month or 6 months?
8. G11 page 32. There was no mention of increased risk of enteric infections, community pneumonia, reduction in vitamin B12, drug interactions, diarrhoea or headache with PPI therapy.
9. G1A-iii page 38. The GSRS is quoted as a quality of life measure. This is incorrect. The GSRS simply measures GI symptoms and has no quality of life dimension (disease specific or generic). Text related to the GSRS needs to be removed from this section.
10. G1B page 39. The guidelines ARE in agreement that PPIs are more effective than H2RAs in ENRD. Quotes from the guidelines mistake “cost-effectiveness” for “effectiveness”. All guidelines agree that PPIs are the most effective in relieving reflux symptoms but there is argument over what is the most cost-effective approach. The statement is all about effectiveness and so it should state guidelines agree.
11. Page 40. The text states that a MA did not support the statement that PPIs are more effective than H2RA in ENRD. This is correct but the meta-analysis is being updated and including current literature would now suggest PPIs are more effective. The lack of statistical significance is because there were few studies when the MA was conducted. The authors did point this out in the discussion text. Furthermore there is another Cochrane review not quoted by the report that suggests PPIs are more effective than H2RAs for maintenance therapy in ENRD (Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *The Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD003245. DOI: 10.1002/14651858.CD003245.pub2).
12. G1C page 42. To make the statement that there is not agreement on whether PPIs are more effective than H2RAs in esophagitis is astonishing! All guidelines agree that PPIs are more effective (again there may be arguments regarding cost-effectiveness).
13. G1C page 42. When outlining the evidence they state this is based on 2 poor quality MAs and 8 RCTs (of varying quality). There is a Cochrane review on this subject in press (Khan M et al. Medical treatments in the short term management of oesophagitis. *Cochrane Library* 2006 in press) which the committee are welcome to see if they request this. This identified 34 eligible RCTs. Given that the authors only identified 8 RCTs, this calls into question the rigor of the process for this report.
14. G1C page 49. The Cochrane review on PPIs versus H2RAs in maintaining remission of GERD again is not quoted in the review. It is hard to understand how this was missed if a rigorous search strategy was employed. The reference is: Donnellan C, Sharma N, Preston C, Moayyedi P. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. *The Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD003245. DOI: 10.1002/14651858.CD003245.pub2.
15. G2A –i page 52. The report states that the efficacy of double dose PPI therapy is inconclusive. Again the Cochrane review in press addresses this. It identified 15 RCTs (compared to the 7 in this report) and suggested a small but statistically significant effect in favour of double dose PPI. The efficacy in LA grades C and D should be mentioned as this seems to be where double dose has an advantage.

16. G3A. Whilst we agree that the evidence is not strong nearly all gastroenterologists would suggest long term PPI therapy for patients with esophageal strictures. PPIs are much better than H2RAs in severe esophagitis in RCTs and esophageal stricture is an example of even more severe esophagitis. It would be considered negligent in a patient with recurrent esophageal stricture not to be given long term PPI therapy given the risk of recurrent endoscopic esophageal dilatation or surgery.
17. G4A page 57. The section on whether all standard dose PPIs are equally effective misses a MA on this subject (Edwards SJ, Lind T, Lundell L. Systematic review of proton pump inhibitors for the acute treatment of reflux oesophagitis. *Alimentary Pharmacology & Therapeutics* 2001; 15: 1729-36).
18. G5B page 62. Again the Cochrane review on long term therapy in esophagitis and ENRD would be useful to quote here. There is also a discussion about current recommendations including prokinetic therapy for chronic GERD management, which is long outdated and not currently recommended.
19. G6Ai page 63. The conclusion reached for this statement is not supported by the evidence. 80% of patients with erosive esophagitis have relapse of their disease upon withdrawal of PPI therapy. It is unclear what is intended by “the need for other medications” as treatment with, for example, a prokinetic in addition to a PPI has been shown to be no better than a PPI alone.
20. G6Bii page 65. There is no evidence to support that the number of prescriptions should be limited. Rather, patients with relapsing disease should have maintenance therapy. Data in support of a step-down approach are weak and limited – most patients need the same dose that initially provided symptom improvement/healing of esophagitis.
21. G6C page 66. We are unaware of any evidence which would support the step down of patients with Grade C and D esophagitis. Rather, most patients with Grade C and D esophagitis require at least full dose, or double dose, PPI therapy.
22. G7 page 67. It must be made explicitly clear that the data only supports this strategy in NERD patients. In patients with esophagitis, symptoms relapse frequently and as such treatment should be continuous.
23. G7A – ii page 68. The report misses another systematic review. This time addressing on-demand therapy in GERD (Zacny J, Zamakhshary M, Sketris I, Veldhuyzen van Zanten S. Systematic review: the efficacy of intermittent and on-demand therapy with histamine H2-receptor antagonists or proton pump inhibitors for gastro-oesophageal reflux disease patients. *Alimentary Pharmacology & Therapeutics* 2005; 21: 1299-312). This systematic review identified 5 RCTs evaluating on-demand PPI therapy in ENRD whilst the COMPUS report only identified three.
24. G9A page 74. Again a systematic review of surgery versus medical therapy should have been included here but wasn't (Allgood PC, Bachmann M. Medical or surgical treatment for chronic gastro-oesophageal reflux? A systematic review of published evidence of effectiveness. *Eur J Surg* 2000;166:713–721). Literature suggests that most patients undergoing surgery will eventually end up taking a PPI once again. This statement should be reworded to indicate that medical and surgical approaches are reasonable however medical therapy is preferred by most patients.

25. G10A page 76. Consider referencing the basic literature and one case-controlled study, which provides the current rationale (albeit weak) for using a PPI in asymptomatic Barrett's esophagus patients.
26. G10B – i page 77. It is stated that surgery doesn't prevent dysplasia. There is no evidence to support this statement as there have been no RCT's comparing dysplasia progression in surgery vs. no surgery. As accurate statement would be that there is currently no evidence that ARS prevents the progression of dysplasia.
27. G11 page 80. It should be clearly noted that the long-term safety considerations are a theoretical concern.
28. The narrative explanations of the economic analyses are fine but it is difficult for the reader to get an overall impression of what they all mean. Also some are old (e.g. 1996) and given changes in evidence and costs since then they are not of much relevance. If these outdated analyses are to be used, it would be important to draw attention to the fact that the strategies used in the model don't currently reflect the 'real world' approach, i.e. inclusion of diagnostic testing for a failed response is considered irrational.
29. The COMPUS report has not fully appraised all available evidence and we suggest the committee meets again and includes a GERD expert in the panel so that all available evidence is interpreted sensibly.
30. The document is very difficult to follow, is repetitive and there is no clear picture emerging from the text as to the place of PPI therapy in the management of GERD. An algorithm may help in this regard.