

Drug Class Review on Proton Pump Inhibitors

Update #5: Preliminary Scan Report

June 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

July 2006 (searches through November 2005)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different PPIs in patients with symptoms of GERD?
 - a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in patients with symptoms of GERD?
 - b. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?
2. What is the comparative effectiveness of different proton pump inhibitors in patients with peptic ulcer and NSAID-induced ulcer?

- a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?
 - b. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?
 - c. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?
 - d. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?
 - e. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?
 - f. In comparisons of PPIs and misoprostol or H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?
 - g. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in preventing NSAID-induced ulcer?
 - h. In comparisons of PPIs and other drugs or placebo, what is the comparative effectiveness of different PPIs in preventing NSAID-induced ulcer?
 - i. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in improving eradication rates in patients with *Helicobacter pylori*?
 - j. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in improving eradication rates in patients with *Helicobacter pylori*?
3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?

4. Are there subgroups of patients based on demographics, other medications, or co-morbidities (including patients with nasogastric tubes, or who cannot swallow solid oral medications) for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Patients with symptoms of gastroesophageal reflux, peptic ulcer, or NSAID-induced ulcer.

Interventions

- Omeprazole (Prilosec[®], Prilosec OTC[®])
- Omeprazole/sodium bicarbonate (Zegerid[®])
- Lansoprazole (Prevacid[®])
- Pantoprazole (Protonix[®])
- Rabeprazole (Aciphex[®])
- Esomeprazole (Nexium[®])

Effectiveness outcomes

- Symptoms
- Endoscopic healing
- Eradication rates
- Functional outcomes
- Quality of life

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events (e.g., diarrhea)

Study designs

1. For effectiveness, study is a randomized controlled trial in an outpatient setting and treatment period is at least 4 weeks duration.
2. For safety, study is a controlled clinical trial or observational study.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from January 2005 through June Week 2 2007, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 118 citations. Of those, there are 20 new potentially relevant new trials (see Appendix, attached):

8 head-to-head trials

- Esomeprazole vs omeprazole for short-term treatment of GERD (2 trials)
- Esomeprazole vs pantoprazole for short-term treatment of GERD
- Esomeprazole vs pantoprazole for maintenance treatment of GERD (2 trials)
- Esomeprazole vs lansoprazole for maintenance treatment of GERD
- Rabeprazole vs omeprazole for peptic ulcer
- Lansoprazole vs omeprazole for Helicobacter pylori eradication

6 trials in children or adolescents

- 5 trials of lansoprazole, pantoprazole, or esomeprazole for short-term treatment of GERD
- 1 trial of omeprazole for helicobacter pylori eradication

6 placebo- and active control trials

- Lansoprazole vs placebo for maintenance treatment of GERD
- Pantoprazole vs placebo for maintenance treatment of GERD
- 2 trials of PPI vs surgical treatment for GERD with 7-year followup
- 2 trials of esomeprazole vs placebo for prevention of NSAID-induced ulcer

New Drugs/Indications

Zegerid[®] (omeprazole/sodium bicarbonate) 20 mg capsules were FDA-approved in February 2006 for short-term treatment of active duodenal ulcer, treatment of heartburn and other symptoms associated with GERD, short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, and maintenance of healing of erosive esophagitis. Zegerid[®] 40 mg capsules were approved for short-term treatment (4-8 weeks) of active benign gastric ulcer. Zegerid[®] chewable tablets were approved in March 2006 for the above indications. (Zegerid[®] suspension was approved in June 2004)

The rabeprazole 10 mg dose has been discontinued; the 20 mg dose is still available.

In April 2007, esomeprazole was FDA-approved for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

New Safety Alerts

There are no FDA or Health Canada safety alerts for any of the proton pump inhibitors. Drug interaction warnings for atazanavir have been added to the omeprazole and esomeprazole product labels, and to the lansoprazole product label for warfarin.

We identified a nested case control study that reported an increased risk of hip fracture in patients taking high-dose PPIs for one year or longer. The risk increased with longer duration of use (Yang, 2006, see Appendix).

APPENDIX. Potentially Relevant New Trials

Head-to-head trials (N=7)

Short-term treatment of GERD (n=3):

Lightdale, C. J., C. Schmitt, et al. (2006). "A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis." *Digestive Diseases & Sciences* **51**(5): 852-7.

The objective of this trial was to compare the efficacy of esomeprazole, 20 mg, with that of omeprazole, 20 mg, in patients with erosive esophagitis (EE). In this multicenter, double-blind, parallel-group trial, 1176 patients with EE confirmed by endoscopy (*Helicobacter pylori*-negative by serology) were randomized to once-daily treatment with 20 mg esomeprazole or 20 mg omeprazole for 8 weeks. The primary outcome was the proportion of patients with healed EE through week 8. Secondary outcomes included diary and investigator assessments of heartburn symptoms. Cumulative life-table healing rates at week 8 were similarly high for 20 mg esomeprazole (90.6%; 95% confidence interval, 88.1%-93%) and 20 mg omeprazole (88.3%; 95% confidence interval, 85.5%-91.0%). The two treatments were comparable for other secondary measures and had similar tolerability profiles.

Schmitt, C., C. J. Lightdale, et al. (2006). "A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis." *Digestive Diseases & Sciences* **51**(5): 844-50.

To compare esomeprazole with omeprazole for healing erosive esophagitis (EE), 1148 patients with endoscopically confirmed EE were randomized to once-daily esomeprazole, 40 mg, or omeprazole, 20 mg, for 8 weeks in this multicenter, double-blind, parallel-group trial. The primary outcome was the proportion of patients with healed EE at week 8. Secondary outcomes included diary and investigator assessments of heartburn symptoms. At week 8, estimated healing rates were 92.2% (95% CI, 89.9%-94.5%) with esomeprazole and 89.8% (95% CI, 87.2%-92.4%) with omeprazole. Healing rates with esomeprazole were significantly higher than those with omeprazole at weeks 8 (88.4% vs 77.5%; $P = 0.007$) and 4 (60.8% vs 47.9%; $P = 0.02$) in patients with moderate to severe (Los Angeles grade C or D) EE at baseline but were not significantly different for patients with mild (Los Angeles grade A or B) EE. Both treatments were comparable for other secondary measures and had similar tolerability profiles.

Vcev, A., I. Begi, et al. (2006). "Esomeprazole versus pantoprazole for healing erosive oesophagitis." *Collegium Antropologicum* **30**(3): 519-22.

The aim of this study was to compare the efficacy of esomeprazole and pantoprazole with regard to healing and relief from gastroesophageal reflux disease-related symptoms. In this multicentre, randomized, single-blind study 180 patients (ITT population) diagnosed with endoscopically proven GERD grade A,B,C received esomeprazole (40 mg once daily (o.d.), $n = 90$) or pantoprazole (40 mg o.d., $n = 90$). Healing and relief from GERD-related symptoms were assessed at first and final visit (after 4 or 8 weeks of treatment). Esomeprazole 40 mg provided

significantly greater healing than pantoprazole 40 mg after 4 weeks of treatment in patients with EE (77.8% vs. 72.2%). Esomeprazole-treated patients were healed after up to 8 weeks of treatment similar those treated with pantoprazole (92.2% vs. 91.1%). The proportion of heartburn-free days was similar in patients treated with esomeprazole and to those treated with pantoprazole.

Longer-term (6 months) maintenance treatment for GERD (n=2)

Devault, K. R., J. F. Johanson, et al. (2006). "Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams." Clinical Gastroenterology & Hepatology 4(7): 852-9.

BACKGROUND AND AIMS: The aim was to compare esomeprazole with lansoprazole for the maintenance of healed erosive esophagitis and resolution of gastroesophageal reflux disease-related symptoms in a United States population. **METHODS:** Patients who entered this double-blind, randomized, parallel-group, multicenter, maintenance trial had been treated and healed (no endoscopic evidence of erosive esophagitis) with esomeprazole 40 mg or lansoprazole 30 mg once daily (patients with Los Angeles grades C and D erosive esophagitis at baseline) or esomeprazole 40 mg (patients with Los Angeles grades A and B erosive esophagitis at baseline) and had no heartburn or acid regurgitation symptoms during the previous week. Patients were randomized to maintenance once-daily therapy with esomeprazole 20 mg (n = 512) or lansoprazole 15 mg (n = 514) for up to 6 months. Esophago-gastroduodenoscopies were done at months 3 and 6, and investigators assessed symptom severity at months 1, 3, and 6. Endoscopic/symptomatic remission was defined as no erosive esophagitis and no study withdrawal as a result of reflux symptoms. **RESULTS:** The estimated endoscopic/symptomatic remission rate during a period of 6 months was significantly higher (P = .0007) for patients who received esomeprazole 20 mg once daily (84.8%) compared with those who received lansoprazole 15 mg (75.9%). Most patients had no heartburn (383/462 and 369/466) or acid regurgitation (401/462 and 400/466) symptoms at 6 months, and there were no significant differences between treatments. Both treatments were well-tolerated. **CONCLUSION:** Esomeprazole 20 mg is more effective than lansoprazole 15 mg in maintaining endoscopic/symptomatic remission in patients with healed erosive esophagitis.

Goh, K.-L., R. Benamouzig, et al. (2007). "Efficacy of pantoprazole 20 mg daily compared with esomeprazole 20 mg daily in the maintenance of healed gastroesophageal reflux disease: a randomized, double-blind comparative trial - the EMANCIPATE study." European Journal of Gastroenterology & Hepatology 19(3): 205-11.

OBJECTIVES: To compare the efficacy and tolerability of pantoprazole 20 mg once daily with that of esomeprazole 20 mg once daily for 6 months as maintenance therapy in patients with previously healed gastroesophageal reflux disease. **METHODS:** In an initial open-label acute phase, outpatients with endoscopically confirmed gastroesophageal reflux disease (Los Angeles grades A-D) received pantoprazole 40 mg once daily for 4 or 8 weeks. Those healed (defined as the absence of esophagitis, and 'no' or 'mild' heartburn and acid regurgitation) were randomized in the double-blind manner for maintenance therapy with pantoprazole

20 mg once daily or esomeprazole 20 mg once daily for 6 months. **RESULTS:** In the acute healing phase, 1452 patients were recruited to receive pantoprazole 40 mg once daily. Healing success was 91% (intent-to-treat analysis). A total of 1303 patients entered the maintenance phase of the study. Pantoprazole 20 mg once daily and esomeprazole 20 mg once daily were equally effective at maintaining patients in remission; 84 and 85% of pantoprazole and esomeprazole recipients remained in combined endoscopic and symptomatic remission at 6 months (intent-to-treat analysis). The confidence interval of the difference was (-5.7; +infinity), showing that pantoprazole is as effective as esomeprazole with a noninferiority margin of 5.8%. Combined endoscopic and symptomatic remission was independent of *Helicobacter pylori* status. Both treatments were well tolerated and safe.

CONCLUSION: Treatment with pantoprazole 20 mg once daily or esomeprazole 20 mg once daily provides similarly effective and well-tolerated maintenance of previously healed gastroesophageal reflux disease irrespective of baseline *H. pylori* status.

Scholten, T., I. Teutsch, et al. (2007). "Pantoprazole on-demand effectively treats symptoms in patients with gastro-oesophageal reflux disease." Clinical Drug Investigation **27**(4): 287-96.

OBJECTIVE: The efficacy of pantoprazole as on-demand therapy for the long-term management of patients with mild gastro-oesophageal reflux disease (GORD) has been demonstrated in clinical studies. In this study, the efficacy of pantoprazole 20mg and esomeprazole 20mg as on-demand therapy for relief of symptoms of mild GORD was compared. **METHODS:** Patients with reflux oesophagitis grade A or B (Los Angeles classification) or endoscopy-negative reflux disease (enGORD) were treated with pantoprazole 20mg once daily for 28 days during the acute phase (AP, n = 236). Patients without heartburn during the final 3 days of the AP entered the long-term phase (LTP, n = 199) and were randomised to either pantoprazole 20mg or esomeprazole 20mg as on-demand treatment for 6 months. Antacids were provided as rescue medication during this phase. The mean intensities of the symptoms of heartburn, acid eructation and pain on swallowing, both separately and as a combined symptom score, together with the mean duration of these symptoms during on-demand treatment, were compared between the two treatment groups. The number of tablets taken was also compared. **RESULTS:** After 4 weeks of treatment with pantoprazole, 87.3% of patients had relief from heartburn, 74.1% from epigastric pain and 80.8% from acid eructation, according to the investigator assessment. A total of 236 patients were eligible for the on-demand phase. Based on patient diary data, on-demand treatment with pantoprazole resulted in significantly lower mean intensity of heartburn compared with that in the esomeprazole group (1.12 for pantoprazole and 1.32 for esomeprazole, respectively [p = 0.012], in the intention-to-treat [ITT] population). The mean symptom intensities of acid eructation and pain on swallowing, together with the duration of these symptoms, were comparable in the two treatment groups. The combined symptom score of the three symptoms heartburn, acid eructation and pain on swallowing was numerically lower in the pantoprazole group compared with the esomeprazole group (1.72 vs 1.99, respectively, in the ITT population). Tablet intake was comparable in both

groups. Relief of symptoms in *Helicobacter pylori*-positive and -negative patients was also similar in both treatment groups. Both treatments were well tolerated with a good safety profile. **CONCLUSION:** On-demand therapy with either pantoprazole 20mg or esomeprazole 20mg is a comparably effective treatment strategy for the long-term treatment of non-erosive and mild GORD. However, the mean intensity of heartburn was significantly lower with pantoprazole treatment.

Peptic ulcer (n=1)

Ji, S., H. S. Kim, et al. (2006). "Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases." Journal of Gastroenterology & Hepatology **21**(9): 1381-7.

AIM: Rabeprazole has been known to inhibit H(+)/K(+)-ATPase more rapidly than omeprazole, the prototype proton pump inhibitor (PPI). The aim of this study was to demonstrate equivalence between low-dose rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of active peptic ulcer and for improvement of symptoms. Also, the effect of CYP2C19 genotypes on ulcer healing rapidity was investigated. **METHODS:** A total of 112 patients with active peptic ulcer were randomized to receive either rabeprazole 10 mg q.d. or omeprazole 20 mg q.d. for 6 weeks. The remaining ratios (%) and complete healing of the ulcer were determined by endoscopy at 1 week and 6 weeks of treatment. The severity of ulcer pain was also investigated during treatment. CYP2C19 genotype was determined by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. **RESULTS:** The remaining ratio of peptic ulcers after 1 week and the complete healing rate after 6 weeks in the rabeprazole versus omeprazole group were 45.5% versus 50.3% ($P = 0.475$) and 80.6% versus 87.0% ($P = 0.423$), respectively. CYP2C19 genotypes had no effect on the remaining ratio of peptic ulcers after 1 week and the healing rate of peptic ulcers after 6 weeks in both groups. The proportions of patients with symptom improvement or resolution were comparable between the two groups. **CONCLUSION:** Low-dose rabeprazole 10 mg has a similar efficacy for the healing rapidity of active peptic ulcer disease and symptom improvement compared with standard-dose omeprazole 20 mg.

Eradication of *Helicobacter pylori* (n=1)

Sancar, M., F. V. Izzettin, et al. (2006). "Pharmacoeconomic comparison of *Helicobacter pylori* eradication regimens." Pharmacy World & Science **28**(4): 207-14.

BACKGROUND: *Helicobacter pylori* is the most important etiologic agent for development of peptic ulcer, chronic gastritis and gastric carcinomas. It is now well established that *H. pylori* eradication treatment is more cost-effective than acid suppressing therapies alone for the treatment of peptic ulcer disease. However, the comparative cost-effectiveness of various *H. pylori* eradication regimens is still not clear. **OBJECTIVE:** This study was designed to make a pharmacoeconomic comparison of different *H. pylori* eradication regimens in patients with peptic ulcer disease or chronic gastritis, using real-world cost and effectiveness data. **SETTING:** Istanbul University Hospital and Marmara University Hospital. **METHOD:** A total of 75 patients diagnosed as *H. pylori* (+) by endoscopy were randomized to receive

one of the seven *H. pylori* treatment protocols. These protocols were as follows: (LAC) = 'lansoprazole 30 mg bid + amoxicillin 1 g bid + clarithromycin 500 mg bid' for 7 days and (OCM) = 'omeprazole 20 mg bid + clarithromycin 250 mg bid + metronidazole 500 mg bid'; (OAM) = 'omeprazole 40 mg qd + amoxicillin 500 mg tid + metronidazole 500 mg tid'; (MARB) = 'metronidazole 250 mg tid + amoxicillin 500 mg qid + ranitidine 300 mg hs + bismuth 300 mg qid'; (OAC) = omeprazole 20 mg bid + amoxicillin 1 g bid + clarithromycin 500 mg bid'; (OCA) = omeprazole 40 mg bid + clarithromycin 500 mg bid + amoxicillin 1 g bid'; (OAB) = 'omeprazole 20 mg bid + amoxicillin 500 mg tid + bismuth 300 mg qid' each for 14 days. Only direct costs were included in the analysis. Effectiveness was measured in terms of "successful eradication". The cost-effectiveness ratios of the regimens were calculated using these effectiveness and cost data. The perspective of the study was assumed as the Government's perspective. MAIN OUTCOME MEASURE: Cost-effectiveness ratios of eradication regimens. RESULTS: MARB and OCA regimens were found to be more cost-effective than the other treatment regimens. The eradication rates and cost-effectiveness ratios calculated for these protocols were 90% (158.7 euros) for MARB and 90% (195.8 euros) for OCA regimen. CONCLUSION: This study confirms the importance of using local pharmaco-economic data. Analyses such as this give decision-makers the tools to choose a better treatment option which is both highly effective yet and has a low cost.

Trials in children and adolescents (N=6)

Short-term treatment of GERD (n=5)

Heyman, M. B., W. Zhang, et al. (2007). "Pharmacokinetics and pharmacodynamics of lansoprazole in children 13 to 24 months old with gastroesophageal reflux disease." Journal of Pediatric Gastroenterology & Nutrition **44**(1): 35-40.

OBJECTIVES: To evaluate the pharmacokinetics and pharmacodynamics of lansoprazole in children between 13 and 24 months of age with gastroesophageal reflux disease (GERD). METHODS: From the population of 66 children with symptomatic GERD, erosive esophagitis (> or = grade 2) or esophageal pH < 4 for > 4.2% of the 24-h period who participated in a phase I/II, open-label, multicenter (11 sites) US study, a subanalysis of 8 toddlers between 13 and 24 months of age was performed. All children were treated, based on body weight, with lansoprazole 15 mg once daily for 8 to 12 weeks. If a child were still symptomatic after 2 weeks of treatment, then the dose of lansoprazole could be increased to twice daily at the discretion of the investigator. Pharmacokinetic parameters were assessed at day 5. Twenty-four-hour median intragastric pH and the percentage of time intragastric pH > 3 or > 4 were assessed at baseline and at day 5 of treatment. Symptom response was assessed by investigator interview and daily diary. Safety was monitored by physical examinations including vital signs, adverse event assessments and laboratory evaluations. RESULTS: Pharmacokinetic analysis of 5 children found a mean time to reach maximum concentration of 1.4 h, maximal plasma concentrations of 894 ng/mL, area under the concentration time curve of 1906 ng *

h/mL and a half-life of 0.66 h. Significant ($P < \text{or} = 0.027$) increases from baseline to day 5 were observed in mean 24-h intragastric pH (2.76-3.52) and the percentages of time pH were > 3 (29.46%-55.36%) and pH was > 4 (16.96%-40.77%). Six of the 8 children had improvement in their overall GERD symptom severity on the basis of investigator assessment, and a reduction was seen in the percentage of days with moderate, severe or very severe GERD symptoms compared with baseline. The dosage of lansoprazole was increased in 3 of the 8 children. Median fasting serum gastrin level increased from 65.0 pg/mL at baseline to 136.5 pg/mL at the final visit. Treatment-related events were mild constipation (1 subject) and mild diarrhea (1 subject). **CONCLUSIONS:** Although larger studies are needed to confirm these results, lansoprazole displays pharmacokinetic and pharmacodynamic parameters in children between 13 and 24 months of age that are similar to those results observed in older children as well as adults.

Pfefferkorn, M. D., J. M. Croffie, et al. (2006). "Nocturnal acid breakthrough in children with reflux esophagitis taking proton pump inhibitors." Journal of Pediatric Gastroenterology & Nutrition **42**(2): 160-5.

OBJECTIVES: We aimed to determine if nocturnal acid breakthrough occurs in children receiving proton pump inhibitors for reflux esophagitis, and to compare the healing of esophagitis in children with nocturnal acid breakthrough receiving proton pump inhibitors +/- ranitidine. **METHODS:** This is a prospective, double-blind study. Endoscopic and histologic esophagitis were scored 0-4 and 0-3, respectively. Patients were treated with a proton pump inhibitor twice daily and esophagogastric pH monitoring was performed at week 3. Patients with nocturnal acid breakthrough were randomized. One group received ranitidine and the other received placebo at bedtime in addition to proton pump inhibitor therapy. Endoscopy was performed on all patients (with pH monitoring on patients with nocturnal acid breakthrough) during the 17th week of therapy. **RESULTS:** We enrolled 18 patients, ages 1 to 13 years (mean = 10.3 years). Mean baseline endoscopic and histologic scores were 3.1 +/- 1.4 and 1.8 +/- 0.7, respectively. Mean dose of proton pump inhibitor was 1.3 mg/kg +/- 0.6. Nocturnal acid breakthrough was documented in 16/18 (89%) patients. Seven patients received ranitidine and 9 received placebo. The reflux index improved: mean of 14.3 at baseline, 2.0 at week 3 ($P = 0.0001$), and 5.1 at week 17 ($P = 0.09$). Nocturnal acid breakthrough persisted in 9/12 (75%) patients, 3 of whom received ranitidine at bedtime. Esophagitis improved in all patients following therapy: mean endoscopy and histology scores were 1.6 +/- 1.8 ($P = 0.0020$) and 0.8 +/- 0.9 ($P = 0.0013$), respectively. Symptoms significantly improved from a mean score of 2.0 at baseline to 0.4 at week 17 ($P = 0.0001$). **CONCLUSIONS:** Nocturnal acid breakthrough is common in pediatric patients treated with proton pump inhibitors. Reflux index remains normal in spite of nocturnal acid breakthrough. Symptoms and esophagitis continued to improve during therapy in spite of nocturnal acid breakthrough. There appears to be no additional benefit to supplementation with ranitidine at bedtime.

Tolia, V., P. R. Bishop, et al. (2006). "Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5-11 years) with symptomatic

gastroesophageal reflux disease." Journal of Pediatric Gastroenterology & Nutrition **42**(4): 384-91.

OBJECTIVE: To evaluate symptom improvement in 53 children (aged 5-11 years) with endoscopically proven gastroesophageal reflux disease (GERD) treated with pantoprazole (10, 20 and 40 mg) using the GERD Assessment of Symptoms in Pediatrics Questionnaire. **METHODS:** The GERD Assessment of Symptoms in Pediatrics Questionnaire was used to measure the frequency and severity over the previous 7 days of abdominal/belly pain, chest pain/heartburn, difficulty swallowing, nausea, vomiting/regurgitation, burping/belching, choking when eating and pain after eating. Individual symptom scores were based on the product of the frequency and usual severity of each symptom. The sum of the individual symptom score values made up the composite symptom score (CSS). The primary end point was the change in the mean CSS from baseline to week 8. **RESULTS:** Mean frequency and severity of each symptom significantly decreased (from $P < 0.006$ to $P < 0.001$) over time. Similar significant decreases in CSS at week 8 versus baseline ($P < 0.001$) were seen in all groups. Significant decreases from baseline in CSS were noted from weeks 1 to 8 in the 20-mg ($P < 0.003$) and 40-mg ($P < 0.001$) groups. The 20- and 40-mg doses were significantly ($P < 0.05$) more effective than the 10-mg dose in improving GERD symptoms at week 1. Adverse events were similar among the treatment groups. **CONCLUSIONS:** Pantoprazole (20 and 40 mg) is effective in reducing endoscopically proven GERD symptoms in children. Both 20 and 40 mg pantoprazole significantly reduced symptoms as early as 1 week.

Tsou, V. M., R. Baker, et al. (2006). "Multicenter, randomized, double-blind study comparing 20 and 40 mg of pantoprazole for symptom relief in adolescents (12 to 16 years of age) with gastroesophageal reflux disease (GERD)." Clinical Pediatrics **45**(8): 741-9.

An age-appropriate questionnaire (GASP-Q) was used to assess the frequency and severity of the gastroesophageal reflux disease (GERD) symptoms: abdominal/belly pain, chest pain/heartburn, pain after eating, nausea, burping/belching, vomiting/regurgitation, choking when eating, and difficulty swallowing, in adolescents age 12 to 16 years. The primary objective was to compare the mean composite symptom score (CSS) at week 8 with baseline after treatment with 20 or 40 mg of pantoprazole. Statistically significant ($p < 0.001$) improvement in CSS occurred in both groups. Safety was comparable between the 2 groups. Pantoprazole was safe, well tolerated, and effective in reducing symptoms of GERD in adolescents.

Zhao, J., J. Li, et al. (2006). "Pharmacokinetic properties of esomeprazole in children aged 1 to 11 years with symptoms of gastroesophageal reflux disease: a randomized, open-label study." Clinical Therapeutics **28**(11): 1868-76.

OBJECTIVE: The aim of this study was to assess the overall exposure, other pharmacokinetic (PK) properties, and tolerability of esomeprazole magnesium after repeated oral doses of 5, 10, and 20 mg in pediatric patients who had symptoms of gastroesophageal reflux disease (GERD). **METHODS:** This randomized, open-label study was conducted at West Coast Clinical Trials, Long Beach, California. Boys

and girls aged 1 to 11 years who had a clinical diagnosis of GERD were included and stratified by age (1-5 years [younger group] and 6-11 years [older group]). For this 5-day study, children in the younger group were randomly assigned to receive 1 esomeprazole 5- or 10-mg capsule p.o. QD, and those in the older group were randomly assigned to receive 1 esomeprazole 10- or 20-mg capsule p.o. QD. On days 1 to 4, study medications were administered with the supervision of the study personnel 1 hour before breakfast. Blood samples were collected within 0.5 hour before and 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours after study drug administration on day 5. Plasma concentrations of esomeprazole were measured using reverse-phase liquid chromatography and mass-spectrometric detection. Tolerability assessments were performed by reviewing the number and severity of adverse events (collected via spontaneous reporting and direct questioning) and findings from the physical examination, which included vital-sign measurements and laboratory analysis (hematology, biochemistry, and urinalysis). Site personnel supervised the administration of the study drug to ensure compliance with treatment. RESULTS: The study included 31 children (17 boys, 14 girls; mean age, 5 years; 18 children in the younger group, 13 in the older group). A total of 27 children were included in the PK analysis. In the younger group, the geometric mean AUC(0-infinity) and C_{max} values in the esomeprazole 10-mg group were >2-fold that in the 5-mg group (AUC(0-infinity), 4.83 and 0.74 pmol x h/L [0.32 and 0.04 micromol x h x L(-1)/kg], respectively; C_{max}, 2.98 and 0.62 micromol/L [0.19 and 0.03 micromol/L x kg(-1)], respectively). In the older group, the geometric mean AUC(0-infinity) and C_{max} values for the 20-mg dose group were approximately 2-fold those for the 10-mg dose group (AUC(0-infinity), 6.28 and 3.70 micromol x h/L [0.21 and 0.12 pmol x h x L(-1)/kg], respectively; C_{max}, 3.73 and 1.77 micromol/L [0.13 and 0.06 micromol/L x kg⁻¹], respectively). For the 10-mg esomeprazole dose, the geometric mean body-weight-normalized apparent oral clearance was approximately 50% higher in the younger group compared with the older group (0.40 and 0.25 L/h x kg(-1), respectively). Thirty patients were included in the tolerability analysis. The adverse events that occurred were skin excoriation, discolored feces, and skin laceration (1 [3.3%] patient each); none were considered related to treatment. CONCLUSIONS: The results of this small study suggest that, in children aged 1 to 11 years who had GERD, the PK properties of esomeprazole may be both dose and age dependent and that younger children might have a more rapid metabolism of esomeprazole per kilogram of body weight compared with older children. Esomeprazole was well tolerated at doses of 5, 10, and 20 mg in the pediatric patients studied.

Helicobacter pylori eradication (n=1)

Kawakami, E., R. S. Machado, et al. (2006). "Furazolidone-based triple therapy for H pylori gastritis in children." *World Journal of Gastroenterology* **12**(34): 5544-9.

AIM: To evaluate the furazolidone-based triple therapy in children with symptomatic H pylori gastritis. METHODS: A prospective and consecutive open trial was carried out. The study included 38 patients with upper digestive symptoms sufficiently severe to warrant endoscopic investigation. H pylori status was defined based both on histology and on positive (13)C-urea breath test. Drug regimen was a

seven-day course of omeprazole, clarithromycin and furazolidone (100 mg, 200 mg if over 30 kg) twice daily. Eradication of H pylori was assessed two months after treatment by histology and (13)C -urea breath test. Further clinical evaluation was performed 7 d, 2 and 6 mo after the treatment. **RESULTS:** Thirty-eight patients (24 females, 14 males) were included. Their age ranged from 4 to 17.8 (mean 10.9 +/- 3.7) years. On intent-to-treat analysis (n = 38), the eradication rate of H pylori was 73.7% (95% CI, 65.2%-82%) whereas in per-protocol analysis (n = 33) it was 84.8% (95% CI, 78.5%-91%). All the patients with duodenal ulcer (n = 7) were successfully treated (100% vs 56.2% with antral nodularity). Side effects were reported in 26 patients (68.4%), mainly vomiting (14/26) and abdominal pain (n = 13). Successfully treated dyspeptic patients showed improvement in 78.9% of H pylori-negative patients after six months and in 50% of H pylori-positive patients after six months of treatment. **CONCLUSION:** Triple therapy with furazolidone achieves moderate efficacy in H pylori treatment. The eradication rate seems to be higher in patients with duodenal ulcer.

Placebo- and active-control trials (N=6)

GERD maintenance treatment (n=2)

Bigard, M. A. and E. Genestin (2005). "Treatment of patients with heartburn without endoscopic evaluation: on-demand treatment after effective continuous administration of lansoprazole 15 mg." *Alimentary Pharmacology & Therapeutics* **22**(7): 635-43.

BACKGROUND: Relapse is frequent after initial treatment for gastro-oesophageal reflux. An alternative strategy to intermittent or continuous therapy may be on-demand treatment. **AIM:** To compare the efficacy and safety of on-demand lansoprazole 15 mg and placebo treatment in patients with gastro-oesophageal reflux. **METHODS:** This was a multicentre, randomized, double-blind study in two parallel groups of patients. In the acute study phase, all included patients (n = 203) were treated with lansoprazole 15 mg (once per day) for 4 weeks. At week 4, asymptomatic patients entered the 6-month, on-demand, follow-up phase and were randomized to receive either lansoprazole 15 mg (once per day) or placebo.

RESULTS: A higher percentage of patients in the lansoprazole group completed the 6-month follow-up than in the placebo group [81% vs. 61% (P = 0.003)]. Only 16% of patients in the lansoprazole group discontinued the study for insufficient control of heartburn vs. 28% in the placebo group (P = 0.046). The mean daily intake in patients who completed the study was 1-5 capsules/day in the lansoprazole 15 mg group. **CONCLUSIONS:** On-demand treatment with lansoprazole 15 mg in symptomatic patients after short-term, continuous treatment is a promising therapeutic alternative to intermittent and continuous treatment to maintain heartburn control in patients with gastro-oesophageal reflux.

Scholten, T., C. P. M. Dekkers, et al. (2005). "On-demand therapy with pantoprazole 20 mg as effective long-term management of reflux disease in patients with mild GERD: the ORION trial." *Digestion* **72**(2-3): 76-85.

AIMS: To compare safety and efficacy of on-demand pantoprazole 20 mg/40 mg versus placebo in the long-term management of patients with mild gastroesophageal reflux disease (GERD) after heartburn relief. **METHODS:** A total of 634 patients with endoscopically confirmed GERD grade 0/I and heartburn were included. During the acute phase, patients were treated with pantoprazole 20 mg once daily for 4 weeks. Those patients relieved from heartburn entered the long-term phase, and were randomly assigned to either treatment group pantoprazole 20 mg, 40 mg or placebo. Over 6 months, patients took study medication on demand (antacids as rescue medication) and discontinued the drug once symptoms abated. **RESULTS:** After 4 weeks a total of 87.1%/90.0% of patients were free of heartburn (ITT/PP), and entered the subsequent long-term phase. The perceived average daily symptom load (placebo: 3.93, pantoprazole 20 mg: 2.91, pantoprazole 40 mg: 2.71, ITT) and the number of antacid tablets taken (average number, placebo: 0.68, pantoprazole 20 mg: 0.45, pantoprazole 40 mg: 0.33, ITT) were significantly higher in the placebo than in both pantoprazole groups ($p < 0.0001$), with no statistically significant difference between the two pantoprazole groups. The discontinuation rate due to insufficient control of heartburn was significantly lower in both pantoprazole groups compared to placebo (placebo: 10.9, pantoprazole 20 mg: 2.8, pantoprazole 40 mg: 0.9, ITT). **CONCLUSIONS:** Our findings favor on-demand treatment with pantoprazole 20 mg for the long-term management of heartburn in patients with uncomplicated GERD (grade 0/I) with superiority to placebo. Copyright (c) 2005 S. Karger AG, Basel.

PPI vs surgical treatment for GERD (n=2)

Lundell, L., P. Miettinen, et al. (2007). "Seven-year follow-up of a randomized clinical trial comparing proton-pump inhibition with surgical therapy for reflux oesophagitis." British Journal of Surgery **94**(2): 198-203.

BACKGROUND: This randomized clinical trial compared long-term outcome after antireflux surgery with acid inhibition therapy in the treatment of chronic gastro-oesophageal reflux disease (GORD). **METHODS:** Patients with chronic GORD and oesophagitis verified at endoscopy were allocated to treatment with omeprazole (154 patients) or antireflux surgery (144). After 7 years of follow-up, 119 patients in the omeprazole arm and 99 who had antireflux surgery were available for evaluation. The primary outcome variable was the cumulative proportion of patients in whom treatment failed. Secondary objectives were evaluation of the treatment failure rate after dose adjustment of omeprazole, safety, and the frequency and severity of post-fundoplication complaints. **RESULTS:** The proportion of patients in whom treatment did not fail during the 7 years was significantly higher in the surgical than in the medical group (66.7 versus 46.7 per cent respectively; $P = 0.002$). A smaller difference remained after dose adjustment in the omeprazole group ($P = 0.045$). More patients in the surgical group complained of symptoms such as dysphagia, inability to belch or vomit, and rectal flatulence. These complaints were fairly stable throughout the study interval. The mean daily dose of omeprazole was 22.8, 24.1, 24.3 and 24.3 mg at 1, 3, 5 and 7 years respectively. **CONCLUSION:** Chronic GORD can be treated effectively by either antireflux surgery or omeprazole therapy. After 7 years, surgery was more effective in controlling overall disease

symptoms, but specific post-fundoplication complaints remained a problem. There appeared to be no dose escalation of omeprazole with time. Copyright (c) 2007 British Journal of Surgery Society Ltd.

Mehta, S., J. Bennett, et al. (2006). "Prospective trial of laparoscopic nissen fundoplication versus proton pump inhibitor therapy for gastroesophageal reflux disease: Seven-year follow-up." *Journal of Gastrointestinal Surgery* **10**(9): 1312-6; discussion 1316-7.

Laparoscopic Nissen fundoplication and proton pump inhibitor (PPI) therapy are both established treatments for gastroesophageal reflux disease (GERD). We have performed a prospective randomized study comparing these two treatments and now have long-term follow-up data. Between July 1997 and August 2001, 183 patients in Norwich took part in a randomized controlled trial comparing laparoscopic Nissen fundoplication and PPI therapy for the treatment of GERD. In October 2005, patients were followed up and asked to complete a reflux symptom questionnaire. Ninety-one patients were randomized to have surgery and 92 to have optimized PPI therapy. After 12 months, those who had been randomized to PPI were offered the opportunity to have surgery. Fifty-four patients went on to have antireflux surgery; the remaining 38 did not. In all three groups, there was a significant improvement in symptom score after the initial 12 months ($P < 0.01$; Mann-Whitney U test). However, those who later had surgery despite having had optimal PPI treatment beforehand experienced further symptomatic improvement ($P < 0.01$) at long-term follow-up (median 6.9 years, range, 4.3-8.3). Both optimal PPI therapy and laparoscopic Nissen fundoplication are effective treatments for GERD. However, surgery offers additional benefit for those who have only partial symptomatic relief whilst on PPIs.

Prevention of NSAID-induced ulcer (n=2)

Chan, F. K. L., V. W. S. Wong, et al. (2007). "Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial.[see comment]." *Lancet* **369**(9573): 1621-6.

BACKGROUND: Guidelines on pain management recommend that patients at risk of ulcers receive either a cyclo-oxygenase (COX 2) inhibitor or a non-steroidal anti-inflammatory drug (NSAID) with a proton-pump inhibitor (PPI). These two treatments have similar effectiveness, but they are insufficient for protection of patients at very high risk for ulcer bleeding. We aimed to test the hypothesis that in patients with previous ulcer bleeding induced by non-selective NSAIDs, combined treatment with the COX 2 inhibitor celecoxib and the PPI esomeprazole would be better than celecoxib alone for prevention of recurrent ulcer bleeding. **METHODS:** 441 consecutively presenting patients who were taking non-selective NSAIDs for arthritis were recruited to our single-centre, prospective, randomised, double-blind trial after admission to hospital with upper-gastrointestinal bleeding. Patients were enrolled after their ulcers had healed and a histological test for *Helicobacter pylori* was negative. All patients were given 200 mg celecoxib twice daily. 137 patients were randomly assigned to receive 20 mg esomeprazole twice daily (combined-treatment group), and 136 to receive a placebo (control group) for 12 months. The

primary endpoint was recurrent ulcer bleeding during treatment or within 1 month of the end of treatment. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00365313. FINDINGS: Combination treatment was more effective than celecoxib alone for prevention of ulcer bleeding in patients at high risk. The 13-month cumulative incidence of the primary endpoint was 0% in the combined-treatment group and 12 (8.9%) in the controls (95% CI difference, 4.1 to 13.7; $p=0.0004$). The median follow-up was 13 months (range 0.4-13.0). Discontinuation of treatment and the incidence of adverse events were similar in the two treatment groups. INTERPRETATION: Patients at very high risk for recurrent ulcer bleeding who need anti-inflammatory analgesics should receive combination treatment with a COX 2 inhibitor and a PPI. Our findings should encourage guideline committees to review their recommendations for patients at very high risk of recurrent ulcer bleeding.

Scheiman, J. M., N. D. Yeomans, et al. (2006). "Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors.[see comment]." American Journal of Gastroenterology **101**(4): 701-10.

OBJECTIVES: Proton pump inhibitors reduce ulcer recurrence in non-steroidal anti-inflammatory drug (NSAID) users, but their impact in at-risk ulcer-free patients using the current spectrum of prescribed agents has not been clearly defined. We assessed esomeprazole for ulcer prevention in at-risk patients ($> \text{ or } = 60$ yr and/or ulcer history) taking NSAIDs, including COX-2 inhibitors. Such studies are particularly relevant, given that concerns regarding adverse cardiovascular outcomes among COX-2 inhibitor users may prompt re-evaluation of their use. METHODS: We conducted two similar double-blind, placebo-controlled, randomized, multicenter studies; VENUS (United States) and PLUTO (multinational). A total of 844 and 585 patients requiring daily NSAIDs, including COX-2 inhibitors were randomized to receive esomeprazole (20 or 40 mg) or placebo, daily for 6 months. RESULTS: In the VENUS study, the life table estimated proportion of patients who developed ulcers over 6 months (primary variable, intent-to-treat population) was 20.4% on placebo, 5.3% on esomeprazole 20 mg ($p < 0.001$), and 4.7% on esomeprazole 40 mg ($p < 0.0001$). In the PLUTO study, the values were 12.3% on placebo, 5.2% with esomeprazole 20 mg ($p = 0.018$), and 4.4% with esomeprazole 40 mg ($p = 0.007$). Significant reductions were observed for users of both non-selective NSAIDs and COX-2 inhibitors. Pooled ulcer rates for patients using COX-2 inhibitors ($n = 400$) were 16.5% on placebo, 0.9% on esomeprazole 20 mg ($p < 0.001$) and 4.1% on esomeprazole 40 mg ($p = 0.002$). Esomeprazole was well tolerated and associated with better symptom control than placebo. CONCLUSIONS: For at-risk patients, esomeprazole was effective in preventing ulcers in long-term users of NSAIDs, including COX-2 inhibitors.

Observational study of adverse events (n=1)

Yang, Y.-X., J. D. Lewis, et al. (2006). "Long-term proton pump inhibitor therapy and risk of hip fracture." JAMA **296**(24): 2947-53.

CONTEXT: Proton pump inhibitors (PPIs) may interfere with calcium absorption through induction of hypochlorhydria but they also may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps. **OBJECTIVE:** To determine the association between PPI therapy and risk of hip fracture. **DESIGN, SETTING, AND PATIENTS:** A nested case-control study was conducted using the General Practice Research Database (1987-2003), which contains information on patients in the United Kingdom. The study cohort consisted of users of PPI therapy and nonusers of acid suppression drugs who were older than 50 years. Cases included all patients with an incident hip fracture. Controls were selected using incidence density sampling, matched for sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date. For comparison purposes, a similar nested case-control analysis for histamine 2 receptor antagonists was performed. **MAIN OUTCOME MEASURE:** The risk of hip fractures associated with PPI use. **RESULTS:** There were 13,556 hip fracture cases and 135,386 controls. The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI therapy was 1.44 (95% confidence interval [CI], 1.30-1.59). The risk of hip fracture was significantly increased among patients prescribed long-term high-dose PPIs (AOR, 2.65; 95% CI, 1.80-3.90; $P < .001$). The strength of the association increased with increasing duration of PPI therapy (AOR for 1 year, 1.22 [95% CI, 1.15-1.30]; 2 years, 1.41 [95% CI, 1.28-1.56]; 3 years, 1.54 [95% CI, 1.37-1.73]; and 4 years, 1.59 [95% CI, 1.39-1.80]; $P < .001$ for all comparisons). **CONCLUSION:** Long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture.