Drug Class Review
on
Proton Pump Inhibitors

Final Report Update 4 Evidence Tables

July 2006

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Update 1 Report Date: April 2003
Update 2 Report Date: April 2004
Update 3 Report Date: May 2005

A literature scan of this topic is done periodically

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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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see timeline on the DERP website for details on the date of its release. Prior versions of the report can be accessed at the DERP website.

TABLE OF CONTENTS

Evidence Tables

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Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Adachi et al, 2003	85 patients at 6 medical institutions in Japan. Mean age 66 (SD 13); 51% male; 100% Asian	Grade A: 24% Grade B: 53% Grade C: 21% Grade D: 2% (Los Angeles classification) 42% h. Pylori positive	Screened NR/eligible NR/85 enrolled 20% of lansoprazole group lost to f/u for endoscopy vs 7% in other groups; but no loss to f/u for reporting of symptoms 85 analyzed for symptoms, 76 for endoscopy	Not reported	(Per protocol analysis on 76 patients): omeprazole 20 mg: 85.7% lansoprazole 30 mg: 85% rabeprazole 20 mg: 92.9% (NS)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Adachi et al, 2003	(Results reported graphically only) Heartburn score significantly lower in rabeprazole group after 2 days than lansoprazole or omeprazole (p=0.045). Differences disappeared by day 5. No significant differences in acid reflux scores.	Not reported	Not reported	Not reported

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Adachi et al, 2003	Fair: open-label, loss to f/u higher in lansoprazole group for healing (20% vs 7%), but okay for symptoms; randomization method not reported	Ministry of Education, Science, and Culture of Japan

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Bardhan et al, 2001	328 patients at 23 centers in Great Britain, the Republic of Ireland, and South Africa. Mean age 44.6 (SD 13.3) in pantoprazole group, 45.2 (SD14.4) in omeprazole group. 52.4% of pantoprazole, 64% of omeprazole group males. Race/ethnicity not reported.	100% Grade I (Savary-Miller classification)	Screened NR/eligible NR/328 enrolled/ 327 analyzed	Intention-to-treat (N=327): pantoprazole 20 mg: 77% omeprazole 20 mg: 81% Per-protocol (N=264): pantoprazole 20 mg: 84% omeprazole 20 mg: 89%	Intention-to-treat (N=327): pantoprazole 20 mg: 81% omeprazole 20 mg: 88% (NS) Per-protocol (N=264): pantoprazole 20 mg: 90% omeprazole 20 mg: 95% (NS)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Bardhan et al, 2001	pantoprazole 20 mg vs omeprazole 20 mg Symptom relief (all main symptoms) 2 weeks: 70% vs 79% 4 weeks: 77% vs 84% Acid eructation 2 weeks: 79% vs 88% 4 weeks: 84% vs 87% Heartburn 2 weeks: 79% vs 86% 4 weeks: 83% vs 87% Pain on swallowing 2 weeks: 83% vs 87% 4 weeks: 87% vs 97% (All NS)	Not reported	Relief of acid eructation, heartburn and pain on swallowing was similar in the two treatment groups at 2 and 4 weeks, irrespective of severity at baseline. A higher proportion with mild symptoms at entry had relief compared with patients with severe symptoms, and this was similar for both treatments.	Not reported

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Bardhan et al, 2001	Fair-Poor: open-label, randomization, allocation concealment method not reported, more smokers in pantoprazole group (31% vs 22%), more males in omeprazole group (64% vs 52%)	Byk Gulden (Germany) pharmaceutical

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Chen et al, 2005	48 patients at a single center in Taiwan. Mean age 53.9 79.2% male Race NR	Grade A: 54.2% Grade B: 29.2% Grade C: 8.3% Grade D: 8.3% (Los Angeles classification)	Screened, eligible NR/48 enrolled 2 withdrawn/2 lost to followup/42 analyzed per protocol, 47 analyzed ITT	esomeprazole 40 mg: NR omeprazole 20 mg: NR	PP patients (n=42) esomeprazole 40 mg: 72.7% omeprazole 20 mg: 50% ITT patients (n=47) esomeprazole 40 mg: 64% omeprazole: 20 mg: 45.5% OR 2.667 (PP: 95% CI 0.739-9.63, P=0.2040)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Chen et al, 2005	NR	*Heartburn:* esomeprazole 40 mg: 50% improved, 50% no change omeprazole 20 mg: 65% improved, 25% no change, 10% worse (p=0.0993) *Regurgitation:* esomeprazole 40 mg: 77.3% improved, 18.2% no change, 4.5% worse omeprazole 20 mg: 85.0% improved, 15.0% no change (p=1.0000) *Dysphagia:* esomeprazole 40 mg: 36.4% improved, 63.6% no change omeprazole 20 mg: 35.0% improved, 60.0% no change, 5.0% worse (p=0.8697) *Epigastric pain:* esomeprazole 40 mg: 27.3% improved, 63.6% no change, 9.1% worse omeprazole 20 mg: 50.0% improved, 50.0% no change (p=0.1895) *Nausea:* esomeprazole 40 mg: 22.7% improved, 68.2% no change, 9.1% worse omeprazole 20 mg: 35.0% improved, 65.0% no change (p=0.5036) *Vomiting:* esomeprazole 40 mg: 22.7% improved, 77.3% no change omeprazole 20 mg: 40.0% improved, 60.0% no change (p=0.3200) *Belching:* esomeprazole 40 mg: 54.5%, 36.4% no change, 9.1% worse omeprazole 20 mg: 45.0% improved, 45.0% no change, 10.0% worse (p=0.8999)	Not quantitatively expressed, see Figure 1. Difference stated as not SS different.	NR

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Chen et al, 2005	Fair	NR (AstraZeneca provided randomization schedule)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Fennerty, 2005	999 patients at multiple centers in the US, with moderate to severe esophagitis. Mean age 47 66% male 82% white, 5% black, <1% Asian, 13% other	Grade C: 79% Grade D: 21% (Los Angeles classification)	4015 screened/ 1381 eligible/ 1001 enrolled/ 11 withdrew/ 18 lost to followup/ 999 analyzed	esomeprazole 40 mg: 55.8% lansoprazole 30 mg: 47.5% (p<0.005)	esomeprazole 40 mg: 77.5% lansoprazole 30 mg: 73.3% (p=0.099)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Fennerty, 2005	*Resolution of heartburn:* esomeprazole 40 mg: 72% lansoprazole 30 mg: 63.6% (p=0.005) *Resolution of acid regurgitation:* esomeprazole 40 mg: 79.5% lansoprazole 30 mg: 76.2% (p=0.203) *Dysphagia:* esomeprazole 40 mg: 93.1% lansoprazole 30 mg: 93.8% (p=0.614) *Epigastric pain:* esomeprazole 40 mg: 83.1% lansoprazole 30 mg: 82.6% (p=0.831)	Not reported	Grade C *Healing at 4 weeks* esomeprazole 40 mg: 60.3% lansoprazole 30 mg: 50.6% (p-value not reported) *Healing at 8 weeks* esomeprazole 40 mg: 80.3% lansoprazole 30 mg: 74.9% (p-value not reported) Grade D *Healing at 4 weeks* esomeprazole 40 mg: 39.8% lansoprazole 30 mg: 34.7% (p-value not reported) *Healing at 8 weeks* esomeprazole 40 mg: 67.6% lansoprazole 30 mg: 66.3% (p-value not reported)	5/499 (1%) esomeprazole vs 9/502 (2%) lansoprazole. Most common adverse event leading to study withdrawal was abdominal pain (two in each group)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Fennerty, 2005	Good	AstraZeneca

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Gillessen, 2004	227 patients at 27 centers in Germany. Mean age 53 (SD 15) in pantoprazole group, 54 (SD 14) in esomeprazole group. 57% of pantoprazole, 50% of esomeprazole group male. 97% of pantoprazole, 98% of esomeprazole group Caucasian (others Asian)	Grade B: 84% pantoprazole, 83% esomeprazole Grade C: 16% pantoprazole, 17% esomeprazole (Los Angeles classification)	Screened NR/eligible NR/227 enrolled/227 analyzed ITT/197 analyzed per protocol	"Early time points" (4 and 6 weeks) Intention-to-treat (N=227): pantoprazole 40 mg: 74% esomeprazole 40 mg: 72% (NS) Per-protocol (N=197): pantoprazole 40 mg: 78% esomeprazole 40 mg: 74% (NS)	"Late time points" (8 and 10 weeks) Intention-to-treat (N=227): pantoprazole 40 mg: 90% esomeprazole 40 mg: 92% (NS) Per-protocol (N=197): pantoprazole 40 mg: 96% esomeprazole 40 mg: 93% (NS)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Gillessen, 2004	Overall relief of symptoms Per-protocol (N=197): pantoprazole 40 mg: 37% esomeprazole 40 mg: 35% (NS for PP or ITT)	Overall relief of symptoms Per-protocol (N=197): pantoprazole 40 mg: 47% esomeprazole 40 mg: 32% (NS for PP or ITT) After 10 weeks: pantoprazole 40 mg: 65% esomeprazole 40 mg: 63% (NS for PP or ITT)	Per-protocol, overall healing by baseline grade Grade B: pantoprazole 40 mg: 92% esomeprazole 40 mg: 95% Grade C: pantoprazole 40 mg: 67% esomeprazole 40 mg: 45% Among patients diagnosed with grade C at baseline, 100% of pantoprazole and 91% of esomeprazole improved to Grade A or B at final visit.	6 patients overall, not reported by group.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Gillessen, 2004	Fair: Randomization, allocation concealment method not reported.	Altana Pharma, Germany

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Kao et al, 2003	100 patients at one center in Taiwan mean age 49 69% male 100% Asian	Grade A: 51% Grade B: 49% (Los Angeles Classification)	Screened NR/eligible NR/100 enrolled	Not reported	Not reported

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Kao et al, 2003	Esomeprazole 40 mg vs omeprazole 20 mg Per-protocol (N=91) Symptom-free on day 1: 28.2% vs 26.2% (NS) Symptom-free before week 1: 56.4% vs 55.6% (NS) Median days to symptom resolution: 4 vs 4 (NS) Achievement of sustained symptom response Week 1: 15.2% vs 15.6% (NS) Week 2: 50% vs 20% (p<0.05) Week 3: 71.7% vs 40% (p<0.01) Week 4: 73.9% vs 51.1% (p<0.05) Week 4 (intention-to-treat): 68% vs 46% (p<0.05)	Efficacy of on-demand therapy (n=34 esomeprazole 40 mg, n=23 omeprazole 20 mg, initiated week 5)	Not reported	Not reported

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Kao et al, 2003	Fair: not clear if patients masked, randomization, allocation concealment methods not reported.	Supported by a grant from the National Cheng Kung University

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Castell 1996	1070 US patients at multiple centers (number excludes placebo), mean age 47, (range 18-84); 60-68.4% male; 85% white, 9% black, 5% Hispanic.	Grade 2: 61%-71% Grade 3: 24%-30% Grade 4: 6%-9% (See Appendix F for scale) 6.5%-8.7% Barrett's esophagus	1284 enrolled, 1226 analyzed (total with placebo)	lansoprazole 15 mg: 72.0% lansoprazole 30 mg: 79.6% omeprazole 20 mg: 87.0% lansoprazole 30 mg vs lansoprazole 15 mg p<.05 omeprazole 20 mg vs lansoprazole 15 mg p<.05 Other comparisons NS	lansoprazole 15 mg: 75.2% lansoprazole 30 mg: 87.1% omeprazole 20 mg: 87.0% lansoprazole 30 mg vs lansoprazole 15 mg p<.05 omeprazole 20 mg vs lansoprazole 15 mg p<.05 Other comparisons NS
Castell et al, 2002	5241 patients, multiple centers, mean age 47 (range 18-75), 57% male, 91% white, 6% black, 3% other.	Grade A: 36% Grade B: 40% Grade C: 18% Grade D: 6% (LA Grade) Heartburn Severity None: 1% Mild: 10% Moderate: 47% Severe: 42%	5241 enrolled, ITT Number screened NR lansoprazole 30 mg (n=2617) esomeprazole 40 mg (n=2624)	esomeprazole 79.4% lansoprazole 75.1% (p<.001) (life-table analysis)	EE esomeprazole 92.6% lansoprazole 88.8% (p=.0001) (life-table analysis)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Castell 1996	Not given	Median percentage of days with heartburn: lansoprazole 15 mg: 12.3% lansoprazole 30 mg: 8.6% omeprazole 20 mg: 11.8% Median percentage with heartburn: lansoprazole 15 mg: 9.3 lansoprazole 30 mg: 6.5 (not ITT) lansoprazole15 mg vs omeprazole 20 mg p<0.05 nights lansoprazole15 mg vs lansoprazole 30 mg p< days and nights All other comparisons NS	When healing rates were adjusted for baseline esophagitis grade, treatment comparison results were similar to those of the overall analyses. Patients with less severe esophagitis (grade 2) at baseline had higher rates with all the active treatments than those with more severe disease (grades 3 and 4). Healing rate at 4 weeks, lansoprazole 15 mg vs lansoprazole 30 mg vs omeprazole 20 mg, by baseline esophagitis grade: grade 2: 83.2% vs 89.4% vs 88.2% grades 3 and 4: 59.5% vs 73.5% vs 69.8% at 8 weeks, lansoprazole 15 mg vs lansoprazole 30 mg vs omeprazole 20 mg, by baseline esophagitis grade:: grade 2: 87.8% vs 94.3% vs 91.6% grades 3 and 4: 62.5% vs 85.3% vs 88.7%	omeprazole 20 mg: 2% lansoprazole 30 mg: 1.7% lansoprazole 15 mg: 0.9%
Castell et al, 2002	Complete resolution of heartburn: lansoprazole 60.2% esomeprazole 62.9% (p<.05) Heartburn-free nights: lansoprazole 85.8% esomeprazole 87.1% (p<.05) Heartburn-free days: NS	Not reported	esomeprazole 75.7% lansoprazole 71.7% (p<0.01, stratified by baseline severity) esomeprazole 87.6% lansoprazole 84.2% (p<0.01, stratified by baseline severity)	No difference in treatment-related adverse effects. Withdrawal due to adverse event 1.8% vs. 1.9%.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Castell 1996	Fair: randomization and allocation method not reported, attrition not reported	Supported by TAP Pharmaceuticals, Inc.
Castell et al, 2002	Good	Supported by AstraZeneca, also listed in author credits

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Corinaldesi 1995	241 patients at 30 centers, Belgium, France, Italy, the Netherlands, median age 50-52, (range 18-88); 63% male; ethnicity not given.	Grade 2: 82% Grade 3: 18% (Savary-Miller)	Number screened not given, 241 randomized, 208 evaluable; 3 withdrew, 23 did not attend f/u.	pantoprazole 40 mg: 67.5% omeprazole 20 mg: 68.6% p=NS	pantoprazole 40 mg: 80.8% omeprazole 20 mg: 79.3% p=NS

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Corinaldesi 1995	Heartburn free: omeprazole 20 mg: 82.2% pantoprazole 40 mg: 87.9% p=NS	Not reported	Not reported	pantoprazole 40 mg: 0.8% omeprazole 20 mg: 1.7%

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Corinaldesi 1995	Poor: randomization and allocation method not reported, no intention-to-treat analysis, baseline characteristics not analyzed.	Last author from Byk Gulden Pharmaceuticals, study supported by same.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Dekkers 1999	202 patients of 27 investigators in 10 European countries, mean age 53 + 15.63, (range 20-86); 62% male; ethnicity not given.	Grade 2: 43% Grade 3: 52% Grade 4: 4% (modified Hetzel-Dent)	Number screened not given, 202 enrolled, 192 completed.	rabeprazole 20 mg: 81% omeprazole 20 mg: 81% (Not ITT) p=NS	rabeprazole 20 mg: 92% omeprazole 20 mg: 94% (Not ITT) p=NS
Delchier 2000	300 patients of 61 investigators at 50 European centers, mean age 53 (+15), (range 18-80); 62% male; ethnicity not given.	Mean grade 2.6-2.7, median 3.9, (modified Hetzel-Dent) 7% had Barrett's esophagus, 41% positive for H. pylori	358 screened, 310 randomized, 298 completed.	rabeprazole 20 mg: 88.5% rabeprazole 10 mg: 85.4% omeprazole 20 mg: 91.2% p=NS	rabeprazole 20 mg: 91.3% rabeprazole 10 mg: 91.3% omeprazole 20 mg: 94.2% p=NS

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Dekkers 1999	Heartburn frequency (resolution): rabeprazole 20 mg: 29.6% omeprazole 20 mg: 26.5% Daytime severity (resolution): rabeprazole 20 mg: 61.9% omeprazole 20 mg: 60.8% Nighttime severity resolution: rabeprazole 20 mg: 61.6% omeprazole 20 mg: 57.3% p=NS for all	Heartburn frequency resolution: rabeprazole 20 mg: 37.8% omeprazole 20 mg: 31.4% Daytime severity resolution: rabeprazole 20 mg:68.0% omeprazole 20 mg: 66.0% Nighttime severity resolution: rabeprazole 20 mg: 64.4% omeprazole 20 mg: 66.7% p= NS for all	Not reported	rabeprazole 20 mg: 1% omeprazole 20 mg: 0
Delchier 2000	Severity of daytime and nighttime heartburn: p=NS (numbers not given)	Severity of daytime and nighttime heartburn: p=NS (numbers not given)	No statistically significant differences between treatment groups after controlling for baseline factors including Hetzel-Dent grade (other factors sex, age, smoking and H. pylori status); data not reported.	rabeprazole 10 mg: 5% rabeprazole 20 mg: 5% omeprazole 20 mg: 2%

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Dekkers 1999	Fair: randomization and allocation method not reported intention-to-treat for symptoms only, not for healing.	Last author (corresponding author) and 5th authors with Eisai Ltd, funding info not given.
Delchier 2000	Fair: randomization and allocation method not reported, followup somewhat high (76%-83%).	Funded by Eisai Ltd, London, last author (corresponding author) from Eisai

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Dupas 2001	461 patients at 29 hospital centers and 45 private practices in France; mean age 54 (+14.6); 74% male; ethnicity not given	83% Grade 2 17% Grade 3 (Savary-Miller)	Number screened not given; 461 randomized, 385 completed	pantoprazole 40 mg ITT: 80.90% lansoprazole 30 mg ITT: 80% p=NS	pantoprazole 40 mg ITT: 89.80% lansoprazole 30 mg ITT: 90% p=NS

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Dupas 2001	Symptom free (all symptoms - heartburn, acid regurgitation, pain or swallowing): ITT: pantoprazole 40 mg: 83% lansoprazole 30 mg: 92% p=NS	Not reported	For both treatments, healing rates after 4 weeks were lower in grade III than in grade II esophagitis (69% vs 89%, per-protocol analysis, p=0.0001), with no grade-dependent significant differences between groups.	pantoprazole 40 mg: 13% lansoprazole 30 mg: 2.5%

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Dupas 2001	Fair: randomized method not clear, allocation method not reported	Funded by BYK France, last author from BYK

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Hatlebakk 1993	229 patients at 9 hospitals in Norway and Sweden; mean age 55; 66% male; ethnicity not given	lansoprazole 30 mg group: Grade 0: 2.6% Grade 1: 34.5% Grade 2: 50.9% Grade 3: 12.1% omeprazole 20 mg group: Grade 0: 2.7% Grade 1: 38.9% Grade 2: 55.8% Grade 3: 2.7% (See Appendix E for scale)	Number screened not given, 229 enrolled.	lansoprazole 30 mg: 61.2% omeprazole 20 mg: 64.6% p=NS	lansoprazole 30 mg: 81.9% omeprazole 20 mg: 85.0% p=NS
Holtmann, 2002	251 patients at multiple centers in Germany, Denmark, and Switzerland; mean age 52; 66% male, 99% Caucasian.	rabeprazole: 78% grade II, 22% grade III; omeprazole: 84% grade II, 16% grade III	274 screened/254 eligible, 251 enrolled/13 withdrawn or no valid data/4 lost to followup/251 analyzed	No difference between groups (data not reported)	per protocol (N=200) rabeprazole 20 mg: 92.7% omeprazole 40 mg: 89.2% (NS)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Hatlebakk 1993	Data not given: states lansoprazole 30 mg had greater improvement in heartburn (p=0.03)	Data not given, but states no significant differences in any symptoms.	At both 4 and 8 weeks, and irrespective of treatment, healing rates were higher for patients with grade 1 esophagitis than grade 2 (p<0.01, two-stage logistic regression analysis). Results by treatment group not reported.	omeprazole 20 mg: 0.9% lansoprazole 30 mg: 0
Holtmann, 2002	Not reported for this time point; difference in relief from heartburn on day 4 not significant between groups.	Not reported for this time point.	Healing rate in patients with GERD grade III (N=45) 4 weeks: 84% rabeprazole vs 72.2% omeprazole (NS) 8 weeks: 88% rabeprazole vs 77.8% omeprazole (NS)	4/125 (3%) rabeprazole vs 2/126 (2%) omeprazole

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Hatlebakk 1993	Poor: randomization and allocation method not reported, no intention-to-treat analysis, eligibility criteria not specified, some differences at baseline.	Not reported
Holtmann, 2002	Fair: Not clear if randomization method adequate, allocation concealment method not reported, more rabeprazole patients grade III esophagitis at baseline (22% vs 16%).	Funded by Eisai and Janssen-Cilag

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Howden et al, 2002	284 patients at multiple centers, mean age 46.5 (range 19-78), 56% male, 80% white, 5% black, 15% other.	Grade 2: 61% Grade 3:30% Grade 4: 8% (see Appendix F for scale)	284 enrolled; # screened, eligible not reported, 277 evaluated lansoprazole 30 mg (n=139) esomeprazole 40 mg (n=138)	lansoprazole 30 mg vs esomeprazole 40 mg 77.0% vs 78.3% (p=NS)	lansoprazole 30 mg vs esomeprazole 40 mg 91.4% vs 89.1% (95% CI of difference -4.7, 9.2)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Howden et al, 2002	Not reported	Not reported	Healing rate or improvement of 2 grades at 8 weeks by baseline grade, lansoprazole 30 mg vs esomeprazole 40 mg: Grade 2: 94.3% (82/87) vs 95.1% (77/81) Grade 3: 92.7% (38/41) vs 81.8% (36/44) Grade 4: 90.9% (10/11) vs 84.6% (11/13) Week 4 healing: healing or improvement of 2 grades of erosive esophagitis from baseline were comparable between treatment groups, regardless of baseline grade of esophagitis (data not reported).	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Howden et al, 2002	Fair: randomization and allocation concealment methods not reported.	Supported by TAP Pharmaceuticals.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Kahrilas 2000	1960 US patients at 140 centers; mean age 46; 60% male; ethnicity not given.	Grade A: 33% Grade B: 40% Grade C: 19% Grade D: 7% (Los Angeles classification) 9.6% H. pylori	3354 screened, 1960 randomized. 44 did not complete study due to an adverse event and 115 for other reasons including loss to f/u and withdrawal of consent.	esomeprazole 40 mg: 75.9% esomeprazole 20 mg: 70.5% omeprazole20: 64.7% (cumulative life table rate) esomeprazole 20 mg vs omeprazole 20 mg p=0.09 esomeprazole 40 mg vs omeprazole 20 mg (p <0.05)	esomeprazole 40 mg: 94.1% esomeprazole 20 mg: 89.9% omeprazole 20 mg: 86.9% (cumulative life table rate) esomeprazole 40 mg vs omeprazole 20 mg p<0.001 esomeprazole 20 mg vs omeprazole 20 mg p<0.05

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Kahrilas 2000	Resolution of heartburn esomeprazole 40 mg: 64.7% esomeprazole 20 mg: 61.0% omeprazole 20 mg: 57.2% esomeprazole 40 mg vs omeprazole 20 mg p=0.005 other comparisons NS	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"	Greater efficacy of esomeprazole 40 mg vs omeprazole 20 mg at 4 weeks was consistent when adjusting for baseline esophagitis grade (data not reported).	esomeprazole 40 mg: 2% esomeprazole 20 mg: 2.6% omeprazole 20 mg: 2%

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Kahrilas 2000	Fair: Randomization methods not reported, baseline characteristics not analyzed, more grade A patients (mild) in esomeprazole 40 mg group than omeprazole 20 mg group at baseline (35.9% esomeprazole vs 31.2% omeprazole 20 mg; calculated p = 0.07).	4 of 9 authors from Astra Zeneca, study supported by grant from Astra Zeneca.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Korner et al, 2003	669 patients at multiple centers, mean age 53.8 (sd 14), 60% male, ethnicity not reported.	84% Grade II 16% Grade III (Savary-Miller)	669 included; number screened, eligible not reported. Pantoprazole 40 mg (n=337) omeprazole MUPS 40 mg (n=332)	ITT results reported as odds ratios only. PP results, pantoprazole 40 mg (n=282) vs omeprazole MUPS 40 mg (n=270) 70.9% vs 72.6%	ITT results reported as odds ratios only. "Healing rates after 8 weeks of treatment were also similar in both groups."
Labenz et al, 2005	3151 patients, multinational, mean age 50.6 (sd 14), 63% male, 97% Caucasian.	Grade A: 32% Grade B: 44% Grade C: 19% Grade D: 5% (LA Classification)	3170 randomized, 3151 analyzed. 9 excluded from analysis because of intake of an unknown study drug, and 10 because of study protocol violations.	**esomeprazole 40 mg vs pantoprazole 40 mg** Observed (per protocol): 78.8% vs 72.8% risk difference 6% (95% CI 3%, 9%) Life table analysis, per protocol: 81.0% vs 74.5% (p<0.001)	**esomeprazole 40 mg vs pantoprazole 40 mg** Observed (per protocol): 91.6% vs 88.9% risk difference 3% (95% CI 1%, 5%) Life table analysis, per protocol: 95.5% vs 92.0% (p<0.001)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Korner et al, 2003	ITT results not reported PP, pantoprazole 40 mg vs omeprazole MUPS 40 mg: Heartburn relief: 83.7% vs 88.1% Relief of pain on swallowing: 83.1% vs 91.9% (p-values not reported)	ITT results not reported PP, pantoprazole 40 mg vs omeprazole MUPS 40 mg: Heartburn relief: 91.1% vs 92.6% Relief of pain on swallowing: 94.1% vs 96.3% (p-values not reported)	Not reported (all patients were Grade II or III)	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS
Labenz et al, 2005	**esomeprazole 40 mg vs pantoprazole 40 mg** Time to achieve sustained heartburn resolution (defined as the first of 7 consecutive days with no heartburn): 6 days vs 8 days (p<0.001)	**esomeprazole 40 mg vs pantoprazole 40 mg** Proportion of heartburn-free days: 70.7% vs 67.3% (p<0.01)	Healing of esophagitis by baseline grade, esomeprazole 40 mg vs pantoprazole 40 mg Week 4, (Observed, per protocol): Grade A: 83.9% vs 83.1% (NS) Grade B: 80.2% vs 75.4% (p<0.05) Grade C: 71.1% vs 60.1% (p<0.01) Grade D: 61.4% vs 40.2% (p<0.01) Week 8 (Life table analysis, per protocol): Grade A: 97.3% vs 97.1% (NS) Grade B: 96.9% vs 93.1% (p<0.05) Grade C: 91.3% vs 87.6% (p<0.01) Grade D: 88.1% vs 73.6% (p<0.05)	2.1% esomeprazole, 1.8% pantoprazole

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Korner et al, 2003	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.
Labenz et al, 2005	Fair/Poor: Randomization and allocation concealment methods not reported. Post-randomization exclusions (19 patients) and no data on excluded patients. Baseline data excludes 19 patients randomized but excluded due to intake of an unknown study drug or protocol violations. No data on excluded patients. Some differences in baseline esophagitis grade at baseline (grade B: 42.6% esomeprazole vs 45.1% pantoprazole; grade D: 4.5% esomeprazole, 5.8% pantoprazole).	AstraZeneca

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Pace et al, 2005	549 patients, multi center Italy, mean age 47.4 (sd 14), male 68.1%	Grade 0: 1% Grade 1: 69% Grade 2: 24% Grade 3: 5.5% Grade 4: 0% (Savary-Miller)	Screened NR, Eligible NR, Enrolled 560, Withdrawn 47, lost to f/u 9	rabeprazole 20 mg: PP 91.0%, omeprazole 20 mg: PP 89.9%, equivalence bet. the two drugs is statistically significant (p<0.001)	rabeprazole 20 mg: PP 97.9%, omeprazole 20 mg: PP 97.5%, equivalence bet. the two drugs is statistically significant (p<0.0001)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Pace et al, 2005	ITT population, mean time to the first day w/ satisfactory heartburn relief, rabeprazole (n=271) 2.8+-0.2 days, omeprazole (n=271) 4.7+-0.5 days (p=0.0045), mean time to complete heartburn relief, rabeprazole 7.2 days, omeprazole 8.4 days (p=NS). Patients w/ complete heartburn relief (day and nighttime) in each day of first week of treatment (ITT patients) Rabeprazole n=245 32.2%, Omeprazole n=243 18.9%	NR	Healing rates of oesophagitis grade at endpoint (4 or 8 weeks), rabeprazole vs omeprazole: grade I: 99.4 vs. 98.8%, grade II: 95.1 vs. 96.4%, grade III: 91.7 vs. 86.7% (PP patients)	No significant difference bet. Treatment groups in single adverse event occurring, with exception of headache (Omeprazole 4.8% and Rabeprazole 1.4%)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Pace et al, 2005	Fair. Lack of ITT analysis, exclusion of people (2%) at baseline.	Janssen-Cilag, Italy

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Mee 1996	604 patients at multiple centers, UK and Ireland, mean age 53; 67% male; ethnicity not given.	Grade 1: 39% Grade 2: 44% Grade 3: 15% Grade 4: 2% (Savary-Miller)	604 enrolled, 565 eligible, 537 evaluable	lansoprazole 30 mg: 62% omeprazole 20 mg: 56.6% p=NS	lansoprazole 30 mg: 75.3% omeprazole 20 mg: 71.1% p=NS

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Mee 1996	Not given	Improvement in daytime epigastric pain lansoprazole 30 mg: 85.9% omeprazole 20 mg: 72.5% Improvement in nighttime epigastric pain lansoprazole 30 mg: 85.9% omeprazole 20 mg: 67.3% p=NS (includes only pts who attended 8-week visit who reported baseline pain)	Healing of esophagitis by baseline grade, lansoprazole vs omeprazole: Week 4: Grade I: 79% vs 68% Grade II: 72% vs 62% Grade III: 45% vs 57% Grade IV: 43% vs 60% Week 8 (cumulative): Grade I: 92% vs 87% Grade II: 88% vs 81% Grade III: 73% vs 72% Grade IV: 50% vs 50% Esophagitis grade and treatment were included in a logistic regression model. Odds ratio of healing on lansoprazole compared with omeprazole was 1.46 (95% CI 0.87, 2.45)	Not reported

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Mee 1996	Good/Fair: Allocation concealment method not given.	1 of 2 authors from Lederle Laboratories, funding info not given.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Mulder 1996	211 patients at multiple centers in The Netherlands; mean age 55; 70% male; ethnicity not given.	Grade 1: 0.47% (1 patient) Grade 2: 68% Grade 3: 24% Grade 4A: 8% (Savary-Miller)	Number screened not given, 211 enrolled, 3 lost to followup, 3 withdrew for lack of efficacy, 1 withdrawn for receiving double dose.	lansoprazole 30 mg ITT 85.50% PP 86.20% omeprazole 40 mg ITT 79% PP 79.6% p=NS	lansoprazole 30 mg ITT: 93.40% PP 95.70% omeprazole 40 mg ITT: 90.50% PP 93.4% p=NS

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Mulder 1996	lansoprazole 30 mg No symptoms: ITT: 73.60% omeprazole 40 mg No symptoms: ITT 71.40%	"Because of the low number of patients not healed at 4 weeks, analysis of symptoms was not performed at 8 weeks."	Healing of esophagitis by baseline grade, lansoprazole vs omeprazole: Week 4: Grade II: 90.8% vs 88.1% Grade III/IV: 81.5% vs 70.6% overall: Grade II: 97.4% vs 98.5% Grade III/IV: 92.6% vs 85.3% (All NS)	None

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Mulder 1996	Fair: randomization and allocation concealment not reported,	Supported by Hoechst Marion Roussel BV and Janssen-Cilag BV, Netherlands

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Mulder et al. 2002	461 patients, multiple centers; mean age 51.2 (range 18-80);59% male; ethnicity NR	Savary-Miller class: I: 59% II: 29% III: 8% IVa: 4% Heartburn Severity None: 4% Mild: 22% Moderate: 45% Severe: 29%	461 enrolled Number screened NR omeprazole MUPS 20 mg (n=151) lansoprazole 30 mg (n=156) pantoprazole 40 mg (n=154)	NR	NR

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Mulder et al. 2002	(omeprazole vs lansoprazole vs pantoprazole) Heartburn relief : 84% vs. 78% vs. 84% omeprazole vs lansoprazole 90% CI -1.44 to 13.24 pantoprazole vs lansoprazole 90% CI -1.07 to 13.49 Satisfied: 79% vs. 76% vs. 79%. omeprazole vs lansoprazole 90% CI -4.04 to 11.68 pantoprazole vs lansoprazole 90% CI -4.94 to 10.80 pantoprazole vs omeprazole 90% cI -4.12 to 7.13	(omeprazole vs lansoprazole vs pantoprazole) Heartburn relief : 87% vs. 81% vs. 89% pantoprazole vs omeprazole 90% CI -4.55 to 7.64 omeprazole vs lansoprazole 90% CI -0.79 to 12.81 pantoprazole vs lansoprazole 90% CI 0.94 to 14.17 Satisfied: 89% vs. 86% vs. 91% omeprazole vs lansoprazole 90% CI -2.68 to 9.69 pantoprazole vs lansoprazole 90% CI -0.97 to 10.99 pantoprazole vs omeprazole 90% CI -4.12 to 7.13	Symptom relief at 4 and 8 weeks was similar for each grade of esophagitis. Maintenance phase (with omeprazole 20 mg or 40 mg only, N=391): symptom relief with omeprazole 20 mg was independent of initial severity of esophagitis; the number of patients in the omeprazole 40 mg maintenance group (N=21) was too small to be divided by initial esophagitis grade.	No difference in AEs between groups. None considered treatment related. Total withdrawals due to AE: 6/461 (1.3%) Total AEs: 73/461 (15.8%)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Mulder et al. 2002	Fair: randomization and allocation methods not reported. More withdrawals in L group.	Supported by AstraZeneca

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Richter et al, 2001a	2425 patients at 163 US centers; mean age 47 (sd 12); 61% male; ethnicity 93.5% Caucasian.	Grade A: esomeprazole 40 mg 35%; omeprazole 20 mg 32% Grade B: esomeprazole 40 mg 39%; omeprazole 20 mg 42% Grade C: esomeprazole 40 mg 21%; omeprazole 20 mg 20% Grade D: esomeprazole 40 mg 5%; omeprazole 20 mg 7% (LA classification)	4798 screened, 2425 randomized; 109 did not complete: 24 for adverse events, 25 investigator-initiated decision, 25 lost to followup, 31 consent withdrawn, 4 lack of therapeutic response.	esomeprazole 40 mg vs omeprazole 20 mg cumulative life table rate: 81.7% vs 68.7% (p<0.001) Crude rates: 78.6% vs 66.6% (p = 0.001 for CMH test) risk difference 12% (95% CI 9%, 16%)	esomeprazole 40 mg vs omeprazole 20 mg cumulative life table rate: 93.7% vs 84.2% (p<0.001) Crude rates: 89.9% vs 81.0% (p = 0.001 for CMH test) risk difference 9% (95% CI 6%, 12%)

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Richter et al, 2001a	esomeprazole 40 mg resolution of heartburn: 68.30% omeprazole 20 mg resolution of heartburn: 58.10%	"Cumulative analysis at week 8 not done because pts could complete the study at week 4 with healed reflux esophagitis, even if symptoms were present"	Greater efficacy of esomeprazole 40 mg vs omeprazole 20 mg at 4 weeks was consistent when adjusting for baseline esophagitis grade. Week 4 healing rates by baseline esophagitis grade (approximate, estimated from figure): esomeprazole 40 mg vs omeprazole 20 mg: Grade A: 88% vs 82% Grade B: 79% vs 66% Grade C: 71% vs 53% Grade D: 55% vs 35% Week 8 healing rates by baseline esophagitis grade (approximate, estimated from figure): esomeprazole 40 mg vs omeprazole 20 mg: Grade A: 93% vs 91% Grade B: 90% vs 82% Grade C: 88% vs 70% Grade D: 80% vs 62% (p=0.001 for CMH test, esomeprazole vs omeprazole)	1% in each group

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Richter et al, 2001a	Good	Supported by Astra Zeneca, one or more authors from Astra Zeneca.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Population, Setting	Esophagitis Grade (Grading Criteria), Other Characteristics	Number Screened, Eligible, Enrolled, Withdrawn, Lost to Followup	Healing Rate at 4 Weeks	Healing Rate at 8 Weeks
Richter et al., 2001b	3510 patients, multiple centers, mean age 47 (range 18-89); 57% male, 88% white, 5% black, 7% other.	Grade 0: <1% Grade 1: 0% Grade 2: 68% Grade 3: 25% Grade 4: 7% (See Appendix F for scale)	3410 enrolled; number screened, eligible not reported.	Not evaluated	Not evaluated
Scholten et al., 2003	217 patients at multiple centers, mean age 53 (sd ~14); 99% white	Grade B: 73% Grade C: 27% (LA Classification)	217 enrolled; number screened, eligible not reported.	Not evaluated	Not evaluated

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Symptoms at 4 Weeks	Symptoms at 8 Weeks	Results by Baseline Severity	Withdrawals Due to Adverse Events
Richter et al., 2001b	lansoprazole 30 mg vs omeprazole 20 mg Sustained resolution of heartburn: 77.2% vs 76.2% (p=NS)	lansoprazole 30 mg vs omeprazole 20 mg Sustained resolution of heartburn: 84.3% vs 83.0% (p=NS) More patients talking lansoprazole did not have a single episode of day or night heartburn (between 10% and 15%, p<0.05, data are presented graphically only)	Not reported	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.
Scholten et al., 2003	pantoprazole 40 mg vs esomeprazole 40 mg No or only mild heartburn: 99% vs 98%	Not evaluated	Not reported (all patients were Grade B or C)	3 patients discontinued due to adverse events not related to study drug (myocardial infarction, headache, allergic reaction). Groups not reported.

Evidence Table 1. Erosive GERD short-term trials of PPI vs PPI

Author Year	Quality rating	Funding source
Richter et al., 2001b	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from TAP Pharmaceuticals
Scholten et al., 2003	Fair: ITT results not reported, randomization and allocation concealment methods not reported.	Supported by a grant from ALTANA Pharma AG, Germany.

Evidence Table 2. Quality assessment of included trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Adachi 2003	Method not reported	Yes	Yes	Yes	No- open	No	No
Ando 2005	Method not reported	Not reported	Some	Yes	Yes	Yes	Yes
Armstrong et al., 2004	Method not reported	Not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified	Described as double-blind, not specified
Bardhan 2001	Method not reported	Not reported	More smokers in pantoprazole group (31% vs 22%), more males in omeprazole group (64% vs 52%)	Yes	No- open	No	No
Bytzer et al., 2004	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Adachi 2003	Attrition and adherence yes	Yes- 20% of lansoprazole group lost to f/u for endoscopy 7% in other groups; but no loss to f/u for reporting of symptoms.	Yes for symptoms	No	Fair-poor
Ando 2005	attrition yes, adherence no, crossovers no, contamination no	No	No	Yes	Fair
Armstrong et al., 2004	No	Not reported	Unable to determine (defined as all randomized patients who took at least one dose of study medication and had post-randomization data, but number withdrawn not reported)	Unable to determine	Fair
Bardhan 2001	Attrition and adherence yes	No	Yes	No	Fair
Bytzer et al., 2004	Attrition yes, others no	No	No (analyzed patients who had data on at least 1 postrandomization visit; number not specified)	No	Fair

Evidence Table 2. Quality assessment of included trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Caos et al., 2005	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Chen, 2005	Yes	Not reported	omeprazole group older (59.0 vs 49.2, p=0.0596), more belching in esomeprazole group (47% vs 25.2%, p=0.0121)	Yes	Yes	Described as double-blind, not specified	Yes (placebo)
Cucchiara 1993	Method not reported	Not reported	Few given, some differences - clinical significance unclear	Yes	Some	No	No
Fennerty 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Florent 1994	Method not reported	Not reported	More patients with previous hemorrhage in O group	Yes	Unclear	Unclear	Unclear
Fock et al., 2005	Yes	Method not reported	More women in esomeprazole group (57.8% vs 39.7%, p=0.051); otherwise similar	Yes	Described as double-blind, tablets inserted in identical capsules	Described as double-blind, tablets inserted in identical capsules	Described as double-blind, tablets inserted in identical capsules
Gillessen 2004	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Holtmann 2001	Not clear if adequate method	Not reported	22% of rabeprazole group Grade III vs 16.4% omeprazole	Yes	Yes	Yes	Yes
Kao 2003	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Not clear

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Caos et al., 2005	Attrition yes, others no	Not reported	Yes (LOCF)	No	Fair
Chen, 2005	Attrition yes, others no	Not high (2), but not reported by group	No	No	Fair
Cucchiara 1993	Attrition yes, adherence no crossovers no, contamination no	19% drop-out, not differential but high	No	Yes	Poor
Fennerty 2005	Attrition and adherence yes	No	Yes	1 in each group (did not take study medication)	Good
Florent 1994	Attrition yes, adherence no, crossovers no, contamination no	14 (19%) excluded from analysis; 7% of L group and 15% of O group	No	Yes	Poor
Fock et al., 2005	Attrition yes, others no	No	No (7 of 134 not analyzed)	Yes	Fair
Gillessen 2004	No	No	Yes	No	Fair
Holtmann 2001	Attrition yes	No	Yes	No	Fair
Kao 2003	Attrition yes	No	Yes	No	Fair

Evidence Table 2. Quality assessment of included trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Labenz 2005a	Method not reported	Not reported	Baseline data excludes 19 patients randomized but excluded due to intake of an unknown study drug or protocol violations. No data on excluded patients. Some differences in baseline esophagitis grade at baseline (grade B: 42.6% esomeprazole vs 45.1% pantoprazole; grade D: 4.5% esomeprazole, 5.8% pantoprazole)	Yes	Yes	Not reported	Yes
Labenz 2005b (Maintenance Therapy)	NR	NR	Yes	Yes	NR	NR	NR
Miehlke 2003	Yes	Not reported	Yes	Yes	No	No	No
Monikes et al., 2005	Method not reported	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified	Described as double-blind, not specified
Moore 2003	Method not reported	Not reported	No	yes	Yes	Yes	Yes
Pace 2005	Yes	centrally, but not clear where	yes(11 patients were omitted from baseline characteristic study)	yes	yes	yes	yes

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Labenz 2005a	Adherence yes, others no	Not reported	No	Yes	Fair-poor
Labenz 2005b (Maintenance Therapy)	Attrition yes, Others no	No	No	Yes	Fair
Miehlke 2003	Attrition yes, adherence yes, crossovers no, contamination no	7% esomeprazole vs 13% omeprazole	Yes	No	Fair-poor
Monikes et al., 2005	Attrition and adherence yes, others no.	No	No (defined as those who took at least one dose of study medication), excluded 10 who did not meet interim eligibility criteria.	Yes (N=10 not eligible)	Fair
Moore 2003	attrition yes, adherence no crossovers no, contamination no	No; unclear	No	Yes	Fair
Pace 2005	attrition yes, others no	No	No; data available to calculate real ITT	unclear	Fair

Evidence Table 2. Quality assessment of included trials

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Peura et al., 2004	Yes	Method not reported	Yes (missing data on 1 lansoprazole, 1 placebo patient; h. pylori data missing on 6 patients)	Yes	Yes (patient diaries)	Described as double-blind, not specified	Yes
Richter et al., 2004	Yes	Method not reported	Differences in race, otherwise similar	Yes	Not reported	Not reported	Yes
Stupnicki, 2003	Yes	Not reported	not clear- baseline characteristics given only for intention-to-treat population	Yes	Yes	Not reported	Yes
Talley, et al., 2001	Method not reported	Not reported	Yes	Yes	Described as double-blind, but not specified	Described as double-blind, but not specified	Yes
Tsai et al., 2004	Method not reported	Yes (sealed envelopes)	Yes	Yes	Yes? States "single blind (investigator)"	No? States "single blind (investigator)"	No
Vakil, 2004a	Yes	Yes	Yes	Yes	Yes	Yes	Yes
van Zyl et al., 2004	Yes	Method not reported	Yes	Yes	Described as double-blind, not specified	Described as double-blind, not specified	Yes
Yang, 2003	Method not reported	Not reported	Yes	Yes	No	No	No

Evidence Table 2. Quality assessment of included trials

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Peura et al., 2004	No	Not reported	No	Yes (excluded if heartburn was predominant symptom)	Fair to Poor
Richter et al., 2004	Attrition and adherence yes, others no	No	Yes	No	Fair
Stupnicki, 2003	Attrition yes	High (18%-19%) but not differential	Yes	No	Fair
Talley, et al., 2001	Attrition yes, others no	No	1 patient missing data	No	Fair
Tsai et al., 2004	Attrition and adherence yes, others no	No	Yes	No	Fair
Vakil, 2004a	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	Yes	Fair
van Zyl et al., 2004	Attrition yes, others no	No	Yes	No	Fair
Yang, 2003	Attrition yes, adherence yes, crossovers no, contamination no	No	Yes	No	Fair

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
	Head-to -head trials				
Armstrong et al., 2004 (FAIR)	Endoscopy-negative N=2645 (in 3 trials) multicenter, parallel group	All patients who had experienced heartburn (defined as a burning feeling, rising from the stomach or lower part of the chest up towards the neck) as their main symptom for 6 months or longer, and for 4 days or more during the last week before the start of each study, and who had a normal endoscopy.	Not reported	NR/NR/NR	NR/NR/2645

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Results	Results	Withdrawals Due to Adverse Events
Armstrong et al., 2004 (FAIR)	Patients with complete resolution of heartburn at 2 weeks (95% CI): Study A esomeprazole 40 mg: 34.6% (30.1%-39.3%) esomeprazole 20 mg: 39.7% (35.0%-44.6%) omeprazole 20 mg: 37.6% (33.0%-42.3%) Study B esomeprazole 40 mg: 41.2% (36.0%-46.6%) omeprazole 20 mg: 42.5% (37.2%-47.9%) Study C esomeprazole 20 mg: 41.4% (36.1%-46.8%) omeprazole 20 mg: 44.3% (38.9%-49.8%)	Patients with complete resolution of heartburn at 4 weeks (95% CI): Study A esomeprazole 40 mg: 56.7% (51.8%-61.5%) esomeprazole 20 mg: 60.5% (51.8%-61.5%) omeprazole 20 mg: 58.1% (53.3%-62.8%) Study B esomeprazole 40 mg: 70.3% (65.2%-75.1%) omeprazole 20 mg: 67.9% (62.7%-72.8%) Study C esomeprazole 20 mg: 61.9% (56.5%-67.1%) omeprazole 20 mg: 59.6% (54.1%-64.9%)	Not reported

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Fock et al., 2005 (FAIR)	Endoscopy-negative N=134 single center, parallel group	Age 21 to 65 years, with GERD symptoms (heartburn or regurgitation or both) present for at least 3 months in the previous year, which need not be continuous. Subjects needed to have experienced at least one period of moderate to very severe heartburn or regurgitation in the past 7 days prior to treatment. At endoscopy, no esophageal mucosal break was observed (i.e., grade 0 according to LA Classification)	Known history of gastroduodenal ulcer; infectious or inflammatory conditions of the intestine (including inflammatory bowel disease); malabsorption syndromes; obstruction; gastrointestinal malignancy; gastric or intestinal surgery including vagotomy; Barrett's esophagus; esophageal structure or pyloric stenosis; scleroderma; erosive esophagitis; positive HIV status and pregnancy. Abnormal laboratory tests at the initial visit (including liver enzymes greater than twice the upper limit of normal); GERD treatment refractory to a 2-month course of H2-blocker or PPI therapy; taken a PPI within 14 days of screening or a H2 blocker or prokinetic agent within 7 days of screening; required daily use of NSAIDs, oral steroids, aspirin (>325 mg/d); or were unable to discontinue the use of anticholinergics, cholinergics, spasmolytics, opiates, or sucralfate.	NR/NR/134	7/0/127

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Results	Results	Withdrawals Due to Adverse Events
Fock et al., 2005 (FAIR)	Median time to first 24-hour symptom-free interval (heartburn) rabeprazole 10 mg: 8.5 days esomeprazole 20 mg: 9.0 days (NS) Median time to first 24-hour symptom-free interval (regurgitation) rabeprazole 10 mg: 6.0 days esomeprazole 20 mg: 7.5 days (NS) Percentage of patients achieving a 24-hour symptom-free interval (heartburn) rabeprazole 10 mg: 84.4% esomeprazole 20 mg: 60.9% (NS) Percentage of patients achieving a 24-hour symptom-free interval (regurgitation) rabeprazole 10 mg: 90.0% esomeprazole 20 mg: 67.9% (NS)	Patients with complete resolution of daytime heartburn at 1 week: rabeprazole 10 mg: 26.9% esomeprazole 20 mg: 23.4% (NS) Patients with complete resolution of nighttime heartburn at 1 week: rabeprazole 10 mg: 28.8% esomeprazole 20 mg: 20.9% (NS) Patients with complete resolution of daytime heartburn at 4 weeks: rabeprazole 10 mg: 55.3% esomeprazole 20 mg: 41.1% (NS) Patients with complete resolution of nighttime heartburn at 4 weeks: rabeprazole 10 mg: 44.4% esomeprazole 20 mg: 41.0% (NS)	1 (headache, esomeprazole)

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
Monikes et al., 2005 (FAIR)	Endoscopy-negative N=529 multicenter, parallel group	Male and female, age 18 or older; patients had to have a history of frequent episodes of GERD-related symptoms during the last 3 months, and acid complaints for at least 3 days during the last week prior to study start; at least 3 episodes of acid complaints within the pre-treatment phase.	Any other gastrointestinal disease, erosive GERD (LA Grade A-D), Barrett's esophagus, acute peptic ulcer and/or ulcer complicatons, Zollinger-Ellison syndrome, pyloric stenosis, esophageal or gastric surgery, indication for H. pylori eradication therapy, and severe diseases of other major body systems. Pregnant and nursing women, or women of child-bearing potential who were not using reliable medical contraception; patients who had taken PPIs during the 10 days prior to study start, prokinetics or H2RAs during the 5 days prior to study start, or other substances for the relief of acid complaints, or systemic glucocorticosteroids, antiinflammatory drugs on more than 3 consecutive days, or PPI-based triple therapy for eradication of H. pylori during the last 28 days; intake of sucralfate during the 3 days prior to study start and concomitant intake of ketoconazole or other medication with pH-dependent absorption; regular intake of acetylsalicylic acid at doses up to 150 mg/day was permitted; patients also excluded if they showed poor compliance with regard to completing ReQuest.	574/564/539	78/NR/529

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Results	Results	Withdrawals Due to Adverse Events
Monikes et al., 2005 (FAIR)	Mean time to first symptom relief (days) pantoprazole 20 mg: 5.9±8.1 esomeprazole 20 mg: 6.4+9.0 Mean time to sustained symptom relief (days) pantoprazole 20 mg: 13.2+11.6 esomeprazole 20 mg: 13.5+11.6 Patients reaching first symptom relief within 2 weeks pantoprazole 20 mg: 86.3% esomeprazole 20 mg: 84.5% Patients reaching sustained symptom relief within 2 weeks pantoprazole 20 mg: 56.4% esomeprazole 20 mg: 54.4% Patients reaching first symptom relief within 4 weeks pantoprazole 20 mg: 92.8% esomeprazole 20 mg: 89.7% Patients reaching sustained symptom relief within 4 weeks pantoprazole 20 mg: 80.2% esomeprazole 20 mg: 79.4%		Not reported

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
	Placebo-controlled trials				
Peura et al., 2004	Endoscopy-negative N=921 multicenter, parallel group	At least 18 years of age, no history of documented or suspected gastroduodenal ulcers within the previous 5 years, and had symptoms of upper abdominal discomfort during the 3 months before the study.	Irritable bowel syndrome, taking more than two doses per week of an NSAID; upper GI endoscopy performed during screening period to exclude patients with erosive or ulcerative esophagitis. Excluded those with an active gastric or duodenal ulcer, duodenal erosion, or more than five gastric erosions. History of gastric or duodenal ulcer within the past 5 years; any other GI disease (including bleeding; gastric, duodenal, or esophageal surgery; esophageal structure requiring dilation; Barrett's esophagus); evidence of any uncontrolled disease involving major organ systems; laboratory results outside of the normal range; evidence of alcohol or drug abuse in the prior 12 months; use of chronic anticoagulant, antineoplastic, antidepressant, or corticosteroid therapy; treatment with an investigational agent within the prior 12 weeks; and use of a PPI, a prokinetic agent, any ulcerogenic drug, or aspirin within the prior 4 weeks.	NR/NR/921	NR/NR/NR

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Results	Results	Withdrawals Due to Adverse Events
Peura et al., 2004	Difference from placebo in median percentage of days with upper abdominal discomfort after 8 weeks (95% CI): lansoprazole 15 mg: –10% (–16% to –5%) lansoprazole 30 mg: –9% (–15% to –4%) (NS) Change from baseline to 8 weeks in percentage of days with upper abdominal discomfort (95% CI): lansoprazole 15 mg: –10% (–16% to –5%) lansoprazole 30 mg: –9% (–15% to –4%) placebo: –9% (–15% to –4%) (NS)		

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Population Setting	Inclusion criteria	Exclusion criteria	Number screened/ eligible/ enrolled	Number withdrawn/ lost to followup/ analyzed
	Active-controlled trials				
van Zyl et al., 2004	Symptomatic GERD (Endoscopy not conducted) N=338 multicenter, parallel group	Males and females, ages 18 to 75 with symptoms of heartburn, acid eructation, or pain on swallowing/dysphagia for 2 days prior to presentation. Presenting GERD symptoms were at least 2 points higher on the Likert scale (I.e., rather severe) than any other GI symptom (i.e., epigastric pain, vomiting, nausea, flatulence, retching, and retrosternal feeling of tightness). History of key GERD symptoms (one episode/month for at least 3 months) prior to entry into the study.	History of GI disease (e.g., peptic ulcer or ulcer complications, Zollinger-Ellison syndrome, esophageal strictures, or irritable bowel disease), concomitant severe disease (e.g., cardiovascular, respiratory and renal disorders, CND disorders, or malignant disease), or if they had any significant laboratory abnormalities. Women of child-bearing potential not taking reliable contraceptive measures, patients who had recently taken part in another clinical study, and patients who had recently taken or were still receiving PPI therapy or agents likely to affect gastric acid secretion or gut motility.	NR/NR/338	132/NR/338

Evidence Table 3. Nonerosive GERD short-term trials

Author Year (Quality rating)	Results	Results	Withdrawals Due to Adverse Events
van Zyl et al., 2004	Patients with relief from key GERD symptoms (heartburn, acid eructation, and pain on swallowing) after 4 weeks: pantoprazole 20 mg: 68.3% ranitidine 300 mg: 43.3% (95% CI for odds ratio 1.84 to 4.51)		

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Caos 2005	Of 497 enrolled patients, 261 patients completed (Phase 1) and 205 patients completed (Phase 2.) Eligible patients were those with endoscopically confirmed healed erosive or ulcerative GERD ≤90 days prior to study entry. Mean age: Rabeprazole 20mg, 54.83 yrs; Rabeprazole 10 mg, 54.32 yrs; placebo 52.70 yrs Gender: Rabeprazole 20mg, 65% male; Rabeprazole 10 mg, 66.1% male; placebo 62.1% male Race: Rabeprazole 20mg: 86.5% Caucasian, 10.4% African-American, 3.1% other; Rabeprazole 10mg: 90.9% Caucasian, 4.8% African-American, 1.2% Asian, 3.0% other; Placebo: 92.9% Caucasian, 3.6% African-American, 1.2% Asian, 2.4% other	NR	NR/NR/497/236(Phase 1)/NR
Carling 1998	248 patients at 23 centers in Denmark, Finland, and Sweden; mean age 56 (+/- 12); 62% male; ethnicity not given	Grade 2: 72% Grade 3: 22% Grade 4: 6% (Savary-Miller)	289 treated , 262 healed, 248 continued to maintenance phase, 226 included in per protocol analysis.

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Jasperson 1998	30 patients in Germany whose esophagitis healed after 6-8 weeks of omeprazole; mean age 57; 60% male; ethnicity not given.	All Grade 4 (Savary-Miller)	36 treated, 6 did not heal, 30 included.
Labenz et al 2005	2766 patients (63% men; mean age 50 years) were required to have EE [photographically documented at baseline endoscopy; Los Angeles (LA) grades A–D] within the 7 days preceding study randomization, a history of GERD symptoms for at least 6 months immediately prior to randomization, and heartburn with an overall severity of moderate or severe on at least 4 days in the week preceding randomization. This multicentre study was conducted at 263 centres in 14 countries.	LA grade A: 32.5% B: 44.4% C: 18.6% D: 4.6% H. pylori positive: 27.2%	Discontinuations due to adverse events (DAE) were reported for 19 patients (1.4%) in the esomeprazole 20 mg group and 18 patients (1.3%) in the pantoprazole 20 mg group.

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Lauritsen et al. 2003	1224 patients in Europe and South Africa with history of heartburn and endo-verified GERD. Mean age: 49 Male: 61% White: 98%	LA grade A: 38% B: 45% C: 14% D: 3% H. pylori positive: 31%	1391 enrolled in healing phase, 1236 (89%) randomized for maintenance treatment. ITT = 1224 (615 esomeprazole, 609 lansoprazole). Healing phase: 31/1391 (2.2%) withdrawn for AE; 63 (4.5%) lack of therapeutic response; 61 (4.4%) lost, excluded, other. Randomized pop. exclusion: 12/1236 (0.1%) excluded from ITT for noncompliance or persistent esophagitis at entry. Maintenance phase: 51/1236 (4.1%) withdrawn for AE; 124 (10.0%) lack of therapeutic response; 50 (4.0%) lost, other. Similar AE profiles between groups.

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Richter et al., 2004	349 patients at 32 sites in the US with either endoscopically confirmed healing of erosive esophagitis in prior acute pantoprazole or other regimen studies (omeprazole, lansoprazole, nizatidine, ranitidine) with confirmed healing at least 1 mo prior to start of study, patients who previously participated in acute studies with no healing; patients with Grade 2 or greater EE who did not participate in acute studies. Patient characteristics: mean age 49.56 yrs; 72.8% male; 90.5% white, 4.3% black, 4.3% Hispanic, 0.3% Asian, 0.6% other	Hetzel-Dent Scale Baseline (n=328): Grade 0: 69.6% Grade 1: 30.4% Acute baseline (n=321): Grade 2: 67.7% Grade 3: 25.0% Grade 4: 7.3%	349 enrolled/178 discontinued by 1 yr including 110 due to lack of efficacy and 19 due to adverse events. Discontinuations due to lack of efficacy most common among pantoprazole 10 mg patients (n=36) and ranitidine 150 mg patients (n=46)

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Population, setting	Esophagitis Grade (grading criteria), other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	243 patients at 21 centers in Europe with a previous diagnosis of erosive GERD healed within 90 days of enrollment; mean age 52.7 (+/- 14.3); 67% male; ethnicity not given.	Grade 0: 77% Grade 1: 22% 1 missing (modified Hetzel-Dent)	210/243 completed one year; 13 withdrew due to adverse events. 123 completed 5 years; 26 withdrew due to adverse events. No differences between groups.

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Results	Quality rating	Funding source and role of funder
Caos 2005	*Primary endpoint:* Relapse rates at 5 yrs were 11% for rabeprazole 20mg, 23% for rabeprazole 10mg and 63% for placebo (p<0.001) Kaplan-Meier probability of GERD erosions being healed at 5 yrs: 87% rabeprazole 20mg, 33% for 10mg, 20% for placebo. No SS difference in relapse based on age. *Secondary endpoints:* Daytime heartburn relapse lower with both doses of rabeprazole v placebo (p<0.001 for 20mg, p≤0.018 10 mg) Night-time relapse rates favored rabeprazole 20mg (p≤0.005)	Fair	Supported by Eisai Inc and Janssen Pharmaceuticals
Carling 1998	*Endoscopic relapse by 48 weeks:* lansoprazole 30 mg: 8.7% omeprazole 20 mg: 8.2% *Symptomatic relapse by 48 weeks:* lansoprazole 30 mg: 0.8% omeprazole 20 mg:1.6% p=NS	Fair: allocation concealment not reported, more excluded from lansoprazole group at entry, more Grade 2 in lansoprazole group at baseline.	Supported by Wyeth Ayerst and Wyeth Lederle

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Results	Quality rating	Funding source and role of funder
Jasperson 1998	*Endoscopic remission at 4 weeks:* omeprazole 20 mg: 90% lansoprazole 30 mg: 20% pantoprazole 40 mg: 30% *Recurrence of reflux symptoms at 4 weeks:* omeprazole 20 mg: 10% lansoprazole 30 mg: 60% pantoprazole 40 mg: 60% omeprazole vs lansoprazole p<0.01 omeprazole vs pantoprazole p<0.01	Fair: allocation concealment not reported, blinding of patients not reported, very small sample size. There was selection bias.	Not reported.
Labenz et al 2005	*Primary endpoint:* Endoscopic plus symptomatic remission for all patients at 6 mos was 74.9% for 20 mg pantoprazole and 87.0% for 20 mg esomeprazole. *Secondary endpoint:* Esomeprazole 20 mg was significantly more effective than pantoprazole 20 mg for maintaining pure endoscopic healing of EE (6-month life table estimates: 88.1%; 95% CI: 86.3–90.0 vs. 76.6%; 95% CI: 74.2–79.0, log-rank test P < 0.0001).		Supported by a grant from AstraZeneca R&D, Sweden.

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Results	Quality rating	Funding source and role of funder
Lauritsen et al. 2003	*Endoscopic remission at 6 months.* esomeprazole 84% vs. lansoprazole 76% (p<.0002)	Fair: small differences at baseline (slightly > males on esomeprazole slightly more H. pylori positive on lansoprazole); not ITT: 12 randomized but not included in ITT analysis for not taking any study drug OR persistent esophagitis at baseline (combined); 4 in esomeprazole group, 8 in lansoprazole group.	Sponsored by AstraZeneca

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Results	Quality rating	Funding source and role of funder
Richter et al., 2004	*Primary endpoint:* Maintained EE healing at 12 mos was 78% for 40 mg pantoprazole; 55% for 20 mg pantoprazole; 46% for 10 mg pantoprazole and 21% for ranitidine 150 mg. 76% of Grade 2 and 72% of Grade 3/4 patients remained healed with pantoprazole 40mg, while 78%, 59% and 21% of Grade 2 patients remained healed with pantoprazole 20mg, pantoprazole 10 mg and ranitidine 150 mg respectively. *Secondary endpoints:* No SS difference of healing maintenance based on h.pylori status; more symptom-free days with pantoprazole 40 mg (83%) than with pantoprazole 10 mg (65%) or ranitidine (58%); less rescue medication use during first 4 mos of study for all pantoprazole doses vs ranitidine ($p<0.05$)	Fair	Supported by Wyeth

Evidence Table 4. Erosive GERD relapse prevention

Author Year	Results	Quality rating	Funding source and role of funder
Thjodleifsson et al. 2000 Thjodleifsson et al. 2003	*Endoscopic relapse at 13 weeks:* rabeprazole 10 mg: 1.2% rabeprazole 20 mg: 2.6% omeprazole 20 mg: 1.2% *Endoscopic relapse at 26 weeks:* rabeprazole 10 mg: 1.2% rabeprazole 20 mg: 3.8% omeprazole 20 mg: 1.2% *Endoscopic relapse at 52 weeks:* rabeprazole 10 mg: 4.9% rabeprazole 20 mg: 3.8% omeprazole 20 mg: 4.8% Endoscopic relapse at 5 years: rabeprazole 10 mg: 9.8% rabeprazole 20 mg: 11.5% omeprazole 20 mg: 13.3% p=NS for all comparisons	Fair: allocation concealment not reported, not clear if maintenance of comparable groups.	Funded by Eisai, Ltd, UK

Evidence Table 5. Non-erosive GERD relapse prevention

Author Year	Population, setting	Heartburn severity, other characteristics	Number screened, eligible, enrolled, withdrawn, lost to followup
Bytzer et al., 2004	535 patients at centers in Greece, Italy, the Netherlands, Spain, France, Portugal, Sweden, Denmark, Ireland, Belgium, United Kingdom, Russia, Poland and Lithuania; mean age: 47; 60% female; ethnicity not given	Patient assessment of heartburn severity scored on 5-point Likert scale; Quality of life assessed with 22-item Psychological General Well-being Index (PGWBI); 100% patients previously achieved complete relief of symptoms during acute treatment phase	668 screened Acute phase: 535 enrolled, 117 withdrawn, 5 lost to followup On-demand phase: 418 enrolled, 71 withdrawn, 9 lost to followup
Talley, et al., 2001	342 patients in 65 centers in Denmark, Finland, Norway and Sweden; mean age: 49; 56% male; ethnicity not given	Heartburn frequency and severity, and severity of related gastrointestinal symptoms with assessed with standardized checklist; 100% patients previously achieved complete relief of symptoms during acute treatment phase	342 enrolled, 123 withdrawn, 2 lost to followup
Tsai et al., 2004	774 enrolled patients, of whom 152 withdrew prior to randomization in 92 general practices and 28 hospitals with at least a 6 mo history of heartburn, including 4 of 7 days preceding study entry and no esophageal mucosal breaks verified by endoscopy up to 14 days prior to enrollment. Patient characteristics: mean age 51.3 yrs; 56% female; ethnicity NR	Severity of heartburn at baseline: Mild: 26.6% (n=195) Moderate: 59% (n=452) Severe: 15.4% (n=118) (n=765 total)	774 enrolled, 152 discontinued prior to randomization into maintenance phase of study, including 18 withdrawals due to AEs, 124 who did not meet eligibility and 10 for other reasons not specified. 622 randomized into maintenance phase, 80 withdrawals during maintenance phase due to adverse event, heartburn or other unspecified reason.

Evidence Table 5. Non-erosive GERD relapse prevention

Results	Quality rating	Funding source and role of funder
Complete relief of symptoms at acute phase by 4 weeks: rabeprazole 10 mg: 83% *Discontinuation due to lack of heartburn control during on-demand phase by 6 months:* rabeprazole 10 mg: 6% placebo: 20% p < 0.00001	Fair	Supported by Janssen Pharmaceutica
Discontinuation due to lack of heartburn control during on-demand phase by 6 months: esomeprazole 20 mg: 14% placebo: 51% *Mean number of days patients remained with on-demand therapy:* esomeprazole 20 mg: 165 placebo: 119	Fair	Supported by AstraZeneca
More lansoprazole 15 mg continuous use vs esomeprazole 20 mg on-demand unwilling to continue use at 6 mos (13% v 6%; p=0.001; 95% CI 9.2-16.8 and 2.8-8.8 respectively.) More esomeprazole patients were satisfied (score of 1-4 on Treatment Satisfaction Questionnaire) at 1 mo compared to lansoprazole patients (93.2% v 87.8%, p=0.02 95% CI 0.88-10.1) The difference in patient satisfaction between the treatment groups lessened at 3 and 6 mos, but exact percentages are not provided in the study.	Fair	Supported by Astra-Zeneca UK

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Moore 2003 South Australia	Mean age 5.4 mo 76% male 100% with gastroesophageal reflux and/or esophagitis, history of frequent spilling, irritability/crying level concerning to parents, previous treatment with pharmacologic treatment for GER	Omeprazole 10mg daily for infants 5-10kg, 10mg twice daily for infants >10kg	Matching placebo	64 eligible 34 enrolled

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Moore 2003 South Australia	***Parent daily diary mean scores of cry/fuss time in min/24h:*** *Baseline:* O: 246 vs placebo: 287 *Period 1 (2 weeks):* O: 203 vs placebo: 204 *Period 2 (2 weeks):* O: 179 vs placebo: 198 ***Visual Analog Scale mean scores of infant irritability:*** *Baseline:* O: 7.1 vs placebo: 6.6 *Period 1 (2 weeks):* O: 5.9 vs placebo: 6.0 *Period 2 (2 weeks):* O: 4.0 vs placebo: 5.7	None reported	Fair

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Cucchiara 1993 Italy	Age range 6 mo-13.4 yrs 50% male 100% diagnosis of GOR oesophagitis, unresponsive to previous antireflux treatment	Omeprazole 40mg/daily or ranitidine 20mg/kg/daily	Ranitidine 20mg/kg/daily	32 enrolled

Evidence Table 6. Randomized controlled trials of esophagitis treatment in children

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Cucchiara 1993 Italy	***Healing rates:*** O: 9(32%) vs R: 8(36%) ***Median percentage of improvement of intraoesophageal and intragastric pH variables:*** *Time of oesophageal pH <4.0:* O: 61.9 vs R: 59.6 *Time of intragastric pH <4.0:* O: 29.0 vs R: 22.3 *Time of intragastric pH <2.0:* O: 61.5 vs R: 62.2 *Median intragastric pH:* O: 60.1 vs R: 37.4 *Intragastric hydrogen activities (mmol/l):* O: 97.9 vs R: 91.0	No serious events requiring discontinuation of treatment observed	Poor

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive	Lansoprazole 30 mg once a day x 4 weeks, then those with healed ulcer randomized to 15 or 30 mg lansoprazole daily x 12 months	Omeprazole 40 mg once a day, then those with healed ulcer switched to omeprazole 20 mg daily x 12 months	251 eligible (167 lansoprazole, 84 omeprazole), unclear number found H. pylori positive who decided not to participate. Maintenance phase: 243 enrolled (164 lansoprazole, 79 omeprazole)
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	Not available	Lansoprazole 30 mg once daily x 4 weeks	Omeprazole 20 mg once daily x 4 weeks	111 enrolled (57 lansoprazole, 54 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Dobrilla 1999 Italy Multicenter	*Healing:* *4 weeks:* (unclear analysis, only 243 of 251 included) 93.9% lansoprazole, 97.5% omeprazole *PP analysis (# not reported):* 4 weeks: 99% lansoprazole, 100% omeprazole *Symptoms:* *No pain at 4 weeks:* 87.9% lansoprazole, 87.4% omeprazole *Maintenance: (unclear analysis)* *6 months:* 4.5% lansoprazole 15 mg, 0% lansoprazole 30 mg, 6.3% omeprazole relapse *12 months:* 3.3% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.5% omeprazole *PP analysis:* *6 months:* 0% relapse in all groups *12 months:* 1.9% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.6% omeprazole relapse *Followup (at 18 months):* 27.3% lansoprazole 15 mg, 20% lansoprazole 30 mg, 26.7% omeprazole relapse	16 during phase I (4 weeks), 10 (6%, lansoprazole), 6 (7.1%, omeprazole) Phase 2 (maintenance): 9 (12.2%, lansoprazole 15 mg), 4 (5.6%, lansoprazole 30 mg), and 8 (11%, omeprazole). The most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 lansoprazole 15 mg, 2 lansoprazole 30 mg, 3 omeprazole) including diarrhea, rash, gynecomastia, asthenia, precordial pain, fever, and weight gain. No significant changes in laboratory tests were found. Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml lansoprazole 30 mg, 35.8pg/ml omeprazole; NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The lansoprazole 15 mg group had the least and the lansoprazole 30 mg group had the highest elevation at 6 and 12 months. At 6 months followup all values were returning to baseline.	Fair-poor
Chang 1995 Taiwan single center (from abstract only – full text not available for this draft)	*Healing:* *4 weeks:* (ITT) 89.5% lansoprazole, 83% omeprazole (PP) 96% lansoprazole, 94% omeprazole	Hypergastrinemia in both groups (approximately 1.6 fold increase) Skin rash and constipation occurred in a few cases (groups not specified)	Not assessed

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Capurso 1995 Italy Multicenter	Reported as 'balanced' for age, sex, weight, smokers, alcohol use, ulcer history, symptoms, ulcer size, and prior complications	Lansoprazole 30 mg a day (morning) x 2 to 6 weeks	Omeprazole 20 mg once daily x 2 to 6 weeks	107 enrolled, (52 lansoprazole, 55 omeprazole)
Ekstrom 1995 Sweden Multicenter	Mean age 55 47% smokers 43% alcohol users 10% NSAID users	Lansoprazole 30 mg once a day x 4 weeks	Omeprazole 20 mg a day x 4 weeks	279 enrolled (143 lansoprazole, 136 omeprazole)
Fanti 2001 Italy Single center	Median age 47 lansoprazole and 48 omeprazole 68% male 56% smokers 54% alcohol users	Lansoprazole 30 mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1 gm x 7 days	Omeprazole 20 mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1 gm x 7 days	43 enrolled (22 lansoprazole and 21 omeprazole)
Chang 1995 Taiwan Single center	Mean age 57 and 61 89% male 47% smokers 93% H. pylori positive	Lansoprazole 30 mg once daily x 4 weeks	Omeprazole 20 mg once daily x 4 weeks	83 enrolled (42 lansoprazole, 41 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Capurso 1995 Italy Multicenter	*Healing rates:* *2 weeks:* 58% lansoprazole, 57% omeprazole *4 weeks:* 94% lansoprazole, 94% omeprazole *Nighttime pain free:* *2 weeks:* 94% l), 87% omeprazole (NS) *Daytime Pain free* *2 weeks:* 92% lansoprazole, 81% omeprazole (NS)	8 adverse effects reported: 3 rabeprazole, 3 lansoprazole, and 2 omeprazole. No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair
Ekstrom 1995 Sweden Multicenter	*Healing rates:* *2 weeks:* *Endo:* 86.2% lansoprazole, 82.1% omeprazole *PPI:* 87.9% lansoprazole, 82.3 omeprazole *4 weeks:* *Endo:* 97.1% lansoprazole, 96.2% omeprazole *PPI:* 97.7% lansoprazole, 96/7% omeprazole *Symptoms:* Most patient's symptoms improved to 'occasional' or 'none' by two weeks, nearly all by 4 weeks in both groups. At 4 weeks the reduction in symptoms favored lansoprazole, p = 0.041 (98% vs 96% with more than occasional symptoms). *Antacids:* no difference found	68 adverse events occurred in 57 patients (23 patients taking lansoprazole, 34 taking omeprazole). No statistically significant difference in the severity was found between the two groups. A statistically significant difference was found in the mean change in ALAT concentration, but the change was minor (0.05 unit increase lansoprazole, 0.03 unit decrease omeprazole).	Fair
Fanti 2001 Italy Single center	*Healing rates:* *8 weeks:* 100% both groups *Symptoms:*"rapid clinical response with disappearance of symptoms in both groups"	"Mild and self-limiting" Total number not reported 1 lansoprazole stomatitis and 1 omeprazole mild diarrhea	Fair
Chang 1995 Taiwan Single center	*Healing:* *4 weeks:* 95.2% lansoprazole, 92.7% omeprazole *H. Pylori eradication:* *4 weeks:* 78.9% lansoprazole, 82.1% omeprazole	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication (of those H. pylori positive)	Fair

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Dekkers 1999 Belgium, England, Germany Multicenter	Mean age 48 (range 20-77) 65% male 51% smokers 54% alcohol users 83% H. pylori positive	Rabeprazole 20 mg once daily. Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing	Omeprazole 20 mg a day x 4 weeks (Duration not clearly stated, but assumed to be 4 weeks based on outcome measure timing)	205 enrolled (102 rabeprazole, 103 omeprazole)
Beker 1995 Multicenter	Median age 44 (range 20 - 86) 70% male 50% smokers 20% alcohol users 58% 2 or more previous ulcers	Pantoprazole 40 mg once daily x 2 to 4 weeks	Omeprazole 20 mg once daily x 2 to 4 weeks	270 enrolled (135 each group)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Dekkers 1999 Belgium, England, Germany Multicenter	*Healing rates (ITT):* *2 weeks:* 69% rabeprazole, 61% omeprazole *4 weeks:* 98% rabeprazole, 93% omeprazole *Healing rates (Endo):* *2 weeks:* 69% rabeprazole, 63% omeprazole *4 weeks:* 99% rabeprazole, 96% omeprazole *Pain frequency:* all patients showed improvement (no statistical difference found) *Pain severity:* All patients reported improvement in both daytime and nighttime pain. The only statistically significant difference was found in daytime pain at 4 weeks (92% vs 83% improved, rabeprazole vs omeprazole, p = 0.038). No difference found in the number pain free.	43 patients reported at least on adverse event. (21 rabeprazole, 22 omeprazole). The most common was headache. The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml rabeprazole and 18.9 pg/ml omeprazole.	Fair
Beker 1995 Multicenter	*Healing:* *(PP analysis)* *2 weeks:* 71% pantoprazole, 65% omeprazole (p=0.31) *4 weeks:* 95% pantoprazole, 89% omeprazole (p= 0.09) ITT analysis results reported as 'similar' *Symptoms:* *Pain free (of those with pain at baseline)* *2 weeks:* 81% pantoprazole, 82% omeprazole (p = 0.87) *Patient diary:* no significant differences in time course of becoming pain free.	21 patients reported adverse events (10 pantoprazole, 11 omeprazole), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 pantoprazole, 4 omeprazole). 3 in the omeprazole group were considered possibly related to study treatment (1 angina pectoris, 1 hypertension, 1 vertigo) and patients were withdrawn from study. The other 2 were GI hemorrhage pantoprazole, and abdominal pain omeprazole and considered not related to study drugs. No clinically significant changes in lab values from baseline values. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.	Fair

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Age, Gender, Race Other Population Characteristics	Intervention	Control	Number
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	Mean age 46 (SD 13) 62% male 100% white 57% smokers all were H. pylori positive	Esomeprazole 20 mg twice daily plus clarithromycin 500 mg and amoxicillin 1 gm twice daily x 1 week, placebo x 3 weeks	Omeprazole 20 mg twice daily mg x 4 weeks plus clarithromycin 500 mg and amoxicillin 1 gm twice daily x 1 week	446 randomized (222 esomeprazole 224 omeprazole)

Evidence Table 7. Randomized controlled trials of duodenal ulcer treatment: PPI vs PPI

Author Year Setting	Outcomes Reported (Results)	Number of Adverse Effects	Quality Rating
Tulassay 2001 Hungary, Poland, Czech Republic Multicenter	*Healing rates:* *4-6 weeks:* (ITT) 91% esomeprazole, 92% omeprazole (PP) 94% esomeprazole, 96% omeprazole *H. pylori eradication:* (ITT) 86% esomeprazole, 88% omeprazole (PP) 89% esomeprazole, 90% omeprazole (NS)	33% of esomeprazole and 29.5% of omeprazole reported at least one adverse event. Most frequent taste perversion, diarrhea, loose stools. 4 discontinued for adverse events (e: 1 for taste perversion/vomiting, o: 1 for rash, 1 allergic reaction, 1 dysmenorrhea). No clinically relevant trends for changes in laboratory safety variables.	Fair

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Dobrilla 1999 Italy Multicenter	Mean age 45 (range 18 - 69) 66% male 52% smokers 34% alcohol use 90% Helicobacter pylori positive 21% NSAID users; 80% treated with lansoprazole x 8-16 weeks for acute ulcer; 95% H-2 antagonist resistant acute ulcer	Lansoprazole 15 or 30 mg daily x 12 months	Omeprazole 20 mg daily x 12 months	Maintenance phase: 243 enrolled (164 lansoprazole, 79 omeprazole)
Lanza 1997 USA Multicenter	Mean age 43 63% male 76% Caucasian 48% smokers 56% alcohol users	Lansoprazole 15 mg once daily x 12 months or until ulcer recurrence	Placebo once daily x 12 months or until ulcer recurrence	186 enrolled (88 placebo, 92 lansoprazole)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Dobrilla 1999 Italy Multicenter	*Maintenance: (unclear analysis)* *6 months:* 4.5% lansoprazole 15 mg, 0% lansoprazole 30 mg, 6.3% omeprazole relapse *12 months:* 3.3% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.5% omeprazole *PP analysis:* *6 months:* 0% relapse in all groups *12 months:* 1.9% lansoprazole 15 mg, 0% lansoprazole 30 mg, 3.6% omeprazole relapse *Followup (at 18 months):* 27.3% lansoprazole 15 mg, 20%lansoprazole 30 mg, 26.7% omeprazole relapse	Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml lansoprazole 30 mg, 35.8pg/ml omeprazole NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The lansoprazole 15 mg group had the least and the lansoprazole 30 mg group had the highest elevation at 6 and 12 months. At 6 months follow up all values were returning to baseline.	Fair/poor	If assigned to lansoprazole during treatment study, randomized to lansoprazole; if assigned to omeprazole for treatment, omeprazole for maintenance
Lanza 1997 USA Multicenter	*Recurrence:* *12 months:* (ITT) 62% placebo, 27% lansoprazole (Endo) 61% placebo, 26% lansoprazole *Symptoms:* Median time to becoming symptomatic >12 months both groups Asymptomatic during 9-12 months: 75% lansoprazole, 58% placebo *Antacid use (tabs/day):* median 0.08 lansoprazole, 0.23 placebo (P<0.05)	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in lansoprazole group than placebo, median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in lansoprazole group compared to placebo group (707cells/mm2 vs 556 cells.mm2), no other differences found.	Fair	

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Kovacs 1999 USA Multicenter	Mean age 57 placebo, 54 lansoprazole 15 mg, 47 lansoprazole 30 mg 88% male 57% smokers 39% alcohol users	Lansoprazole 15 or 30 mg once daily for up to 12 months	Placebo once daily for up to 12 months	19 placebo, 18 lansoprazole 15 mg, 19 lansoprazole 30 mg, other 3 not reported)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Kovacs 1999 USA Multicenter	*Recurrence:* *1 month:* 27% placebo, 13% lansoprazole 15 mg, 6% lansoprazole 30 mg *12 months:* 30% lansoprazole 15 mg, 15% lansoprazole 30 mg All patients on placebo experienced recurrence or withdrew from study by 6 months. *Symptoms:* *Symptom free at* *12 months:* 82% lansoprazole 15 mg, 76% lansoprazole 30 mg All patients on placebo experienced symptoms, recurrence or withdrew from study by 6 months *Antacid use:* median use (tabs/day): 0.21 placebo, 0 lansoprazole 15 mg, 0.01 lansoprazole 30 mg NS	40 patients reported adverse events (11 placebo, 15 lansoprazole 15 mg, 14 lansoprazole 30 mg). Adverse events possibly or probably related to study drug: 2 placebo, 2 lansoprazole 15 mg, 6 lansoprazole 30 mg. None were severe. Withdrawals due to adverse events: 2 placebo, 3 lansoprazole 15 mg, 1 lansoprazole 30 mg. No significant changes from baseline on labs, physical exam, or ECG. Serum gastrin levels increased significantly in both lansoprazole groups compared to placebo (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3 lansoprazole 15 mg, 5 lansoprazole 30 mg) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug. Changes in Grimelius-positive	Fair	Prior to enrollment, healing was achieved in all patients with lansoprazole 30 mg.

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Russo 1997 Italy Multicenter	Mean age 44 68% male 55% smokers (43% >15/day) 32% alcohol users H. pylori positive: 91%	If lansoprazole 30 mg during healing trial: lansoprazole 15 mg or placebo once daily x 12 months or until recurrence	If rabeprazole during healing trial: ranitidine or placebo 150 mg once daily x 12 months or recurrence	Healing: 132 enrolled (68 lansoprazole, 64 ranitidine) Maintenance: 108 enrolled (30 (lansoprazole 30 mg/lansoprazole 15 mg), 28 (lansoprazole 30 mg/placebo), 24 (ranitidine/ranitidine), 26 (ranitidine/placebo)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Russo 1997 Italy Multicenter	*Recurrence:* (ITT) *3 months:* 7% (lansoprazole/lansoprazole), 14% (lansoprazole/placebo), 8% (ranitidine/ranitidine), 27% (ranitidine/placebo) *6 months:* 17% (lansoprazole/lansoprazole), 32% (lansoprazole/placebo), 33% (ranitidine/ranitidine), 46% (ranitidine/placebo) *9 months:* 23% (lansoprazole/lansoprazole), 36% (lansoprazole/placebo), 38% (ranitidine/ranitidine), 50% (ranitidine/placebo) *12 months:* 23% (lansoprazole/lansoprazole), 39% (lansoprazole/placebo), 46% (ranitidine/ranitidine), 50% (ranitidine/placebo) (P=0.081 (l/l) vs (ranitidine/ranitidine) *Symptoms:* results not reported	*Maintenance*: Reported as 3% (lansoprazole/lansoprazole), 18% (lansoprazole/placebo), 0% (ranitidine/ranitidine); (ranitidine/placebo) not reported	*Healing:* Good/Fair *Maintenance:* Fair/Poor	Healing: lansoprazole 30 mg or ranitidine. baseline information on maintenance phase participants not reported. Attrition/compliance for maintenance not reported. Results for symptoms during healing phase not reported.

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Age, Gender, Race, Other Population Characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Graham 1992 USA Multicenter	Mean age 48 omeprazole, 50 ranitidine, 47 placebo % male: 75% omeprazole, 67% ranitidine, 69% placebo Mean index ulcer size cimetidine: 0.9 omeprazole, 0.8 ranitidine (P<0.01); placebo not reported other variables reported as NS	None	None	240 enrolled (80% of omeprazole, 63% of ranitidine and 27% of placebo patients eligible enrolled)

Evidence Table 8. Duodenal ulcer recurrence rates on maintenance therapy

Author, Year Setting	Outcomes Reported	Number of Adverse Effects	Quality Rating	Comments
Graham 1992 USA Multicenter	Life table analysis relapse rates: 78% omeprazole, 60% (ranitidine), 50% placebo (NS)	None reported	Fair	Followup study of omeprazole 20 mg vs ranitidine or omeprazole 20 mg vs placebo

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	Mean age 55 57% male 52% smokers 57% H. Pylori positive 24% antacid use 96% had >/= 0.5cm ulcer	Rabeprazole 20mg once daily. Duration not clearly stated, but assumed to be 6 weeks based on outcome measure timing.	20 mg of omeprazole	227 enrolled	***Healing rates by ITT:*** *3 weeks:* 58% (r), 61% (o) *6 weeks:* 91% (r and o) *3 weeks:* 58% (r), 63% (o) *6 weeks:* 93% (r and o) *3 weeks:* 60% (r), 59% (o) *6 weeks:* 52% (r), 44% (o) ***Pain severity:*** no pain *3 weeks:* 68% (r), 61% (o) *6 weeks:* 84% (r), 68% (o) Overall well-being at 3 and 6 weeks comparable for both groups
Ando, 2005	Mean age 51 77% male 83% H. pylori positive 16% poor metabolizers	Rabeprazole 10 mg once daily 8 weeks	20 mg of omeprazole	80 enrolled	***Healing rates by ITT:*** *2 weeks:* 85.9%% (r), 76.5% (o) 8 *weeks:* 88.9% (r) 87.8% (o)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Dekkers 1998 Belgium, England, Germany, Iceland, Ireland, Netherlands, Poland, Spain, Sweden Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r)and 10.0 pg/ml (o).	Fair
Ando, 2005	8 adverse events reported in 5 patients R: abdominal pain, nausea, headaches O: diarrhea, abdominal pain, nausea flatulence, headache	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Florent 1994 France	Mean age 56 64% male 49% smokers	Lansoprazole 30 mg once daily 4 to 8 weeks	20 mg of omeprazole	126 enrolled	***Healing Rates by PP:*** *4 weeks:* 82% (l), 68% (o) *8 weeks:* 93% (l), 82% (o) ***Pain Relief:*** *Daytime:* 86% (l), 60% (o) *Nocturnal pain:* 100% (l), 70% (o) *Time to daytime pain relief:* 6.6 d (l), 11 d (o)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Florent 1994 France	23 adverse events were reported (8 (l), 15 (o)). The most common adverse event with L was diarrhea, and was headache and diarrhea with O.	Poor- open label, high drop-out rate, differential loss to followup, not ITT

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
DiMario 1994 Italy Multicenter Maintenance study	Mean age 47.9 (23-75) 71% male 13% gastric ulcers, 79% duodenal ulcers, 8% both gastric and duodenal ulcer All ulcers resistant to H2 blocker therapy (unhealed after 8 weeks of therapy)	Omeprazole 20 or 40 mg daily for 4 weeks, extended to 8 weeks if necessary. After healing: omeprazole 20 mg daily (30 patients) omeprazole 20 mg every other day (29 patients) omeprazole 20 mg twice weekly (29 patients)	Ranitidine 150 mg (12 patients only)	# screened, eligible not reported, 102 enrolled	***Recurrence (6 months) by ITT:*** 23.3% Omeprazole 20 mg daily (p <0.02 vs ranitidine) 19.4% Omeprazole 20 mg every other day (p<0.005 vs ranitidine) 58.6% Omeprazole 20 mg twice weekly 66.7% Ranitidine 150 mg

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
DiMario 1994 Italy Multicenter Maintenance study	No side effects were reported during the maintenance treatment period; 1 patient reported headache in healing period (at oemp 40 mg daily; resolved). 11 patients dropped out (27% in omep 20 mg every day group, 0 in omep every other day, 73% in omep 20 mg twice weekly)	Poor- open, differential loss to followup

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Kovacs 1999 USA Multicenter Maintenance Study	Mean age 58 (pl), 57 (l15), 58 (l30) 85% male 67% smokers 47% alcohol users 96% acute disease H-2 RA resistant	Lansoprazole 15 or 30mg once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	Placebo once daily for up to 12 months (if recurrence occurred, treated with open-label lansoprazole 30mg daily x 8 weeks, then resumed originally assigned maintenance treatment).	52 patients eligible, 49 enrolled	***Recurrence:*** median < 2 months (pl), > 12 months (l groups) *At 1 month:* 40% (pl), 0% (l15), 7% (l30) *12 months:* 0% (pl), 17% (l15), 7% (l30) (P<0.001 (l groups vs (pl)) ***Symptoms:*** Of those asymptomatic at baseline 0%? (pl), 100% (l15), 59% (l30) no symptoms at 12 months *Antacid use:* (tabs/day) Median 0.38 (pl), 0.02 (l15), 0.01 (l30)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Kovacs 1999 USA Multicenter Maintenance Study	39 patients reported 1 or > adverse events reported (13 (pl), 14 (l15), 12 (l30), NS. The most common adverse events that were possibly or probably related to study drug were diarrhea (0%(pl), 0% (l15), 13.3% (l30) and constipation (12.5% (pl), 5.3% (l15), 0% (l30)). 7 patients withdrew due to adverse events (4 (pl), 1 (l15), 2 (l30)). No clinically significant lab changes, vital signs, or ECG seen. Serum Gastrin Significantly (P</= 0.003) greater changes from baseline seen in (l) groups vs (pl) 4 (l15), and 15 (l30) fasting levels > 200 pg/ml during study Increases occurred within 1 month of starting (l) and returned to baseline within 1 month of stopping drug Gastric Mucosal Biopsy Increases in Grimelius positive cell density in the corpus (from baseline) 121 cells/mm2 (pl), 146 cells/mm2 (l15), 176 cells/mm2 (l30) (P=0.001 vs (pl)). No other cell changes seen.	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Cooperative Study 1990 UK Multicenter	Mean age: 57 (o), 61 (ran) 54% male 65% smokers 74% alcohol users	Omeprazole 40mg once daily x 2 to 8 weeks	Ranitidine 150mg twice daily x 2 to 8 weeks	46 enrolled (21 (o), 25 (ran)) 27 enrolled in followup study (12 (o), 15 (ran))	***Healing (PP):*** *4 weeks:* 81% (o), 58% (ran)(NS) *8 weeks:* 93% (o), 87% (ran)(NS) ***Pain free (baseline not reported)*** *2 weeks:* 53% (o), 42% (ran)(NS) *4 weeks:* 73% (o), 38% (ran)(NS) *8 weeks:* 50% (o), 44% (ran) (NS) Nighttime pain at 2 weeks (o) < (r), data not reported, (P<0.03) Daytime pain (o) < (ran)in weeks 3 and 4 by diary card, data not reported, (P<0.03) ***Recurrence:*** *6 months:* 42% (o), 67% (ran)(NS)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Cooperative Study 1990 UK Multicenter	1 death judged to be unrelated to study. 9 patients reported adverse events (5 (o), 4 (ran)). The most common were GI symptoms.	Poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	Mean age 55 (o20), 57 (o40), 58 (ran) % smokers 61% (o20), 60% (o40), 56% (ran) % alcohol users 60% (o20), 57% (o40), 50% (ran) NSAID use 11% (o20), 12% (o40), 11% (ran)	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	602 enrolled (436 gastric ulcers, 166 prepyloric ulcers)	***Healing:*** ***Gastric + prepyloric (PP analysis):*** *4 weeks:* 69% (o20), 80% (o40), 59% (ran) *8 weeks:* 89% (o20), 96% (o40), 85% (ran) ***ITT analysis reported as 'similar'*** *Prepyloric only:* (PP analysis) *2 weeks:* 33% (o20), 42% (o40), 27% (ran)(NS) ***NSAID users (PP analysis)*** *4 weeks:* 61% (o20), 81% (o40), 32% (ran) *8 weeks:* 82% (o20), 95% (o40), 53% (ran) ***Symptoms:*** *None at 2 weeks:* 62% (o20), 69% (o20), 55% (ran)((o40) vs (ran)P= 0.02) *Followup Study:* *Healing maintained at 6 months:* 59% (O40 and O20), 53% (ran) (P=0.03 (o40) vs (ran)) *No symptoms 'during followup':* 52% (O40 and O20), 48% (ran)(P=0.02 (o40) vs (ran))

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Walan 1989 13 countries (primarily European plus Australia and Canada), 45 centers	106 patients reported adverse events (34 (o20), 32 (o40), 40 (ran)). The most common were GI symptoms, similar in all groups. Numbers withdrawn or lost to follow up: 21 (o20), 19 (o40), 22 (ran) 3 patients died during study (all on (o40)) of causes shown to be unrelated to study drug, 2 patients withdrawn due to abnormal labs also shown to be unrelated to study drugs ((1 (o40), 1 (ran)).	Good/Fair Comment: Patients enrolled in followup study not well described, attrition not described.

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Rossini 1989 Italy Single center	Data not reported – stated to be similar	Omeprazole 20mg or 40mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	18 enrolled (number per group not stated)	***Healing*** *4 weeks:* 78% (o), 50% (ran) *8 weeks:* 100% (o), 87% (ran) Pain disappeared almost completely in both groups by two weeks
Classen 1985 Germany Multicenter	Data not reported – stated to be similar	Omeprazole 20mg once daily x 4 to 6 weeks	Ranitidine 150mg twice daily x 4 to 6 weeks	184 enrolled	***Healing (PP analysis only):*** *2 weeks:* 43% (o), 45% (ran) (NS) *4 weeks:* 81% (o), 80% (ran) (NS) *6 weeks:* 95% (o), 90% (ran) NS ***Symptoms:*** "equally good with either drug"

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Rossini 1989 Italy Single center	None reported in either group	Fair/poor
Classen 1985 Germany Multicenter	Not reported	Poor Comment: This appears to be a report in English of two trials previously published in German, therefore the quality of the trials may be higher than appears from this paper.

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Bardhan 1994 United Kingdom and Sweden Multicenter	Mean ages 60 (l60), 59(l30), 57(r) 57% males 65% UK 35% Sweden 52% smokers 60% alcohol use 11% NSAID use	Lansoprazole 30mg or 60mg once a day x 4 to 8 weeks	Ranitidine 300mg every night x 4 to 8 weeks	250 enrolled	***Healing rates:*** *4 weeks:* *of those with endoscopy:* 78% (120), 84% (160), 61% (ran) ***ITT:*** 72% (l30), 73% (l60), 52% (ran) ***PP:*** 80% (l30), 78% (l60) 57% (ran) *8 weeks:* *of those w/endoscopy:* 99% (l30), 97% (l60), 91% (ran) ***ITT:*** not reported ***PP:*** 98% (l30), 100% (l60), 90% (ran) *Symptoms:* proportion symptom free at 4 weeks: *Pain:* 75% (l30), 72% (l60), 65% (ran) *Nausea:* 88% (l30), 89% (l60), 76% (ran) *Vomiting:* 100% (l30), 87% (l60), 89% (ran)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Bardhan 1994 United Kingdom and Sweden Multicenter	69 patients experienced 91 adverse events, 26% (l30), 27% (l60), 30% (ran). The most common thought to be possibly or probably related to study drug were diarrhea and headache.	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Michel 1994 France Multicenter	Mean age 52 (l), 56 (ran) 69% male 38% smokers 52% alcohol users 42% NSAID users mean ulcer size 12mm (l), 11mm (ran)	Lansoprazole 30mg once daily x 4 to 8 weeks	Ranitidine 150mg twice daily x 4 to 8 weeks	158 enrolled	***Healing:*** *4 weeks:* ITT 68% (l), 56% (ran)NS PP: 80% (l), 62% (ran)(p<0.05) *8 weeks:* ITT 81% (l), 76% (ran)(NS) PP: 100% (l), 87% (ran)(P<0.05) *No epigastric pain:* (at baseline 26% (l), 22% (ran)) *4 weeks:* 73% (l), 72% (ran)(NS) *8 weeks:* 95% (l), 92% (ran)(NS)
Capurso 1995 Italy Multicenter	Data not reported – stated to be similar	Lansoprazole 30mg once daily x 2 to 8 weeks	Ranitidine 300mg once daily x 1 x 2 to 8 weeks	74 enrolled (34 (l), 35 (o), 5 not reported)	***Healing rates:*** *2 weeks:* 41.4% (l), 26.5% (ran) *4 weeks:* 79.3% (l), 61.8% (ran) *8 weeks:* 96.6% (l), 94.1% (ran) ***Pain:*** at 2 weeks no significant difference between groups 64% pain free

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Michel 1994 France Multicenter	38 patients reported adverse events. 4 withdrawn due to serious adverse events all (r)group). 3 of these were deaths (1 acute heart failure, 2 acute respiratory distress), the forth withdrawn due to femur fracture resulting from hypotension. GI symptoms (diarrhea, constipation were the most common adverse effects reported in both groups).	Fair Comment: Numbers of subjects in PP analysis do not add up. Table 2 shows 3 patients withdrawn due to adverse events, but text reports 4. Table 2 reports 16 lost from (l) (79 - 16 = 63) but only 62 included in PP analysis. Likewise, number analyzed at 4 weeks on (ran)reported as 68, but 12 reported lost (79 - 12 = 67)
Capurso 1995 Italy Multicenter	8 adverse effects reported: 3 (ran), 3 (l), and 2 (o) No biochemistry abnormalities, no significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Hotz 1995 Germany Multicenter (28)	Median age 55 (p), 57 (r) 60% male 45% smokers 9.7% everyday alcohol users mean ulcer diameter 10.9 (p), 11.2 (r)	Pantoprazole 40mg once daily x 2, 4 or 8 weeks depending on healing. (2:1 randomization p:r)	Ranitidine 300mg every night x 2, 4 or 8 weeks depending on healing	248 enrolled.	***Healing:*** *2 weeks:* ITT: 33% (p), 17% (ran) (P<0.01) PP: 37% (p), 19% (ran) (P<0.01) *4 weeks:* ITT 77% (p), 52% (ran) (P<0.001) PP: 87% (p), 57% (ran) (P<0.001) *8 weeks:* ITT 86% (p), 72% (ran) (P<0.01) PP: 97% (p), 80% (ran) (P<0.001) No pain:(13% (p), 8% (ran) at baseline) (PP) *2 weeks: 7* 2% (p), 68% (ran) (NS) Based on diary card, no difference between groups in time to becoming pain free Other GI symptoms also improved in both groups
Tsuji 1995	Mean age 64 81% male 50% H. pylori positive	Lansoprazole 30mg once x 4 to 8 weeks	Famotidine 40mg x 16 4 to 8 weeks		***Healing:*** *4 weeks:* 71% (l), 29% (f) *8 weeks:* 83% (l), 57% (f) Symptoms not reported

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Hotz 1995 Germany Multicenter (28)	26 patients reported adverse events (15 (p), 11 (ran). The most frequent was diarrhea (3) and headache (2) on (pl), and sleep disorder (2) on (ran). 4 (p) and 3 (ran) withdrew due to adverse events, 1 (r) patient had elevated serum transaminase levels, otherwise lab values were normal. Median change in serum gastrin levels at 8 weeks: 30pg.ml (pl), 12pg/ml (ran), median values at all time points were higher in the (p) group.	Good/Fair
Tsuji 1995	None	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Okai 1995	Mean age 54 (range 36-86) (l30) 59 (range 39-80) (f) 75% male 71% smokers 38% ulcer size >15mm	Lansoprazole 30mg once daily x 2 to 8 weeks	Famotidine 40mg once daily x 2 to 8 weeks	24	***Healing:*** *4 weeks:* 50% (l), 0% (f) *8 weeks:* 54.5% (l), 18.2% (f) (from Kovacs, 1998) **Symptoms:** Pain free at week 1:80% (l), 60% f) (NS)
Bate 1989 UK and Republic of Ireland Multicenter	Mean age 57 47% male 59% smokers 3% ulcer size >10mm	Omeprazole 20mg once daily x 4 to 8 weeks	Cimetidine 800mg x 4 to 8 weeks	197 enrolled (105 (o), 92 (c))	***Healing (ITT):*** *4 weeks:* 73% (o), 58% (c) (P<0.05) *8 weeks:* 84% (o), 75 (c) (NS) ***Symptoms*** ***Pain free*** *4 weeks:* 81% (o), 60% (c) (P<0.01) *8 weeks:* "difference no longer significant" *4 weeks* (but not at 8 weeks) Daytime pain and heartburn less in (o) (P<0.05) data not reported. No difference in nocturnal pain or nausea Diary cards: 2 weeks: (o) better than (c) for daytime pain (P<0.01), nighttime pain (P<0.05) and antacid use (P<0.0001)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Okai 1995	None	Fair
Bate 1989 UK and Republic of Ireland Multicenter	32 patients reported adverse events (19% (o), 15% (c)). 2 were serious, but considered unrelated to study. 7 (4 (o),3 (c)) withdrew due to adverse events (2 in (o) were due to lack of efficacy). The most common adverse events were GI and CNS system related in both groups	Fair/Poor

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Lauritsen 1988 Denmark Multicenter	Mean age 57 45% male 74% smokers mean ulcer 9.7, 10.7 mm	Omeprazole 30mg once daily x 6 weeks	Cimetidine 1000mg x 6 weeks	179 eligible, 176 enrolled (3 chose not to participate)	***Healing:*** *2 weeks:* ITT: 54% (o), 39% (c) PP: 55% (o), 42% (c) *4 weeks:* ITT 81% (o), 73% (c) PP: 85% (o), 77% (c) *6 weeks:* ITT 86% (o), 78% (c) PP: 89% (o), 86% (c) ***No pain:*** (24% (o), 14% (c) at baseline) *2 weeks:* 48% (o), 29% (c) *4 weeks:* 57% (o), 47% (c) *6 weeks:* 62% (o), 58% (c) Number of hours of pain at 6 weeks: 7.5 (o), 10.5 (c)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Lauritsen 1988 Denmark Multicenter	12 reports of adverse events. (o): one each: headache, fatigue, transient diarrhea, gastroenteritis, muscle pain. (c): one each of headache, dry mouth, 2 each of dizziness, impotence	Fair

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Age, Gender, Race, Other Population Character-istics	Interventions	Control	Number Screened/ Eligible/ Enrolled	Outcomes Reported (Results)
Danish Omeprazole Study Group 1989	Median age 60 (range 52-71) (o) 61 (range 50-72) (c) 48% male 69% smokers	Omeprazole 30mg x 2 to 6 weeks	Cimetidine 1000mg x 2 to 6 weeks	161 enrolled 146 evaluated	***Healing:*** *2 weeks:* 41% (o), 41% (c) *4 weeks:* 77% (o), 58% (c) *6 weeks:* 88% (o), 82% (c) ***Symptoms*** ***Mean days with pain:*** *2 weeks:* 5 (o), 5.5 (c) *4 weeks:* 4.3 (o), 3.8(c) *6 weeks:* 2.4 (o), 2.4(c) (all NS) 6-month followup (untreated) no difference in relapse rate (Endo):17% (o), 19% (c)
Aoyama 1995	Data not reported – stated to be similar	Lansoprazole 30mg x 2 to 8 weeks	Cimetidine 800mg x 2 to 8 weeks	107 enrolled 84 evaluated	***Healing:*** *2 weeks: 14% (l), 6% (c)* *4 weeks:71% (l), 47% (c)* *6 weeks:* 94% (l), 75% (c)

Evidence Table 9. Randomized controlled trials of gastric ulcer treatment

Author Year Setting	Number of Adverse Effects	Quality Rating
Danish Omeprazole Study Group 1989	3 withdrawals due to adverse effects in (c) group due to 'other diseases' and urticarial reaction. 19 other adverse events reported. (o) group: allergic edema, itching, diarrhea (2 cases), tremor, polyuria, shoulder pain, and pulmonary edema.. (c) group: itching, diarrhea, constipation (2), dizziness (2), fatigue (2), insomnia, and back pain (2).	Poor
Aoyama 1995	Not reported.	Poor

Evidence Table 10. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Hawkey 1998 International (14 countries including USA) Treatment or prevention	Mean age 58 (range 20 to 85) 38% male 23% smokers 39% H. pylori positive 8% history of bleeding ulcer 41% gastric ulcer 38% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily (duration not clearly stated, assumed to be 8 weeks)	200 mcg of misoprostol four times daily	935 enrolled

Evidence Table 10. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Hawkey 1998 International (14 countries including USA) Treatment or prevention	***Treatment Success at 8 weeks:*** 76% (o20), 75% (o40), 71% (m) (NS) ***ITT analysis:*** 75% (o20), 75% (40), 71% (m) ***GU only:*** 87% (o20), 80% (o40), 73% (m) (P=0.004 (o20) vs (m); 0.14 (o40) vs (m) ***GU and DU:*** 85% (o20), 79% (o40), 74% (m) ***DU only:*** 93% (o20), 89% (o40), 77% (m) ***Erosions only:*** 77% (o20), 79% (o40), 87% (m) ***H. pylori positive:*** 83% (o20), 83% (o40), 69% (m) ***H. pylori negative:*** 73% (o20), 70% (o40), 74% (m) ***Symptoms:*** Reduction in mod-severe dyspepsia at 4 weeks 34% (o20), 39% (o40), 27% (m) Proportion of days with abdominal pain 43% (o20), 43% (o40), 50% (m) Proportion of days with heartburn 16% (o20), 14% (o40), 29% (m) QOL (completed by 68% (o20), 66% (o40), 62% (m)) Gastrointestinal Symptom Rating Scale at 8 weeks change in total score-0.47 (o20), -0.36 (o40), -0.20 (m) change in reflux score: -0.82 (o20), -0.75 (o40), -0.33(m) change in diarrhea score: -0.24 (o20), -0.06 (o40), +0.22 (m) Nottingham Health Profile change in sleep score: -3.1 (o20), -8.6 (m), (o40 not reported)	470 patients reported adverse events (48% (o20), 46% (o40), 59% (m) Most common reported was diarrhea (4.5% (o20), 5.3% (o40), 11.4 % (m)	Fair Comment: Patients without healing at eight weeks received open treatment with 40 mg of omeprazole daily for a further four to eight weeks.

Evidence Table 10. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Yeomans 1998 International (15 countries) Treatment or prevention	Mean age 57 33% male 10% history of bleeding ulcer 39% gastric ulcer 46% H. pylori positive 44% rheumatoid arthritis	20 mg or 40 mg of omeprazole once daily for four or eight weeks	150 mg of ranitidine twice daily for four or eight weeks	541 enrolled

Evidence Table 10. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Yeomans 1998 International (15 countries) Treatment or prevention	***Treatment Success at 8 weeks:*** 80% (o20), 79% (o40), 63% (ran) ***GU only:*** 84% (o20), 87% (o40), 64% (ran) ***DU only:*** 92% (o20), 88% (o40), 81 (ran) ***Erosions only:*** 89% (o20), 86% (o40), 77% (ran) ***H. pylori positive****:* 83% (o20), 82% (o40), 72% (m) *H. pylori negative:* 75% (o20), 71% (o40), 55% (m) ***Symptoms:*** *reduction of 'moderate to severe' category at 4 weeks:* 46% (o20), 38% (ran) (o40 not reported)	190 moderate to severe adverse events were reported (30% (o20), 38% (o40), 40% (r) GI effects (diarrhea, nausea, constipation, and flatulence) were the most common reported Discontinuation of therapy due to either and adverse event or lack of efficacy (not reported separately): 2.8% (o20), 3.2% (o40), 8.5% (ran)	Fair

Evidence Table 10. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Age, Gender, Race, Other population characteristics	Interventions	Control	Number Screened/ Eligible/ Enrolled
Agrawal 2000 USA and Canada, multicenter healing only	Mean age 60 35% male 90% white 21% smokers 31% alcohol users 29% H. pylori positive	Lansoprazole, 15 or 30 mg once daily for 8 weeks	Ranitidine 150 mg twice daily for 8 weeks	Endoscopy was performed on 669 patients, 353 met inclusion criteria.

Evidence Table 10. Randomized controlled trials of NSAID-induced ulcer treatment

Author Year Setting Purpose	Outcomes reported (results)	Number of adverse effects	Quality rating
Agrawal 2000 USA and Canada, multicenter healing only	***Healing: Gastric Ulcer*** *4 weeks:* 47% (l15), 57% (l30), 30% (ran) *8 weeks:* 69% (l15), 73% (l30), 53% (ran) ***GU and DU 8 weeks****:* 93% (l15), 81% (l30), 88% (ran) ***GU or erosions 8 weeks:*** 85% (l15), 100% (l30), 86% (l30) ***H. pylori positive: 8 weeks:*** 67% (l15), 82% (l30), 60% (ran) ***H. pylori negative****:* 70% (l15), 69% (l30), 51% (ran) ***Symptoms:*** *4 weeks:* no daytime pain 66% (l15), 64% (l30), 60% (ran) no nighttime pain 67% (l15), 69% (l30), 64% (ran) % days antacids used 67% (l15), 70% (l30), 62% (ran) *8 weeks:* no daytime pain 70% (l15), 66% (l30), 63% (ran) no nighttime pain 71% (l15), 71% (l30), 69% (ran) % days antacids used 69% (l15), 71% (l30), 64% (ran)	33 patients reported an adverse event, 15 patients stopped taking study medication because of adverse events (5 (l15), 4 (l30), 6 (ran)). The most commonly reported treatment-related event was diarrhea.	Good/Fair

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Lai et al. 2002	123 patients, double blind, ITT. Hong Kong, mean age 70 (range 18-80), female 28%, race NR. 245 screened, 171 eligible by H. pylori, 127 treated, 4 H. pylori uneradicated.	History of cerebrovascular accident (52%) or heart disease (48%) - endo revealed gastric (74%), duodenal (21%) or gastroduodenal (5%) ulcer.	- History of stroke or ischemic heart disease requiring long-term aspirin therapy; - Ulcer developed after at least one month low-dose aspirin therapy; - H. pylori infection; - Ulcer and H. pylori successfully eradicated during initial healing phase of study; - No esophagitis, history of ulcer surgery, comcomitant treatment with NSAIDs, corticosteroids or anticoagulant agents, active cancer, or allergic to study drugs.	30 mg (l) + 100 mg aspirin bid for median 12 months	Matching placebo + 100 mg aspirin bid
Graham, 2002	US and Canada Multicenter Mean age 60 65% female 90% white, 6% black, 4% other.	No H. pylori; reason for long-term NSAID use not reported, previous GI disease: 59% reflux esophagitis, 50% duodenal ulcer, 99% gastric ulcer.	Age 18 or older, h/o endoscopically-documented gastric ulcer with or without coexisting duodenal ulcer or GI bleeding, and treatment with stable, full therapeutic doses of an NSAID (except nabumetone or aspirin >1300 mg/day) for at least the previous month.	lansoprazole 15 or 30 mg for 12 weeks	misoprostol 200 mcg qid for 12 weeks

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Lai et al. 2002	Antacid permitted, advised to avoid other NSAIDs if possible	Primary endpoint: recurrence of ulcer complications (bleeding, outlet obstruction, perforation). Secondary endpoint: recurrence of ulcer.	Clinical Bleeding: (l) = 0, (pl) = 8 (p<.01) Ulcer recurrence: (l) = 1, (pl) = 9 (p=.008) H. pylori recurrence: (l) = 0, (pl) = 4 (p<.05)	Death: (l) = 1, (pl) = 0 Other adverse effects NR.	
Graham, 2002	40% ibuprofen, 35% naproxen, 32% diclofenac, 22% aspirin or aspirin combinations, 17% piroxicam, 34% other NSAIDS	Occurrence of gastric ulcer (definition of gastric ulcer not specified), included analysis with withdrawals considered treatment failures (having a gastric ulcer).	*Treatment success:* *Free of gastric ulcer by week 12 (per protocol):* *(pl)* :51% (m): 93% (l15): 80% (l30): 82% *Treatment success:* *Results when withdrawals classified as treatment failures:* *(pl)* :34% (m): 67% (l15): 69% (l30): 68%	Withdrawals due to adverse events: (pl) 6.7%, (m) 10.4%, (l15) 2.9%, (l30) 7.5%; Higher percentage of treatment related adverse events in misoprostol group (31% (m), 10% (pl), 7% (l15), 16% in (l30); most common diarrhea. One upper GI tract hemorrhage (l15).	Fair: randomization and allocation method not reported.

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Bianchi Porro 2000	Italy Single center Mean age 59.9 (range 22-80) 83% female ethnicity not given	63% rheumatoid arthritis 38% osteoarthritis.	Over age 18, with rheumatoid arthritis or osteoarthritis, treated with effective and constant doses of NSAIDs (diclofenac, ketoprofen, indomethacin) for at least 8 weeks prior to start of study. Lanza endoscopic grade 0,1, or 2.	pantoprazole 40 mg	placebo
Labenz et al. 2002	2264 patients screened, 832 randomized, 660 analyzed - in 3 countries in central Europe, double blind, not ITT. Mean age: 55 Male: 38%	Systemic inflammatory disease (24%), noninflammatory disease (73%), mild dyspepsia (42%), Lanza score "0" on study entry (stomach 68%; duodenum 89%).	Age >18 years with inflammatory disease of musculoskeletal system requiring NSAID treatment >5 weeks, and H. pylori positive. Excluded for ulcer or history of ulcer, clotting disorders, prior regular use of NSAIDS (except aspirin <100 mg/day), antibiotics, PPIs, misoprostol, or bismuth salts within 4 weeks; regular use of H2R antagonists, prokinetics or sucralfate; systemic corticosteroids, known or suspected intolerance to study drug, severe concomitant diseases; previous gastric surgery; pregnancy or nursing; and dyspepsia therapy.	OAC-O = omeprazole 40 mg + amoxicillin 2 g +clarithro-mycin 1000 mg for 1 week, then 20 mg ome for 4 weeks. O-O = 20 mg ome for 5 weeks.	OAC-P = OAC for 1 week, then placebo for 4 weeks. P-P = placebo for 5 weeks.

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Bianchi Porro 2000	37% diclofenac, 34% ketoprofen, 35% indomethacin.	Occurrence of gastric or duodenal ulcers (grade 4, Lanza classification) after 4 and 12 weeks, or patients who discontinued the study due to lack of efficacy leading to discontinuation of the study medication, an adverse event which was assessed by the study investigator as possibly or definitely related to the study medication.	*Ulcer status assigned (treatment failure):* (p)*:* 13 with endoscopically-proven peptic ulcer, 3 due to lack of efficacy, 2 adverse events (pl)*:* 9 with endoscopically-proven peptic ulcer (1 with both gastric and duodenal ulcer), 1 lack of efficacy , 2 adverse events. *Endoscopically proven duodenal and/or gastric ulcers:* (p)*:* 13 (pl)*:* 9	4.3% (p) (m) unrelated to treatment, vomiting possibly related, diarrhea definitely related), 5.9% (pl) (diarrhea possibly related, asthenia definitely related), all withdrew for adverse events.	Fair/Good: concealment of allocation not reported
Labenz et al. 2002	NSAID treatment: diclofenac 100-150 mg, and could add tramadol 200 mg. Dyspeptic therapy with an antacid.	Primary endpoint: endoscopically proved peptic ulcer. Secondary endpoints: dyspeptic complaints, signs of gastrointestinal bleeding.	OAC-O vs. O-O vs. OAC-P vs. P-P Developed peptic ulcers - Total: 2/173 (1.2%) vs. 0/155 vs. 2/161 (1.2%) vs. 10/171 (5.8%) - Duodenal: 0/173 vs. 0/155 vs. 2/161(1.2%) vs. 7/171(4.1%) - Gastric: 2/173 (1.2%)vs. 0/155 vs. 0/161 vs. 3/171 (1.8%) (Bonferroni p-value significant for all ome groups vs. pla) Dyspepsia developed requiring therapy: 10.4% vs. 12.3% vs. 10.6% vs. 19.9% (All treatment groups significantly different from pla only group - p-value NR) Negative H. pylori status: 85.3% vs. 21.9% vs. 81.3% vs. 11.8%	201 of 660 patients reported 302 adverse events (no details reported): OAC-O 31% O-O 16% OAC-P 26% P-P 26% Diarrhea more frequent in antibiotic groups: OAC-O 8.8% O-O 3.0% OAC-P 8.4% P-P 3.3%	

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Hawkey, 1998	93 centers in 14 countries mean age 58 (range 20-85) 64% female ethnicity not given	38% rheumatoid arthritis, 47% osteoarthritis, 13% other, 2% combinations.39% gastric ulcer with or without erosions, 20% duodenal ulcer with or without erosions, 4% gastric and duodenal ulcer with or without erosions, 36% erosions only.	Patients who successfully healed during treatment phase of study. Age 18 to 85, with any condition requiring continuous treatment with oral or rectal NSAIDS above a predetermined minimal dose (no maximal dose). Minimal (and mean) daily oral doses: 50 mg (129 mg) diclofenac, 100 mg (137 mg) ketoprofen, 500 mg (844 mg) naproxen. By endoscopy, any or all of the following: ulcer, defined as a mucosal break at least 3 mm in diameter with definite depth in the stomach, duodenum, or both, more than 10 gastric erosions, and more than 10 duodenal erosions.	omeprazole 20 mg	misoprostol 200 mcg bid or placebo
Yeomans 1998	73 centers in 15 countries; mean age 56 (range 20-80); 69% female; ethnicity not given	44% rheumatoid arthritis, 32% osteoarthritis, 6% psoriatic arthritis, 5% anklyosing spondylitis	Age 18 to 85, with any condition requiring continuous therapy with NSAIDs above specified therapeutic doses (no maximal dose),and not more than 10 mg prednisolone or equivalent per day. By endoscopy, any or all of the following: ulcers 3 mm of more in diameter, more than 10 erosions in stomach, more than 10 erosions in the duodenum. (Lanza scale)	omeprazole 20 mg	ranitidine 150 mg bid

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Hawkey, 1998	At baseline (all patients):most common diclofenac (23%), naproxen (22%), ketoprofen (16%).	Development of any of the following: an ulcer, more than 10 gastric erosions, more than 10 duodenal erosions, at least moderate symptoms of dyspepsia, or adverse events resulting in the discontinuation of treatment.	*In remission at 6 months:* **(**o20):61%(m): 48%(pl): 27%p = 0.001 for (o20) vs (m) *Gastric ulcers at relapse:(* o20):13%(m):10%(pl):32% *Duodenal ulcers at relapse:(* o20): 3%(m):10%(pl):12%	Withdrawals due to adverse events: (o20): 3.9%, (m): 7.7%, (pl): 1.9%; most common diarrhea (7.6% (o20), 8.4% (m), 4.5% (pl), abdominal pain (5.1% (o20), 4.7% (m), 5.8% (pl). One perforated duodenal ulcer after 31 days of (pl).	Fair: randomization and allocation method not reported, not intention-to-treat.
Yeomans 1998	Not reported for maintenance phase. Most common at baseline (including healing phase) diclofenac (29%), indomethacin (23%), naproxen (16%)	Remission defined as absence of a relapse of lesions, dyspeptic symptoms, and adverse events leading to the discontinuation of treatment.	*In remission at 6 months:* **(**o20): 72%(r): 59%p = 0.004	Any adverse event: (o20): 64%, (r): 58%; withdrawals due to adverse events: 6.1% (o20), 3.2% (ran). Most common arthritis, rheumatoid arthritis, vomiting (2.9% (o20), 2.3% (ran)), abdominal pain (2.9% (o)o, 1.9% (ran)), diarrhea (3.3% (o20), 1.4% (ran)). One bleeding duodenal ulcer after 10 days of (o20).	Fair: randomization and allocation method not reported, not intention-to-treat.

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Population setting	Diagnosis	Eligibility criteria	Interventions	Control
Stupnicki et al. 2003	515 patients, multiple European countries Multicenter, double-blind 73% female median age 64 (range 31-93) ethnicity not reported	55% erosions at entrance exam; 45% 1-5 erosions; 32% H. pylori positive; 41% osteoarthritis, 30% rheumatoid arthritis, 2% spondylitis, 7% spondylosis, 19% multiple disease.	Outpatients aged 55 or older receiving or planned to receive continuous NSAID therapy for rheumatoid arthritis, osteoarthritis, arthrosis, spondylosis, or spondylitis, and who experienced gastrointestinal symptoms of at most moderate intensity. No signs of reflux esophagitis (endoscopically-proven). At least one of the following criteria: history of endoscopically proven peptic ulcer (including bleeding and/or perforation) within the last 5 years, or history of repeated gastrointestinal symptoms within the last year, or intake of more than one NSAID (the second NSAID could be dosed below the minimal dose), or regular intake of corticosteroids as concomitant medication, or regular intake of anticoagulants as concomitant medication, or NSAID treatment since maximally 4 weeks, or change of the NSAID drug substance since maximally 4 weeks.	pantoprazole 20 mg for 6 months	misoprostol 400 mcg for 6 months

Evidence Table 11. Randomized controlled trials of PPIs for prevention of NSAID-induced ulcer

Author Year	Other Medications	Definition of Treatment Failure/Success	Outcomes Reported (Results)	Adverse Effects	Quality Rating
Stupnicki et al. 2003	17% more than one NSAID, 17% corticosteroids, 2% anticoagulants	Therapeutic failure: more than 10 erosions/petechiae in the stomach/duodenum, peptic ulcer, reflux esophagitis, discontinuation of study due to an adverse event assessed as "likely" or "definitely" related to the study medication.; discontinuation of study due to severe gastrointestinal symptoms Endoscopic failure: more than 10 erosions/petechiae in the stomach/duodenum, peptic ulcer, reflux esophagitis Symptomatic failure: severe gastrointestinal symptoms	*In remission at 3 months:* 76% pantoprazole vs 63% misoprostol In remission at 6 months: 67% pantoprazole vs 52% misoprostol *Remission rates for therapeutic failure (pantoprazole vs misoprostol)* 3 months: 93% vs 79% (p<0.001) 6 months: 89% vs 70% (p<0.001) *Remission rates for endoscopic failure (pantoprazole vs misoprostol)* 3 months: 98% vs 95% (NS) 6 months: 95% vs 86% (p=0.005) *Remission rates for symptomatic failure (pantoprazole vs misoprostol)* 3 months: 99% vs 92% (p=0.005) 6 months: 99% vs 92% (p=0.002)	Withdrawals due to adverse events: 5% pantoprazole vs 13% misoprostol (events assessed by investigator as likely or definitely related to study drug) 3 deaths in pantoprazole group; all assessed as not related to study drug. serious adverse events: 18 pantoprazole vs 16 misoprostol patients serious adverse events classified as at least 'likely' related to study drug: 0 pantoprazole vs 2 misoprostol (hypertensive crisis and diarrhea)	Fair: Allocation concealment method not reported, baseline characteristics given for ITT population only.

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Johnson et al. 2002 UK & Ireland Multicenter Crossover	Chronic PPI treatment for benign ulcers or GERD	omeprazole 20 mg/day	rabeprazole 20 mg/day	240	30/240 (12.5%)
Beker 1995 European Multicenter	Duodenal ulcer	pantoprazole 40mg	omeprazole 20mg	270 enrolled (135 each group)	0.74% (p)2.9% (o)
Capruso 1995 Italy Multicenter	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	107 enrolled, (52 (l), 55(r))	Not reported
Chang 1995 Taiwan Single center	Duodenal ulcer	lansoprazole 30mg once a day x 4 weeks	omeprazole 20mg a day x 4 weeks	111 enrolled (57 (l), 54 (o)	Not stated in abstract

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Johnson et al. 2002 UK & Ireland Multicenter Crossover	(o) = 115 (51%) reported 114 mild, 117 moderate, and 30 serious treatment-emergent AEs. (r) = 120 (52.6%) reported 97 mild, 118 moderate, and 28 severe treatment-emergent AEs. No significant differences in AEs between groups. No difference in general preference for (o) or (r). - More patients prefer (r) for "absence of side effects" (p=.047), among those with any preference (46%). - More patients prefer (r) for "unexpected positive side effects" (p=.019), among those with any preference (28%). - More patients prefer tablet form of (r) as "easy to swallow" (p=.0001), among those with any preference (52%). - More patients prefer capsule form of (o) as "easy to pick up and hold" (p=.0003), among those with any preference (47%).
Beker 1995 European Multicenter	21 patients reported adverse events (10, 7% (p), 11, 8% (o)), with a total of 23 events reported. Diarrhea was the most common adverse event reported. 5 were considered serious (1 (p), GI hemorrhage and 4 (o), angina pectoris, hypertension, vertigo and abdominal pain. These patients were withdrawn from study. Serum gastrin levels rose in both groups at both 2 and 4 weeks, the change was statistically significant within but not between groups.
Capruso 1995 Italy Multicenter	8 adverse effects reported: 3 (r), 3 (l), and 2 (o). No significant difference between therapies for changes in gastrin levels or changes in endocrine cells from biopsies
Chang 1995 Taiwan Single center	Hypergastrinemia with both agents. A few occurrences of reversible skin rash and constipation.

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Chang 1995 Taiwan Single-center	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	83 enrolled (42 (l), 41 (o))	None reported
Dekkers 1999 European Multicenter	Duodenal ulcer	rabeprazole 20mg	omeprazole 20mg	205 enrolled (102 (r), 103 (o))	1.9% (o) 0% (r)
Dobrilla 1999 Italy Multicenter	Duodenal ulcer	lansoprazole 30mg, then those with healed ulcer randomized to 15 or 30mg lansoprazole x 12 months	omeprazole 40mg, then those with healed ulcer switched to omeprazole 20mg x 12 months	251 eligible (167 (l), 84 (o)) Maintenance phase: 243 enrolled (164 (l), 79(o))	Treatment:2.3% (o), 9% (l)Maintenance:4% (l15), 2.8% (l30), 1.4% (o)
Ekstrom 1995 Sweden Multicenter	Duodenal ulcer	lansoprazole 30mg	omeprazole 20mg	279 enrolled (143 (l), 136 (o))	Not reported
Fanti 2001 Italy Single center	Duodenal ulcer and H. pylori	lansoprazole 30mg once a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	omeprazole 20mg a day x 4 weeks Plus clarithromycin 500 and tinidazole 1gm x 7 days	43 enrolled (22 (l) and 21 (o))	None
Kovacs 1999 USA Multicenter	Duodenal ulcer maintenance	lansoprazole 15 or 30mg once daily for up to 12 months	placebo once daily for up to 12 months	56 enrolled19 (pl),18 (l15), 19 (l30)	21.5%(pl)17% (l15)5.3% (l30)

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Chang 1995 Taiwan Single-center	Serum PGA was elevated in both groups (NS), and had returned to baseline at 8 weeks. In both groups, the elevation in PGA was significantly higher in those found to have H. pylori eradication
Dekkers 1999 European Multicenter	43 patients reported at least one adverse event. (21 (r), 22 (o)). The most common was headache. 2 (o) withdrew due to adverse events (evaluated as unrelated to study)The mean elevations in serum gastrin levels at 4 weeks were 39.8 pg/ml (r) and 18.9 pg/ml (o).
Dobrilla 1999 Italy Multicenter	16 during phase I (healing): 10 (6%, l), 6 (7.1%, o) 21 during Phase 2 (maintenance): 9 (12.2%, l15), 4 (5.6%, l30), and 8 (11%, o) Most common adverse event was diarrhea. 8 patients withdrew due to adverse events (3 (l15), 2 (l30), 3 (o))Serum gastrin levels were elevated in both groups at 4 weeks (increase of 23.8pg/ml (l30), 35.8pg/ml (o) NS), and continued to be elevated at 6 and 12 months of maintenance therapy. The (l15) had the least and the (l30) had the highest elevation at 6 and 12 months. At 6 months all values were returning to baseline.
Ekstrom 1995 Sweden Multicenter	68 adverse events occurred in 57 patients (23 (l), 34 (o)) (NS). A statistically significant difference was found in the mean change in ALT concentration, but the change was minor (0.05 unit increase (l), 0.03 unit decrease (o).
Fanti 2001 Italy Single center	“Mild and self-limiting” Total number not reported.1 (l) stomatitis and 1 (o) mild diarrhea
Kovacs 1999 USA Multicenter	40 patients reported adverse events (11 (pl), 15 (l15), 14 (l30)). Adverse events possibly or probably related to study drug: 2 (pl), 2 (l15), 6 (l30). None were severe. Serum gastrin levels increased significantly in both (l) groups compared to (pl) (P<0.001). Elevations occurred within 1 month of starting study. 8 patients (3(l15), 5 (l30)) had levels >200pg/ml during study. All returned to baseline within 1 month of stopping study drug.

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Lanza 1997 USA Multicenter	Duodenal ulcer maintenance	lansoprazole 15mg once daily x 12 months or until ulcer recurrence	placebo once daily x 12 months or until ulcer recurrence	186 enrolled 88 (pl), 92 (l))	4.5% (pl) 2.2% (l)
Russo 1997 Italy Multicenter	Duodenal ulcer maintenance	If (l30) during healing trial: Lansoprazole 15 mg or Placebo once daily x 12 months or until recurrence	If (r) during healing trial: Ranitidine or placebo 150mg once daily x 12 months or recurrence	108 enrolled 30 (l30/l15)28 (l30/p), 24 (ran/ran),26 (ran/p)	Not reported
Dekkers 1998 European Multicenter	Gastric ulcer	rabeprazole 20mg	omeprazole 20 mg	227 enrolled	Not reported
Adachi, 2003	GERD	rabeprazole 20 mg	omeprazole 20 mg or lansoprazole 30 mg	85	Not reported
Bardhan, 2001	GERD	pantoprazole 20 mg	omeprazole 20 mg	328	Not reported

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Lanza 1997 USA Multicenter	9 adverse events possibly or probably related to study drug. The most common was diarrhea. No significant differences between groups. Serum gastrin levels were significantly higher in (l) group than (pl), median 92pg.ml vs 52 pg/ml (P0.001). Values reached a plateau after one month of treatment and returned to baseline one month after treatment stopped. Gastric biopsies: significant increase in Gastrin cell density in (l) group compared to (pl) group (707cells/mm2 vs 556 cells.mm2), no other differences found.
Russo 1997 Italy Multicenter	Maintenance: 3% (l/l), 18% (l/pl), 0% (ran/ran). (ran/pl) not reported.
Dekkers 1998 European Multicenter	60 patients reported at least one adverse event. (25 (r), 35 (o)). The most common was headache. No difference by sex, age, race.Slightly elevated creatine phosphokinase at 6 weeks was found in 6 (o) patients. The mean elevations in serum gastrin levels at 6 weeks were 12.7 pg/ml (r) and 10.0 pg/ml (o).
Adachi, 2003	Not reported
Bardhan, 2001	57% of pantoprazole vs 50% omeprazole experienced adverse events. Severe in 10% pantoprazole and 13% omeprazole patients. Most events judged unrelated or unlikely to be related to the study drug. Most common adverse events (pantoprazole vs omeprazole): nausea (8% vs 7%), diarrhea (5% vs 6%), and headache (6% vs 3%).

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Castell 1996 US Multicenter	GERD	lansoprazole 15 mg or 30 mg	omeprazole 20 mg	1070	(o20): 2% (l30): 1.7% (l15): 0.9%
Chen et al 2005	GERD	esomeprazole 40mg	omeprazole 20 mg	48 (25 esomeprazole, 23 omeprazole)	Not reported
Corinaldesi 1995 European Multicenter	GERD	pantoprazole 40 mg	omeprazole 20 mg	241	(p40): 0.8% (o20): 1.7%
Dekkers 1999 European Multicenter	GERD	rabeprazole 20 mg	omeprazole 20 mg	202	(r20): 1% (o20): 0
Delchier 2000 European Multicenter	GERD	rabeprazole 20 mg or ransoprazole 10 mg	omeprazole 20 mg	300	(r10): 5% (r20): 5% (o20): 2%
Dupas 2001 France Multicenter	GERD	pantoprazole 40 mg	lansoprazole 30 mg	461	(p40): 1.3% (l30): 2.5%

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Castell 1996 US Multicenter	Any adverse event:(l15) 44.5%, (l30) 55.7%, (o20) 53.4%. Most commonly reported events headache, diarrhea, nausea. More patients in (ll5) reported nausea (p<0.05). 6 severe events possibly or probably related to medication (4 in (o20) , 1 in (l15), 1 in (l30).
Chen et al 2005	No treatment related serious AEs reported. 7 esomeprazole and 6 omeprazole patients reported non-serious AEs, most commonly constipation (6.3% of all patients) and dry skin (8.3% of all patients.)
Corinaldesi 1995 European Multicenter	Adverse events reported by 15% of patients in (p40), 12% in (o20). Diarrhea, abdominal pain, hyperlipemia and constipation most frequently reported in (p40) , diarrhea most frequently (o20).
Dekkers 1999 European Multicenter	32% (r20) and 28% (o20) reported at least one adverse event. Headache, diarrhea, flatulence most common. Flatulence more common (o20) gr (4% vs 0%). One serious event (r20) (t wave changes).
Delchier 2000 European Multicenter	21% (r20), 26% (r10), and 23% (o20) reported at least one event. Abdominal pain, pharyngitis, bronchitis, headache, diarrhea most common. Four serious events, none related to medication. At week 4, incidences of elevated serum gastrin levels 16% (r20), 27% (r10), 20% (o20) (NS)
Dupas 2001 France Multicenter	Adverse events reported in 28% in p40 group, 17% in l30. Most common headache, diarrhea, elevation of hepatic enzymes, abdominal pain, skin disorders. 11 serious events (5 (p40) 6 (l30)).

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Fennerty, 2005	GERD	esomeprazole 40 mg	lansoprazole 30 mg	1001	5/499 (1%) esomeprazole vs 9/472 (2%) lansoprazole.
Gillessen, 2004	GERD	pantoprazole 40 mg	esomeprazole 40 mg	227	6 patients overall, not reported by group.
Hatlebakk 1993 Norway/ Sweden Multicenter	GERD	lansoprazole 30 mg	omeprazole 20 mg	229	(o20): 0.9%(l30):0
Holtmann, 2002	GERD	rabeprazole 20 mg	omeprazole 20 mg	251	4/125 (3%) rabeprazole vs 2/126 (2%) omeprazole
Howden et al. 2002	GERD	lansoprazole 30 mg	esomeprazole 40 mg	284	2/143 (1.4%) lansoprazole vs 5/141 (3.5%) esomeprazole

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Fennerty, 2005	33.1% esomeprazole vs 36.9% lansoprazole reported an adverse event. Most were mild or moderate. No treatment-related adverse events reported. Most common adverse events (occurring in >2% of patients) were Barrett's esophagus, gastritis, diarrhea, and headache. Most common adverse event leading to study withdrawal was abdominal pain (2 in each group).
Gillessen, 2004	23/113 (20%) pantoprazole vs 20/114 (18%) esomeprazole had an adverse event. None judged definitely related to study medication, 9% pantoprazole, 28% esomeprazole likely related. Two serious adverse events in one patient in pantoprazole group (icterus and malignant hepatic neoplasm (not related to medication). Most frequent adverse event was dizziness (2%).
Hatlebakk 1993 Norway/ Sweden Multicenter	32.8% (l30), 29.2% (o20) reported adverse event, One (o20) withdrawn for severe diarrhea. Headache in 4 pts (o20), none (l30).2 severe events (l30) (1 pharyngitis, 1 nausea, vomiting).
Holtmann, 2002	About 25% of patients in both groups experienced any adverse event. Most frequent were gastrointestinal system in 25 patients (10%) and nervous in 11 patients (4.4%). Seven GI events judged drug-related. Most events mild to moderate; 10 of 90 rated as "severe." No obvious differences in tolerability between treatments (data not reported by group).
Howden et al. 2002	Lansoprazole vs esomeprazole: Incidence of all adverse events 46.2% vs 52.5% Of these, 16.1% vs 19.1% considered "possibly", "probably", or "definitely" treatment-related. Most frequently reported treatment-related effects: diarrhea (5% vs 5%), headache (2% vs 5%), eructation (5% vs 2%), abdominal pain (2% vs 4%), flatulence (1% vs 4%), nausea (2% vs 2%). Most events mild to moderate. Esomeprazole one severe case each of eructation, dizziness, and paresthesia; lansoprazole one severe case each of abdominal pain, diarrhea, eructation, rectal disorder, and somnolence.

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Kahrilas 2000 US Multicenter	GERD	esomeprazole 40 mg or 20 mg	omeprazole 20 mg	1960	(e40): 2% (e20): 2.6% (o20): 2%
Kao, 2003	GERD	esomeprazole 40 mg	omeprazole 20 mg	100	Not reported
Korner et al. 2003	GERD	pantoprazole 40 mg	omeprazole MUPS 40 mg	669	4/337 (1%) pantoprazole, 7/332 (2%) omeprazole MUPS
Labenz 2005 Multinational, Multicenter	GERD	esomeprazole 40 mg	pantoprazole 40 mg	3151	33/1562 (2.1%) esomeprazole vs 29/1589 (1.8%) pantoprazole

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Kahrilas 2000 US Multicenter	Total or per group not reported. Most common: headache 8.6% (e40), 8.7% (e20), 6.9% (o20) abdominal pain 3.7% (e40), 3.7% (e20), 4.2% (o20) diarrhea (4.6% (e40), 4.7% (e20), 3.9% (o20) flatulence (1.8% (e40), 3.5% (e20), 4.0% (o20) gastritis 2.5% (e40), 3.5% (e20), 2.5% (o20) nausea 3.8% (e40), 2.9% (e20), 3.1% (o20). No differences observed according to gender, age, or race. No serious drug-related events reported.
Kao, 2003	Not reported
Korner et al. 2003	Pantoprazole vs omeprazole 6% vs 7%, mostly mild or moderate. 2.1% vs 1.2% severe. Most frequently reported adverse event headache for pantoprazole (1%), diarrhea for omeprazole (2%).
Labenz 2005 Multinational, Multicenter	Serious adverse events: 1.5% esomeprazole vs 1.3% pantoprazole. Most commonly reported in esomeprazole group: nausea (6 patients), dizziness (5 patients); In pantoprazole group: headache (5 patients), diarrhea (4 patients).

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Mee 1996 UK and Ireland Multicenter	GERD	lansoprazole 30 mg	omeprazole 20 mg	604	Not reported
Mulder 1996 Netherlands Multicenter	GERD	lansoprazole 30 mg	omeprazole 40 mg	211	None
Richter 2001 US Multicenter	GERD	esomeprazole 40 mg	omeprazole 20 mg	2425	1% in each group
Richter 2001b	GERD	lansoprazole 30 mg	omeprazole 20 mg	3410	40/1754 (2%) lansoprazole 33/1756 (2%) omeprazole.
Scholten et al. 2003	GERD	pantoprazole 40 mg	esomeprazole 40 mg	217	3 (groups not reported)
Caos et al, 2005	GERD relapse prevention	rabeprazole 10 or 20 mg	placebo	497	rabeprazole 10 mg 11% (n=18) rabeprazole 20 mg 12% (n=19) placebo 4% (n=7)
Richter et al 2004	GERD relapse prevention	pantoprazole 20 or 40 mg	ranitidine 150 mg	349	Not reported

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Mee 1996 UK and Ireland Multicenter	51% of all patients had at least one event, not broken down by treatment group. Most frequent events: headache (12% (l30), 11% (o20) diarrhea (9.4% (l30), 8% (o20) nausea (4.3% (l30), 4.7% (o20). 2 serious events (o20) (esophageal cancer (pre-existing) and vasovagal syncope and loose stools)
Mulder 1996 Netherlands Multicenter	19% (l), 21% (o) No difference in change in gastrin levels between groups. No other events reported.
Richter 2001 US Multicenter	At least one adverse event reported in 32.2% in(e40), 34.3% in (o20). Most common: headache 6.2% (e40), 5.8% (o20) diarrhea 3.9% (e40), 4.7% (o20) nausea 3.0% (e40), 3.0% (o20) abdominal pain 2.6% (e40) 2.7% (o20) < 1% in each group had a serious event (0 considered treatment related)
Richter 2001b	44% in both groups, most mild or moderate. Lansoprazole vs omeprazole significant differences in incidence of diarrhea (10% vs 8%), increased appetite (0.3% vs 0%), melena (0.1% vs 0.7%), asthma (0.4% vs 0%).
Scholten et al. 2003	14% of patients reported an adverse event, most assessed as "not related" to the study drug. Three patients in each group had an event assessed as "likely" or "definitely" related to study drug. No significant differences between groups in frequency or type of adverse events.
Caos et al, 2005	8%(n=42) of patients experienced AE judged to be drug related, only serious AE occurred in placebo patient. Most common non-serious AEs 20 mg rabeprazole v 10 mg rabeprazole v placebo respectively were: rhinitis (33%, 32%, 12%); diarrhea (28%, 27%, 12%); flu syndrome (23%, 20%, 8%); headache (21%, 25%, 12%); pharyngitis (21% for both treatment groups, 9% for placebo); surgical procedure (20%, 19%, 4%); back pain (19% for both treatment groups, 8% for placebo); abdominal pain (17%,19%,6%); nausea (18%,16%, and 8%) and pain (18%,25%,6%). p≤0.018 v placebo for all comparisons.
Richter et al 2004	Specific serious AEs not reported, however 6.5% or pantoprazole patients and 3.4% of ranitidine patients are reported as having serious AEs. Other AEs were headache (13% of pantoprazole and 6% of ranitidine patients; p=0.093) Pantoprazole patients also reported as having abdominal pain (11%) diarrhea (10%) and infection (11%.)

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Disease	Intervention	Control	Number Enrolled	Number withdrawn due to adverse events
Tsai et al, 2004	GERD relapse prevention	Acute phase: esomeprazole 20 mg/day Maintenance phase: esomeprazole 20 mg on-demand	lansoprazole 15 mg/day	Acute phase: 774 Maintenance phase: 622	Acute phase: 18 Maintenance phase:40 - 10 (3%) esomeprazole and 30 (10%) lansoprazole
Armstrong et al., 2004	NERD	esomeprazole 20 mg or 40 mg	omeprazole 20 mg	2645 (in 3 trials)	Not reported
Fock et al., 2005	NERD	rabeprazole 10 mg	esomeprazole 20 mg	134	1 esomeprazole (headache)
Monikes et al., 2005	NERD	pantoprazole 20 mg	esomeprazole 20 mg	529	Not reported
Peura et al., 2004	NERD	lansoprazole 15 mg, or 30mg	placebo	921	Not reported
van Zyl et al., 2004	NERD	pantoprazole 20 mg	ranitidine 300 mg	338	9/338 (2.6%)

Evidence Table 12. Adverse effects in short term RCTs: PPI vs PPI

Author Year Setting	Adverse effects
Tsai et al, 2004	17 patients reported 24 serious AEs, including 3 AEs during the acute phase. During the maintenance phase, 9 esomeprazole patients reported 14 serious AEs and 5 lansoprazole patients reported 6 serious AEs. All but one AE (anaphylaxis in a lansoprazole patient) considered unrelated. AEs reported (serious and non-serious) by 42% of acute phase patients and 71% of maintenance phase patients, most commonly headache and diarrhea. Lansoprazole patients were more likely to discontinue due to AEs than esomeprazole patients (7% v 2%, p=0.0028) and more likely to have diarrhea (14% v 5%, p<0.001)
Armstrong et al., 2004	Not reported: "Overall, esomeprazole 40 mg and 20 mg, and omeprazole 20 mg were well-tolerated and the proportions of patients experiencing AEs were similar between treatment groups during the study period."
Fock et al., 2005	AEs considered related to study drug: 22% rabeprazole, 18.2% esomeprazole (NS). Elevation in ALT: 1 rabeprazole, 4 esomeprazole Increase in AST: 1 rabeprazole, 2 esomeprazole (not clinically significant)
Monikes et al., 2005	Not reported: "Both therapies were well tolerated and safe."
Peura et al., 2004	Diarrhea: 6 lansoprazole 15mg, 8 lansoprazole 30mg, 4 placebo Headache: 5 lansoprazole 15mg, 7 lansoprazole 30mg, 9 placebo
van Zyl et al., 2004	Diarrhea: 1 pantoprazole, Constipation: 1 pantoprazole, 1 ranitidine Urticaria: 1 pantoprazole, 1 ranitidine Nausea: 2 ranitidine, Pruritus: 1 ranitidine Vertigo: 1 ranitidine Lower abdominal pain: 1 ranitidine