

# Pharmacoeconomic Evaluation of Gastrointestinal Tract Events During Treatment With Risedronate or Alendronate: A Retrospective Cohort Study

Sunanda Kane, MD, MSPH; Natalie N. Borisov, PhD;  
and Diana Brixner, RPh, PhD

## Abstract

**Objective:** To assess the cost of treating gastrointestinal (GI) tract events associated with alendronate and risedronate treatments.

**Methods:** GI-related direct medical costs associated with alendronate or risedronate use were obtained from a large administrative medical and pharmaceutical claims database for the period from November 1, 2000, to February 28, 2002. Direct GI-related costs were evaluated in the initial 4 months of newly started bisphosphonate therapy in patients aged 65 years and older with no history of GI events in the 6-month pretreatment period.

**Results:** A total of 4259 women and men were included in the analysis. There were no differences between treatment groups (alendronate, n = 3636; risedronate, n = 623) in age, gender, or duration of bisphosphonate treatment. Fewer patients treated with risedronate (21 of 623; 3.4%) experienced GI tract events compared with patients treated with alendronate (196 of 3636; 5.4%) during the first 4 months of bisphosphonate treatment. Both inpatient and outpatient visits were less common in the risedronate group than in the alendronate group (inpatient, 0.8% vs 1.4%; outpatient, 2.6% vs 4.0%, respectively). The estimated average annual GI-related cost for patients treated with alendronate was approximately \$72 000 per 1000 patients compared with \$26 000 per 1000 patients treated with risedronate.

**Conclusion:** In a patient population 65 years or older initiating bisphosphonate therapy for osteoporosis, risedronate was associated with markedly lower GI-related diagnoses, medical resource utilization, and direct medical costs compared with alendronate. The substantially higher cost of managing and treating alendronate-related GI events should be considered when choosing among bisphosphonate therapies.

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Alendronate and risedronate are the 2 most commonly prescribed oral bisphosphonates for the treatment of postmenopausal and glucocorticoid-induced osteoporosis. Both agents have demonstrated gastrointestinal (GI) tract adverse event profiles similar to placebo in controlled trials.<sup>1,2</sup> However, clinical trials for alendronate excluded patients with major upper GI tract disease (eg, peptic ulcers or dyspepsia), whereas trials for risedronate did not.<sup>3-5</sup>

Although the GI tract adverse event profiles of alendronate and risedronate have been well documented in the clinical literature, there is a relative dearth of data on the burden of these events from a payer perspective. There have been no head-to-head studies designed to evaluate differences in the cost of GI tract adverse events associated with alendronate and risedronate. One observational study reported significantly higher GI-related medical costs in patients treated with alendronate than in population-based controls.<sup>6</sup> A better understanding of the GI-related costs with different bisphosphonates is important to managed care organizations (MCOs) and other healthcare providers for making optimal use of their resources.

The purpose of this study was to estimate and compare medical costs of GI-related events associated with the use of alendronate and risedronate in patients enrolled in the Protocare Sciences Proprietary Managed Care Database. Direct medical costs of GI-related events were evaluated in the 4-month treatment period following the initiation of bisphosphonate therapy for osteoporosis in a sample of patients aged 65 years and older who had newly started bis-

phosphonate therapy and had no reported GI events in a 6-month pretreatment period.

### Methods

**Data.** A retrospective cohort study was conducted using Protocare Sciences integrated administrative medical and pharmaceutical claims data. The Protocare Sciences proprietary database is composed of claims and eligibility records for more than 10 million lives covered under various public (Medicaid) and private benefit plans since 1991. The private benefit plan information includes data on medical services and pharmacy claims provided through commercial health maintenance organizations (HMOs), preferred provider organizations (PPOs), Medicare plans, and other indemnity products. Patients were tracked longitudinally, and approximately 76% of the members in the private benefit plan database belonged to commercial HMOs or PPOs. The remaining membership was enrolled in Medicare plans (Medicare Risk and Medicare Supplement products) and a variety of specialty and administrative services-only products, including group life, dental, disability income, workers' compensation, and pharmacy management services.

**Study Population.** A dataset of administrative, medical, and pharmaceutical records was obtained between June 1, 2000, and June 30, 2002, for patients aged 65 years or older. Patients were selected with a new prescription for risedronate 5 mg daily or alendronate 5 or 10 mg daily (35 or 70 mg weekly) between November 1, 2000, and February 28, 2002 (a 16-month capture period). The date of the first alendronate or risedronate prescription for each patient was defined as the index date. Therefore, all patients included in the cohort had 6 months of observation before their index date (pretreatment period) and 4 months following initiation of the therapy (treatment period). A 4-month follow-up period was considered to be clinically sufficient to detect effects related to treatment, because GI adverse events typically occur early in bisphosphonate dosing.<sup>7</sup>

Patients who had a prescription for a bisphosphonate and/or any GI event and/or GI-

related medications during the 6-month pretreatment period were excluded from the cohort to allow for an analysis of a "clean" GI-related history population. GI events were defined using GI-related primary *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis and/or primary *Current Procedural Terminology (CPT-4)* codes (Appendices 1 and 2). GI medications included prescriptions for H<sub>2</sub> antagonists, proton pump inhibitors (PPIs), and cytoprotectives (Appendix 3).

Patients who had at least 1 prescription for risedronate 30 mg or alendronate 40 mg (doses typically used for Paget's disease) as well as *ICD-9-CM* code of Paget's disease at any point during the study period were excluded from the study cohort. Patients who switched between alendronate and risedronate during the treatment periods were excluded from the study as well to allow valid comparisons of GI-related medical costs attributable only to the specific bisphosphonate.

**GI-related Medical Resource Utilization.** Resource utilization was evaluated during the 4-month treatment period following initiation of the bisphosphonate therapy in terms of GI-related outpatient and inpatient visits and GI medications. Primary *ICD-9-CM* diagnosis codes and primary *CPT-4* codes identified a priori were used to determine GI-related inpatient and outpatient visits. Only primary *ICD-9-CM* and *CPT-4* codes were used for the analysis as a conservative approach for investigating GI-related resource utilization and its association with bisphosphonate use. This approach avoids counting secondary and tertiary resource utilization, thereby enhancing specificity.

GI-related inpatient visits consisted of visits to surgical suites, extended care facilities, emergency rooms, and inpatient hospital stays. An inpatient hospital stay was defined as a single episode of care and counted as a single visit, even if the hospital stay was longer than 1 day. GI-related outpatient visits included both outpatient hospital stays and physician office visits. Patients with GI-related events could have more than 1 inpatient and/or outpatient visit

in the first 4 months after initiating bisphosphonate therapy.

**GI-related Direct Medical Costs.** From the database, we assessed GI-related direct medical costs using reported reimbursed amounts in 2002 US dollars. Direct medical costs were measured in the 4-month treatment period following initiation of the bisphosphonate therapy in terms of GI-related (1) “outpatient cost” defined as a cost of hospital outpatient and physician office visits; (2) “inpatient cost” defined as a cost of stay as a hospital inpatient, or in an emergency room, surgical suite, or extended care facility; (3) “GI medication cost” defined as a cost of prescription for H<sub>2</sub> antagonists, PPIs, and cytoprotectives; and (4) “other GI-related costs.”

All costs associated with GI-related outpatient care as defined above included tests and procedures in outpatient locations. Likewise, all costs associated with GI-related inpatient care included tests and procedures performed in the inpatient care locations. For example, GI-related surgery was a part of inpatient cost, and GI-related laboratory tests were a part of outpatient cost. GI medication cost included pharmacy dispensing fees. Cost of over-the-counter (OTC) GI medications was not included because the database does not track OTC use. Other costs included the GI-related costs of skilled nursing facilities, nursing homes, and ambulances.

A conservative approach was employed to address cost outliers. A GI-related cost of

less than \$5 was excluded from the analysis, because this cost was likely the result of capitated reimbursement. Including such costs in the analysis would introduce bias to cost estimates, because capitated reimbursement does not represent a true service cost to an MCO. Patients with a total cost of more than \$2000 (a midpoint of the reported average total GI-related medical costs to an MCO: \$1368-\$2780<sup>8</sup>) were examined further and were checked against the secondary diagnosis. If the secondary diagnosis indicated a severe condition that was not GI related (eg, heart failure or diabetes), the reimbursement for the entire service claim was excluded from the total cost of this patient.

**Statistical Analysis.** All cost and resource utilization comparisons between alendronate and risedronate patients were performed using the 2-sample, 2-sided *t* test. A 0.05 level of significance was used to determine statistically significant differences between bisphosphonate treatments.

**Results**

**Baseline Characteristics of the Patient Population and GI Events During Follow-up.** A total of 4259 women and men aged 65 years and older fulfilled the inclusion criteria and were included in the analysis. Of these patients, 623 (15%) received risedronate treatment and 3636 (85%) received alendronate treatment, a reflection of the market share of these drugs at the time of the study. There were no differences between the risedronate and alendronate patient cohorts in age, gender, or exposure to bisphosphonates (Table 1). Each cohort was comprised of 94% women, and the mean age was approximately 75 years in both groups. An average overall exposure time taking each bisphosphonate therapy was approximately 80 days. No difference in NSAID use between cohorts in either the 6-month pretreatment period or 4-month treatment period was observed.

Patients treated with alendronate daily (5 or 10 mg/day) and alendronate weekly (35 or 70 mg/week) were comparable in terms of GI-related medical resource utilization and associated direct medical cost (Table 2). Although the total medical cost

**Table 1.** Baseline Characteristics and Duration of Bisphosphonate Treatment During Follow-up in Patients Who Received Risedronate or Alendronate

	Risedronate n = 623	Alendronate n = 3636
Mean age (SD), years	75.7 (6.4)	75.4 (6.6)
Female, n (%)	586 (94)	3404 (94)
Mean time (SD) receiving bisphosphonates, days	81 (38)	80 (40)

SD indicates standard deviation.

**Table 2.** GI-related Total Direct Medical Cost and Medical Resource Utilization Among Patients Who Received Alendronate Daily or Alendronate Weekly

	Alendronate Daily* n = 987	Alendronate Weekly* n = 2469	P <sup>†</sup>
<b>GI-related medical resource utilization<sup>‡</sup> (95% CI)</b>			
Inpatient visits	4.3 (1.4, 7.2)	6.5 (4.0, 8.8)	.258
Outpatient visits	16.7 (10.7, 22.7)	15.1 (11.6, 18.5)	.646
GI medication	30.4 (22.0, 38.8)	21.1 (16.8, 25.3)	.051
<b>GI-related direct medical cost<sup>§</sup> (95% CI)</b>			
Inpatient costs	\$3540 (850, 6230)	\$2450 (1190, 3720)	.474
Outpatient costs	\$2720 (980, 4460)	\$2160 (1250, 3060)	.572
GI medication costs	\$870 (540, 1200)	\$720 (520, 920)	.428
Other costs <sup>  </sup>	\$220 (20, 450)	\$310 (70, 550)	.576
Total cost	\$7350 (3290, 11 410)	\$5640 (3820, 7460)	.451

\*Cohort excludes patients who switched between daily and weekly doses.

<sup>†</sup>Between-group comparison, 2-sample, 2-sided *t* test.

<sup>‡</sup>Values are given as mean utilization per 1000 members per month.

<sup>§</sup>Values are given as mean costs per 1000 members per month.

<sup>||</sup>Includes skilled nursing facility, nursing home, ambulance, and other miscellaneous costs.

GI indicates gastrointestinal; CI, confidence interval.

was lower for patients treated with alendronate weekly, the difference in cost between daily and weekly alendronate was not statistically significant. Therefore, daily and weekly doses of alendronate were combined for the analyses.

The incidence of specific GI events during the 4-month follow-up period among alendronate- and risedronate-treated patients is enumerated in Table 3. Overall, a lower proportion of patients taking risedronate experienced GI-related events during the 4-month follow-up period (3.4% vs 5.4%,  $P = .034$ ). These frequencies represent unique GI events (based on specific GI-related ICD-9-CM codes) experienced by unique patients in each GI-related category (ie, GI bleeding, ulcers, GI symptoms, abdominal pain, and other). However, a patient may have experienced GI events in different categories and, thus, the same patient may be present in multiple GI-related categories.

The distribution of patients who experienced GI events and/or GI medications, and GI-related outpatient and inpatient visits during the 4-month period following initiation of bisphosphonate therapy is presented

in Table 4. A higher proportion of alendronate-treated patients required GI-related outpatient care compared with risedronate-treated patients (4.0% vs 2.6%,  $P = .055$ ) (Table 4).

**GI-related Medical Resource Utilization.** Medical resource utilization per 1000 members per month associated with bisphosphonate-related GI events in the follow-up period is presented in Table 5. Risedronate-treated patients consistently utilized fewer medical resources (outpatient and inpatient visits) compared with alendronate-treated patients in the first 4 months after initiating bisphosphonate therapy. Risedronate-treated patients averaged just over half the number of outpatient visits incurred by alendronate-treated patients (8.8 vs 15.3 visits per 1000 members per month,  $P = .027$ ). Risedronate-treated patients averaged fewer than half the number of inpatient visits of alendronate-treated patients (2.4 vs 6.0 visits per 1000 members per month,  $P = .016$ ).

**Direct Medical Cost of GI Events.** A comparison of the direct medical costs of GI

**Table 3.** Occurrence of Specific GI Events During Follow-up in Patients Who Received Risedronate or Alendronate

GI Events Category	Risedronate n = 623	Alendronate* n = 3636	P†
	Number of Unique Patients (%)		
Overall	21 (3.4)	196 (5.4)	.034
GI bleeding	2 (0.3)	39 (1.1)	.076
Ulcer‡	1 (0.2)	16 (0.4)	.307
GI symptoms§	4 (0.6)	36 (1.0)	.405
Abdominal pain	12 (1.9)	183 (5.0)	<.001
Esophageal reflux	0	16 (0.4)	.097
Other	10 (1.6)	51 (1.4)	.694

\*Cohort includes patients of both daily and weekly doses of alendronate.

†Between-group comparison,  $\chi^2$  test.

‡Includes gastric, peptic, duodenal, and esophageal ulcers.

§GI symptoms include dysphagia, vomiting, nausea, heartburn.

||Other includes gastritis, esophagitis, stomach function disorders.

GI indicates gastrointestinal.

**Table 4.** Distribution of Patients Receiving Risedronate or Alendronate Who Experienced GI Events During Follow-up

Patients Who Had	Risedronate n = 623	Alendronate n = 3636	P*
	Number of Unique Patients (%)		
GI events	21 (3.4)	196 (5.4)	.034
Without GI medication	16 (2.6)	132 (3.6)	.181
With GI medication	5 (0.8)	64 (1.8)	.080
GI medication without GI event	28 (4.5)	133 (3.6)	.312
Outpatient visit	16 (2.6)	145 (4.0)	.055
Inpatient visit	5 (0.8)	51 (1.4)	.224

\*Between-group comparison,  $\chi^2$  test.

GI indicates gastrointestinal.

events and/or GI medications in patients receiving alendronate or risedronate is provided in Table 6. During the first 4 months after initiation of bisphosphonate therapy, the total average GI-related direct medical cost per 1000 members per month was significantly lower for risedronate-treated patients compared with alendronate-treated patients (\$2164 vs \$5996,  $P < .001$ ).

Furthermore, when comparing the risedronate with alendronate weekly dose only, the total average GI-related direct medical cost per 1000 members per month remains significantly lower for risedronate-treated patients (\$2164 vs \$5639,  $P = .001$ ).

An average GI-related inpatient cost per 1000 members per month for risedronate-treated patients was 6 times lower than the inpatient cost for alendronate-treated patients (\$436 vs \$2691,  $P < .001$ ). For outpatient care, the average GI-related cost per 1000 members per month for risedronate-treated patients was more than 2.5 times lower than the corresponding cost for alendronate-treated patients (\$860 vs \$2223,  $P = .009$ ).

**Discussion**

This study estimated the GI event rates, medical resource utilization, and direct medical costs of GI events in an elderly population initiating bisphosphonate therapy. An important observation is the differences in clinical versus economic impact of managing these events. GI-related medical cost during the first 4 months of treatment for patients with osteoporosis taking alendronate was nearly 3 times higher than the cost for patients taking risedronate (\$5996 vs \$2164, per 1000 members per month). The cost of inpatient care appeared to be the primary reason for the differential in total cost observed between alendronate- and risedronate-treated patients. This suggests that alendronate-treated patients may have experienced more severe GI events that led to inpatient care. Inpatient visits—typically the most expensive component in overall medical care—were 2.4 and 6 visits per 1000 members per month for risedronate and alendronate, respectively. This 2.5-fold difference in inpatient visits translates to a 6-fold difference in inpatient cost (\$436 vs \$2691 per 1000 patients per month for risedronate and alendronate, respectively). These differences between GI-related costs for risedronate versus alendronate represent a substantial potential savings in overall costs for an MCO. It is important for MCOs to look beyond the clinical differences between treatments and also consider the financial impact to a plan and its members.

**Table 5.** GI-related Medical Resource Utilization

	<b>Risedronate n = 623</b>	<b>Alendronate n = 3636</b>	
	<b>GI-related Medical Resource Utilization* (95% CI)</b>		<b>P<sup>†</sup></b>
Inpatient visits per month	2.4 (0.2, 4.6)	6.0 (4.1, 7.8)	.016
Outpatient visits per month	8.8 (3.9, 13.7)	15.3 (12.4, 18.1)	.027
GI medication prescriptions per month	26.9 (15.4, 38.4)	23.6 (19.8, 27.3)	.591

\*Values are given as average utilization per 1000 members.

<sup>†</sup>Between-group comparison, 2-sample, 2-sided *t* test.

GI indicates gastrointestinal; CI, confidence interval.

**Table 6.** GI-related Average Direct Medical Costs in 2002 US Dollars

	<b>Risedronate n = 623</b>	<b>Alendronate n = 3636</b>	
	<b>GI-related Direct Medical Cost* (95% CI)</b>		<b>P<sup>†</sup></b>
Inpatient costs per month	\$436 (0, 970)	\$2691 (1560, 3820)	<.001
Outpatient costs per month	\$860 (190, 1520)	\$2223 (1450, 2990)	.009
GI medication costs per month	\$762 (300, 1220)	\$754 (590, 920)	.974
Other costs <sup>‡</sup> per month	\$106 (0, 310)	\$328 (120, 530)	.139
Total cost per month	\$2164 (1130, 3200)	\$5996 (4330, 7660)	<.001
Total cost per year	\$25 968 (13 560, 38 400)	\$71 952 (51 960, 91 920)	<.001

\*Values are given as average costs per 1000 members.

<sup>†</sup>Between-group comparison, 2-sample, 2-sided *t* test.

<sup>‡</sup>Includes skilled nursing facility, nursing home, ambulance, and other miscellaneous costs.

GI indicates gastrointestinal; CI, confidence interval.

In examination of the specific events, there was a higher proportion of GI bleeding in patients with alendronate, which may have led to increased medical resource utilization in all categories (inpatient and outpatient care). Ulcers and GI symptoms both trended higher for patients taking alendronate, with esophageal reflux occurring only among patients taking alendronate. The small numbers preclude a thorough evaluation of specific GI event categories. Overall, GI events showed a statistically significant difference between alendronate- and risedronate-treated patients. When taking into

account prophylaxis or treatment with GI medications, the observed GI event rate was still higher for patients treated with alendronate. As expected, fewer patients receiving GI medications had a GI event.

Although both daily and weekly doses of alendronate have demonstrated GI tract adverse event profiles similar to placebo in controlled trials,<sup>9-11</sup> postmarketing studies of alendronate daily have found an association with GI tract adverse events,<sup>7,12-15</sup> suggesting a safer GI tract adverse event profile for alendronate weekly. In contrast, statistically significant differences in GI-related medical

resource utilization and associated direct medical costs between patients taking alendronate weekly versus alendronate daily dosing were not observed.

Our findings have important implications for managed care systems and national healthcare programs. Osteoporosis is a prevalent disease in the elderly, and healthcare systems will be under increasing pressure to treat this disorder as the proportion of elderly patients continues to rise. For a typical MCO, the estimated average GI-related cost per 1000 alendronate-treated patients per year would be \$71 952 compared with \$25 968 per 1000 risedronate-treated patients per year. This is a savings of almost \$46 000 per year for every 1000 patients who would initiate risedronate therapy instead of alendronate therapy. If only 50% of patients started osteoporosis therapy with risedronate instead of alendronate within a given plan, the savings could be substantial.

There are several limitations in conducting this type of investigation. The approach of using a large administrative database does not allow for individual chart review to validate GI-related *ICD-9-CM* codes, although the identification of GI-related prescriptions or procedures can provide internal validation of the diagnosis. It does not capture the use of OTC GI medications either, thus the burden of GI medication use and its cost may be underestimated. Some GI medications captured in the database may have been prescribed for prophylaxis rather than treatment, adding to the overall cost of the medication. The potential bias of this type of medication prescribing or use would not necessarily favor one treatment over the other, because there were no apparent differences between the 2 groups in the cost of prescription GI medications. We included any prescription GI medication use as a part of total GI-related costs since any bisphosphonate-related GI medication use constitutes an additional economic burden for an MCO, regardless of the indication. Also, the database does not allow distinguishing between inpatient medical costs that correspond to primary or secondary diagnosis; therefore, inpatient cost might be slightly overestimated. At the same time, we exclud-

ed very high GI-related inpatient cost when the secondary diagnosis indicated a severe condition that was not GI related for patients with total direct medical costs of more than \$2000.

In spite of these limitations, the use of an integrated claims database provides an opportunity to observe treatment patterns that occur in real-world practice. Such databases have the additional advantage of including a large number of patients and incorporating many types of health plans and physician specialties, permitting a more complete picture of GI-related events, prescribing habits, and costs once a drug is in use across large populations.

**Sensitivity Analysis.** In this study we applied the following restrictions to the analysis: (1) only primary *ICD-9-CM* and *CPT-4* codes were included in the analysis to define GI-related resource utilization and associated medical costs, and (2) the reimbursement for the entire service claim was excluded from the total cost of a patient with a total cost of more than \$2000 if the secondary diagnosis indicated a severe condition that was not GI related (eg, heart failure, diabetes). To assess whether these restrictions introduced any bias in the results of this study, we compared the GI-related medical cost of risedronate-treated patients to the cost of alendronate-treated patients without applying these restrictions. Adding secondary GI-related diagnoses and procedures to the definition of a GI event should contribute to higher GI-related total direct medical costs for both risedronate- and alendronate-treated patients. Including upper bound outliers in the analysis, however, should have an impact only on the total medical cost of the alendronate cohort caused by nonexistent outliers in the risedronate cohort.

There were 10 patients in the alendronate cohort who had total GI-related medical costs of more than \$2000; however, only 3 alendronate-treated patients had secondary conditions that were not GI related and were contributing to the higher inpatient costs for these patients. When these costs are added back, the inpatient cost of alendronate-treated patients increased from \$2691 to \$3432 per 1000 patients per month.

When both GI-related primary and secondary diagnoses are included in the analysis, the total GI-related medical cost increased for both risedronate- and alendronate-treated patients. However, the significantly lower total average GI-related direct medical cost per 1000 members per month for risedronate-treated patients compared with alendronate-treated patients was still evident (\$7961 vs \$29 410,  $P = .036$ ).

**Conclusion**

In a patient population 65 years of age or older initiating bisphosphonate therapy for osteoporosis, risedronate was associated with markedly lower GI-related diagnoses, medical resource utilization, and direct medical costs compared with alendronate.

These data suggest that risedronate use has the potential to reduce GI-related healthcare resources use and associated direct medical costs relative to alendronate. Physicians and managed care decision makers should consider cost differences among oral bisphosphonates, because they relate to clinically significant GI events, when determining agents for inclusion onto managed care formularies.

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**REFERENCES**

1. Bauer DC, Black D, Ensrud K, et al. Upper gastrointestinal tract safety profile of alendronate: the Fracture Intervention Trial. *Arch Intern Med.* 2000;160:517-525.
2. Taggart H, Bolognese MA, Lindsay R, et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clinic Proc.* 2002;77:262-270.
3. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med.* 1995;333:1437-1443.
4. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet.* 1996;348:1535-1541.
5. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA.* 1998;280:2077-2082.
6. Colby CJ, Levin TR, Boyko WL, Schein JR. Cost of acid-related disorders associated with alendronate use for osteoporosis in a large MCO. Paper presented at: 21st Annual Meeting of the American Society for Bone and Mineral Research; September 30, 1999; St. Louis, Mo.
7. Ettlinger B, Pressman A, Schein J. Clinic visits and hospital admissions for care of acid-related upper gastrointestinal disorders in women using alendronate for osteoporosis. *Am J Manag Care.* 1998;4:1377-1382.
8. Levin TR, Schmittiel JA, Kunz K, et al. Costs of acid-related disorders to a health maintenance organization. *Am J Med.* 1997;103:520-528.
9. Greenspan S, Field-Munves E, Tonino R, et al. Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. *Mayo Clin Proc.* 2002;77:1044-1052.
10. Watts N, Freedholm D, Daifotis A. The clinical tolerability profile of alendronate. *Int J Clin Pract Suppl.* 1999;101:51-61.
11. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Ageing (Milano).* 2000;12:1-12.
12. Liberman UI, Hirsch LJ. Esophagitis and alendronate. *N Engl J Med.* 1996;335:1069-1070.
13. Graham DY. What the gastroenterologist should know about the gastrointestinal safety profiles of bisphosphonates. *Dig Dis Sci.* 2002;47:1665-1678.
14. Park BJ, Clouse J, Shatin D, Stergachis A. Incidence of adverse oesophageal and gastric events in alendronate users. *Pharmacoepidemiol Drug Saf.* 2000;9:371-376.
15. de Groen PC, Lubbe DF, Hirsh LJ, et al. Esophagitis associated with the use of alendronate. *N Engl J Med.* 1996;335:1016-1021.

**Appendix 1. ICD-9-CM Diagnosis Codes for GI Events**

<b>Code</b>	<b>Condition</b>
530.1X	Esophagitis
530.2	Ulcer of esophagus
530.3	Stricture of esophagus
530.4	Perforation of esophagus
530.7	Mallory-Weiss syndrome
530.81	Esophageal reflux (GERD)
530.82	Esophageal hemorrhage
531.XX	Gastric ulcer
532.XX	Duodenal ulcer
533.XX	Peptic ulcer, site NOS
535.0X	Acute gastritis
535.4X	Gastritis NEC
535.5X	Gastritis/duodenitis NOS
535.6X	Duodenitis
536.2	Persistent vomiting
536.8	Dyspepsia and other specified disorders of stomach
578.X	GI hemorrhage
787.0X	Nausea and vomiting
787.1	Heartburn
787.2	Dysphagia
789.0X	Abdominal pain

*ICD-9-CM indicates International Classification of Diseases, Ninth Revision, Clinical Modification; GI, gastrointestinal; GERD, gastrointestinal reflux disease; NOS, not otherwise specified; NEC, not elsewhere classified.*

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**Appendix 2. GI-related CPT-4 Codes**

Code	Procedure
43200	Endoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)
43235	Upper GI endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic with or without collection of specimen(s) by brushing or washing (separate procedure)
43202	Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure) with biopsy, single or multiple
43239	Upper GI endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic with or without collection of specimen(s) by brushing or washing (separate procedure) with biopsy, single or multiple
43227	Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure) with control of bleeding, any method
43255	Upper GI endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic with or without collection of specimen(s) by brushing or washing (separate procedure), with control of bleeding, any method
74240	Radiologic examination, GI tract, upper; with or without delayed film, without KUB
74241	Radiologic examination, GI tract, upper; with or without delayed films, with KUB
74245	Radiologic examination, GI tract, upper; with small bowel, includes multiple serial films
74246	Radiologic examination, GI tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glycygon; with or without delayed films, with KUB
74247	Radiologic examination, GI tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glycygon; with or without delayed films, without KUB
74249	Radiologic examination, GI tract, upper, air contrast, with specific high density barium, effervescent agent, with or without glycygon; with small bowel follow-through

GI indicates gastrointestinal; CPT-4, *Current Procedural Terminology*; KUB, kidney, ureter, bladder.

**Appendix 3. GI Medications: Generic and Brand Names**

Therapeutic Drug Class	Generic (Brand)
H <sub>2</sub> antagonists	Ranitidine (Zantac) Ranitidine Bismuth Citrate (Tritec) Cimetidine (Tagamet) Famotidine (Pepcid) Nizatidine (Axid)
Proton pump inhibitors	Omeprazole (Prilosec) Esomeprazole (Nexium) Lansoprazole (Aciphex) Pantoprazole (Protonix)
Cytoprotectives	Misoprostol (Cytotec) Sucralfate (Carafate)

GI indicates gastrointestinal.



