

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 29, 2000

FROM: Joyce Weaver, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director *Signed 12-29-00 by*
Division of Drug Risk Evaluation I, HFD-430

TO: Jonca Bull, M.D., Acting Division Director
Division of Antiinflammatory and Ophthalmic Drug Products, HFD-550

SUBJECT: OPDRA Postmarketing Safety Review
Drugs: Etodolac (Lodine NDA 18-922, NDA 20-584)
Celecoxib (Celebrex NDA 20-998)
Rofecoxib (Vioxx NDA 21-042, NDA 21-052)
Reaction: US Deaths related to Gastrointestinal bleeding,
obstruction, perforation, or stenosis

INTRODUCTION/ EXECUTIVE SUMMARY

Our objective was to summarize serious gastrointestinal events reported in postmarketing for celecoxib and rofecoxib relating to gastrointestinal bleeding, obstruction, perforation, or stenosis. A summary of similar events for the nonselective nonsteroidal anti-inflammatory drug, etodolac was also performed. We concentrated on the most serious gastrointestinal events, those resulting in death.

We evaluated 82 US deaths related to gastrointestinal bleeding, obstruction, perforation, or stenosis in the AERS database. All cases were temporally related to therapy with etodolac (9), celecoxib (36), or rofecoxib (37). Generally, the cases occurred in high-risk elderly patients. In 5 of the etodolac cases, 30 of the celecoxib cases, and 26 of the rofecoxib cases, the patients were at increased risk of bleeding or having a poor outcome with a bleed. The patients were at increased risk because of past medical history, a recent major systemic medical event, or concomitant therapy with aspirin or another antiplatelet drug, corticosteroids, warfarin, or another NSAID. Many patients had more than one risk factor. Eleven of the patients taking celecoxib had a past history of peptic ulcer disease, and 6 patients had experienced gastrointestinal bleeding in the past. Four patients taking rofecoxib had a past history of peptic ulcer disease, and one patient had experienced gastrointestinal bleeding in the past. Thirteen patients each taking celecoxib and rofecoxib were taking aspirin and/or warfarin concomitantly.

We conclude that the labeling for celecoxib and rofecoxib reflect the risk of fatal gastrointestinal bleeding, obstruction, perforation, and stenosis observed in the postmarketing experience.

DRUG INFORMATION/LABELING

Etodolac is a nonsteroidal anti-inflammatory drug indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis and rheumatoid arthritis and for the management of pain. Etodolac was approved January 31, 1991. The labeling for etodolac includes information about gastrointestinal bleeding in the *Warnings* and *Adverse Reactions* sections. The possibility of fatal outcomes is discussed. The *Warnings* section presents risk factors for developing gastrointestinal bleeding, including a prior history of serious GI events and risk factors known to be associated with peptic ulcer disease; for example, alcoholism and smoking.

Celecoxib is a nonsteroidal anti-inflammatory drug indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care. Celecoxib was approved December 31, 1998. The labeling for celecoxib includes information about gastrointestinal bleeding in the *Warnings* and *Adverse Reactions* sections. The possibility of fatal outcomes is discussed. The *Warnings* section presents additional risk factors not addressed in the labeling for etodolac; for example, treatment with oral corticosteroids or anticoagulants. Intestinal obstruction is included in the *Adverse Reactions* section of the labeling. The *Drug Interactions* section states that celecoxib can be used with low dose aspirin; however, concomitant administration of aspirin with celecoxib may result in an increased rate of GI ulcerations. Additionally, the *Drug Interactions* section states there is an increased risk of bleeding complications with concomitant use of warfarin, particularly in elderly patients.

Rofecoxib is a nonsteroidal anti-inflammatory drug indicated for relief of the signs and symptoms of osteoarthritis, for the management of acute pain, and for the treatment of primary dysmenorrhea. Rofecoxib was approved May 20, 1999. The labeling for rofecoxib includes information about gastrointestinal bleeding and obstruction in the *Warnings* and *Adverse Reactions* sections. The possibility of fatal outcomes is discussed. The *Warnings* section presents information about risk factors in a manner similar to the labeling for celecoxib. The *Drug Interactions* section states that concomitant administration of aspirin or warfarin with rofecoxib may result in an increased rate of GI complications.

MEDICAL LITERATURE SUMMARY

MEDLINE was searched for additional case reports of gastrointestinal bleeding or obstruction. A MEDLINE search performed December 7, 2000 using the MESH terms *Etodolac*, *Celecoxib*, *Rofecoxib*, *Intestinal Obstruction*, and *Gastrointestinal Hemorrhage* did not locate any additional case reports with fatal outcomes in the medical literature.

SELECTION OF CASE SERIES

On October 25, 2000 we searched the AERS database for cases of gastrointestinal bleeding, perforation, obstruction, or stenosis related to etodolac, celecoxib, and rofecoxib. The cases were identified using the higher level group terms (HLGTs) *Gastrointestinal Haemorrhages NOS*, *Gastrointestinal Stenosis and Obstruction*, and *Gastrointestinal Ulceration and Perforation*. AERS contained 214 reports (190 domestic) linked to etodolac, 744 (705 domestic) linked to celecoxib, and 829 (613 domestic) linked to rofecoxib. We limited our summary to domestic cases of gastrointestinal bleeding, perforation, obstruction, or stenosis resulting in death linked to these 3 drugs. AERS contained 82 unique domestic deaths, 9 linked to etodolac, 36 linked to celecoxib, and 37 linked to rofecoxib.

SUMMARY OF CASES

See Attachment 1 for a summary of the data for all 3 drugs.

Etodolac

Demographic data and a summary of the 9 cases are provided below.

Age in years	Mean 79, median 78, range 69 to 94
Gender	Male (5), Female (3), Unknown (1)
Year	1991 (2), 1992 (4), 1993 (1), 1994 (1), 1996 (1)
Indication	Osteoarthritis (2), Gouty arthritis (1), Unknown (6)
Time to onset	Mean 35.7, median 30 (range, 17 to 60) days
Dose	At or below labeled range (3), Unknown (6)
GI event	Hemorrhage (6), Perforation (2), Melena (1), Hematemesis (1), Stenosis/Obstruction (1)
Location	Esophageal (1), Gastric (2), Duodenal (1), Large intestine (1), Unknown (4)
Pertinent PMH	Diabetic gastroparesis (1), Bowel obstruction (1), CAD (3)
Major event preceding bleed	CABG (1)
Significant concomitant medications	Warfarin (1)

Eight patients taking etodolac died after experiencing gastrointestinal bleeding, and one patient died after experiencing esophageal stenosis. In the latter patient, death occurred after an etodolac capsule or tablet lodged in the patient's esophagus. One death was not directly due to bleeding, but was instead the result of a cerebrovascular accident resulting from discontinuation of warfarin after serious gastrointestinal bleeding occurred. The site of bleeding was not reported in 4 cases. Gastric bleeding occurred in 2 cases. In one case each bleeding occurred in the duodenum and the large intestine.

The mean age of the patients was 79 years. In most cases the indication for which etodolac was prescribed was not stated. The mean onset of gastrointestinal bleeding was 35.7 days after instituting therapy with etodolac. In one case bleeding occurred on the day of hospital discharge after coronary artery bypass surgery. In 5 of the 9 cases the patients were at increased risk of bleeding or having a poor outcome with a bleed because of past medical history, a recent major systemic medical event, or concomitant therapy with warfarin.

Two cases are presented below.

AERS 4932128, MFR 892324001B, US (FL), 1992

An 82-year-old man with a prior medical history of cataracts, unspecified prostate surgery, and diabetes was prescribed etodolac 300 mg as needed for unspecified pain. After taking etodolac for 2 to 3 months, the patient experienced coffee-ground emesis, and he was hospitalized. Nasogastric aspiration resulted in retrieval of 900 milliliters of coffee-ground material. Surgery was performed to repair a perforated gastric ulcer. The patient died 3 days after admission to the hospital.

AERS 4919199, Direct, US (IA), 1992

A 79-year-old woman taking etodolac for an unknown period for unspecified arthritis was hospitalized after a 2-to-3-month history of dark stools and a 2-week history of vomiting. Hemoglobin and hematocrit on admission were 5.8 g/dL and 16.6%, respectively. A bleeding duodenal ulcer was diagnosed. The patient was treated with surgery, an H₂-receptor antagonist, and blood transfusions. She died after 26 days of hospitalization.

Celecoxib

Demographic data and a summary of the 36 cases are provided below.

Age in years	Mean 77, median 78.5, range 46 to 99
Gender	Male (12), Female (22), Unknown (2)
Year	1999 (30), 2000 (6)
Indication	Osteoarthritis (12), Rheumatoid arthritis (4), Acute pain (3), Unspecified arthritis (3), Other (5), Unknown (9)
Time to onset	Mean 25.7, median 14 (range, 1 to 115) days
Dose	At or below labeled range (18), Higher than labeled range (2), Unknown (16)
GI event	Hemorrhage (22), Perforation (2), Melena (7), Hematemesis (10)

Location	Gastric (3), Duodenal (5), Rectal (2), Small intestine (1), Unknown (25)
Pertinent PMH	Alcoholism (3), Anemia (5), CAD (7), Cirrhosis (1), CVA (1), Diabetes (6), Diverticulitis (1), Esophageal varices (1), Factor V def (1), Gastritis (2), GI AVM (2), Gastrectomy (1), previous GI bleed (6), Malignancy (4), PUD (11), Thrombocytopenia (1)
Major event preceding bleed	Exacerbation of asthma, inc in steroid dose (1), Hospitalization for CP & anemia (1), Liver failure (2), Metastatic ca (2), Multiple myeloma (1), Pancreatitis (1), Pneumonia (1), Surgery (2), TEN (1)
Significant concomitant medications	Alendronate (1), ASA (8), Corticosteroid (5), NSAID (4), Warfarin (5), H ₂ -blocker or PPI (8)

Thirty-six patients taking celecoxib died after experiencing gastrointestinal bleeding or perforation. In 4 cases, gastrointestinal bleeding apparently precipitated other events that directly caused death. The immediate causes of death were probable septic shock, aspiration pneumonia, multiple organ failure, and unspecified cardiac complications.

The mean age of the patients was 77 years. The case series had a 1.8:1 predominance of females. Celecoxib was prescribed most often for osteoarthritis. The mean time to onset of gastrointestinal bleeding was 25.7 days after instituting therapy with celecoxib. The site of bleeding was not reported in most cases. Gastric bleeding occurred in 4 cases and duodenal bleeding occurred in 5 cases. In one case each bleeding occurred in the rectum and the small intestine.

In 30 of the 36 cases the patients were at increased risk of bleeding or having a poor outcome with a bleed because of past medical history, a recent major systemic medical event, and/or concomitant medication. Many patients had more than one risk factor for bleeding. Five patients were taking warfarin concomitantly with celecoxib, 8 patients were taking aspirin concomitantly, 5 patients were taking corticosteroids concomitantly, and 4 patients were taking another nonsteroidal anti-inflammatory drug concomitantly with celecoxib.

About one-half of the patients had clinically significant prior medical histories. Eleven patients had a prior medical history of peptic ulcer disease and 6 patients had experienced gastrointestinal bleeding before celecoxib was prescribed. One of the patients with a history of gastrointestinal bleeding had required banding of esophageal varices. Five patients had a history of anemia, 4 patients had a history of malignancy, 7 patients had arteriosclerotic heart disease, and 3 patients were alcoholic.

Additionally, the gastrointestinal bleeding in 12 patients may have been precipitated by a major systemic event. The major events included exacerbation of asthma accompanied by an increase in corticosteroid dose, hospitalization for chest pain and anemia, liver failure,

metastatic solid organ cancer, multiple myeloma, pancreatitis, pneumonia, surgery, and toxic epidermal necrolysis.

Eight patients bled despite taking an H₂-receptor antagonist or proton pump inhibitor concomitantly with celecoxib.

Two cases are presented below.

AERS 3305112, MFR 990709-SK489, US (MD), 1999

An 87-year-old woman with past medical history of peptic ulcer disease, arteriosclerotic heart disease, aortic valve disorder, and diabetes was prescribed an unknown dose of celecoxib to treat osteoarthritis. Her concomitant medications included warfarin. After 37 days of therapy with celecoxib, the patient presented to the emergency room with gastrointestinal bleeding. She died in the emergency room.

AERS 3472602, US (NC), 2000

A 92-year-old female nursing home resident with past medical history of hypertension, chronic obstructive pulmonary disease, glaucoma, parkinsonism, and arteriosclerotic heart disease, but with no history of peptic ulcer disease, was prescribed celecoxib 100 mg twice a day for an unknown reason. After receiving celecoxib for an unknown period of time, she was transferred to the hospital with lethargy, nausea, diarrhea, and abdominal pain. Her hemoglobin and hematocrit dropped from 12 g/dL and 36%, respectively, on admission to 10.7 g/dL and 31.7%, respectively, after one day of hospitalization. Esophagogastroduodenoscopy (EGD) revealed a one-centimeter bleeding ulcer. Epinephrine was injected in an attempt to stop the bleeding. The patient's condition deteriorated, a do-not-resuscitate (DNR) order followed, and the patient died.

Rofecoxib

Demographic data and a summary of the 37 cases are provided below.

Age in years	Mean 76, median 80, range 28 to 93
Gender	Male (14), Female (22), Unknown (1)
Year	1999 (3), 2000 (34)
Indication	Osteoarthritis (14), Acute pain (6), Unspecified arthritis (6), Other (6), Unknown (5)
Time to onset	Mean 43, median 21 (range, 0 to 131) days
Dose	At or below labeled range (24), Higher than labeled range (1), Unknown (12)
GI event	Hemorrhage (23), Perforation (7), Melena (4), Hematemesis (6), Erosions (1), Stenosis/Obstruction (1), Other (10)
Location	Gastric (13), Duodenal (5), Large intestine (2), Other (2), Unknown (15)
Pertinent PMH	Anemia (1), ASA allergy (1), sulfa allergy (1), Crohn's disease (1), CVA (1), Diabetes (1), Diverticulitis (1), Functional intestinal disorder (1), Gastrostomy (1), Previous GI bleed (1), Irritable bowel syndrome (1), Hepatic dysfunction (1), PUD (4)

Major event preceding bleed	Metastatic gastric cancer (1), Pancreatitis, hepatitis (1), Shock (1) Surgery (3)
Significant concomitant medications	ASA (8), Clopidogril (2), Corticosteroid (2), Warfarin (6) Antacid, H2 blocker, or PPI (4)

Thirty-seven patients taking rofecoxib died after experiencing gastrointestinal bleeding, perforation, stenosis, or obstruction. One death might have been the result of a cerebrovascular accident resulting from discontinuation of warfarin because of serious gastrointestinal bleeding. In another case, a patient died after gastrointestinal bleeding precipitated an exacerbation of congestive heart failure. Four deaths occurred as a result of postoperative complications following surgery to repair ulcers or perforations.

The mean age of the patients was 76 years. The case series had a 1.6:1 predominance of females. Rofecoxib was prescribed most often for osteoarthritis. The mean time to onset of gastrointestinal bleeding was 43 days after instituting therapy with rofecoxib. Gastric bleeding was most commonly reported, occurring in 13 cases. Duodenal bleeding occurred in 5 cases, and bleeding in the large intestine occurred in 2 cases.

In 26 of the 37 cases the patients were at increased risk of bleeding or having a poor outcome with a bleed because of past medical history, a recent major systemic medical event, and/or concomitant medication. Six patients were taking warfarin concomitantly with rofecoxib, 8 patients were taking aspirin concomitantly, 2 patients were taking corticosteroids concomitantly, and 2 patients were taking clopidogril concomitantly with rofecoxib.

About one-third of the patients had clinically significant prior medical histories. These included anemia, cerebrovascular accident, Crohn's disease, diabetes, diverticulitis, functional intestinal disorder, gastrostomy, irritable bowel syndrome, and hepatic function impairment. Four patients had a prior medical history of peptic ulcer disease, and previous gastrointestinal bleeding was reported for one patient.

Gastrointestinal bleeding in 6 patients may have been precipitated by a major systemic event. The major events included previously undiagnosed metastatic gastric cancer, pancreatitis, hepatitis, and surgery.

Four patients bled despite taking a gastrointestinal-protectant drug concomitantly with rofecoxib.

Two cases are presented below.

AERS 3397744, WAES 99111907, US (FL), 1999

An 87-year-old female independent retirement village resident with a past medical history of irritable bowel syndrome, paroxysmal atrial tachycardia, hypertension, and spastic colon, but no history of peptic ulcer disease, was prescribed rofecoxib 25 mg a

day for sciatic neuralgia. Five days later she presented to the emergency room via ambulance with diaphoresis, weakness, and hypotension. The diagnosis on admission was septic or cardiogenic shock. An exploratory laparotomy revealed a perforated duodenal ulcer. Two liters of dark grayish fluid were removed from the peritoneal cavity, and the perforated ulcer was repaired. The patient was transferred to the post-anesthesia care unit on vasopressor support with a blood pressure of 80/30 mm Hg, a heart rate of 60 beats per minute, and respiratory rate of 13 per minute. She went into cardiac arrest and died despite attempts to resuscitate her.

AERS 3424661, WAES 00010945, US (SC), 2000

An 85-year-old man with a history of atrial fibrillation, and an unspecified vascular disorder was prescribed rofecoxib to treat back pain. Concomitant medications included clopidogril and warfarin. Six days later the patient was hospitalized with unspecified gastrointestinal bleeding confirmed by endoscopy. On admission, the patient's hemoglobin was 5-7 g/dL. Rofecoxib and warfarin were discontinued. Vitamin K and 4 units of packed red blood cells were administered, and the patient stabilized. However, 3 days later the patient developed an arrhythmia and died suddenly. The attending physician believed the patient might have had a cerebrovascular accident caused by discontinuation of warfarin.

CONCLUSION

We evaluated 82 deaths from gastrointestinal bleeding, obstruction, perforation, or stenosis in the AERS database temporally related to therapy with etodolac, celecoxib, or rofecoxib. The patients in the case series were mostly high-risk elderly patients. In 56% (5/9) of the etodolac cases, 83% (30/36) of the celecoxib cases, and 70% (26/37) of the rofecoxib cases the patients were at increased risk of bleeding or having a poor outcome with a bleed because of past medical history, a recent major systemic medical event, or concomitant medication. Many patients had more than one risk factor. Eleven of the patients taking celecoxib had a past medical history of peptic ulcer disease, and 6 of these patients had experienced gastrointestinal bleeding in the past. Four patients taking rofecoxib had a past medical history of peptic ulcer disease, and one of these patients had experienced gastrointestinal bleeding in the past. Thirteen (36%) of the patients taking celecoxib and 13 (35%) of the patients taking rofecoxib were taking aspirin or warfarin concomitantly. Twelve patients, 16% of the cases in the celecoxib and rofecoxib series, bled and died despite taking a gastrointestinal-protectant drug concomitantly.

We conclude that the labeling for celecoxib and rofecoxib reflect the risk of fatal gastrointestinal bleeding, obstruction, perforation, and stenosis observed in the postmarketing experience.

Signed 12-29-00 by

Joyce Weaver, Pharm.D., Safety Evaluator

Concur:

Signed 12-29-00 by

Claudia B. Karwoski, Pharm.D., Team Leader

Attachment 1. Summary Data—Domestic Cases of Fatal Gastrointestinal Bleeding, Perforation, Obstruction, or Stenosis

Drug	Lodine (Etodolac)
Total cases	9
Mean age	79
Median age	78
range	69 – 94
Gender	M—5 F—3 Unk—1
Event date	1991—2 1992—4 1993—1 1994—1 1996—1
Indication	Osteoarthritis—2 Gouty arthritis—1 Unknown—6
Mean onset	35.7 days
Median onset	30 days
range	17 – 60 days (Onset data available for 3 cases)
Dose at or below labeled range	Yes—3 Unk—6
GI event [†]	Hemorrhage—6 Perforation—2 Melena—1 Hematemesis—1 Stenosis/obstr—1
Location of GI event	Esophageal—1 Gastric—2 Duodenal—1 Large intestine—1 Unknown—4
Mean nadir Hgb and Hct	Hgb 5.8 Hct 16.6 (Info from 1 case)
Concomitant NSAID	
Concomitant warfarin	1
Concomitant corticosteroid	
Concomitant antiplatelet	
Concomitant ASA	
Concomitant alendronate	
ETOH use	
Smoker	
Pertinent PMH [†]	Diabetic gastroparesis (1) Bowel obstruction (1) CAD (3)
Major systemic illness preceding bleed [†]	CABG (1)
Concomitant H2 blocker, antacid, or PPI	
Bleeding other than GI	
Diagnosis confirmed by diagnostic procedure	4 Surgery (2) CT scan (1) EGD (1)
Pos Dechallenge	

Drug	Lodine (Etodolac)
Pos Rechallenge	
Reviewer impression of quality of report	Good—0 Adequate—2 Poor—7

† more than one possible per case

Drug	Celebrex (Celecoxib)
Total cases	36
Mean age Median age range	77 78.5 46 – 99
Gender	M—12 F— 22 Unk—2
Event date	1999—30 2000—6
Indication	RA—4 Osteoarthritis—12 Acute pain— 3 Unspecified arthritis—3 Other—5 Unknown—9
Mean onset Median onset range	25.7 days 14 days 1 – 115 days
Dose at or below labeled range	Yes—18 No—2 Unk—16
GI event [†]	Hemorrhage—22 Perforation—2 Melena—8 Hematemesis—10
Location of GI event	Gastric—3 Duodenal—5 Rectal—2 Small intestine—1 Unknown—25
Mean nadir Hgb and Hct	Hgb 8 (range, 6 – 10.8) Hct 26.1 (range, 20.1 – 31.8)
Concomitant NSAID	4 Ibuprofen (1) Nabumetone (2) Naproxen (1)
Concomitant warfarin	5
Concomitant corticosteroid	5
Concomitant antiplatelet	
Concomitant ASA	8 80 mg—1 325 mg—1 Yes, dose unk—6
Concomitant alendronate	1
ETOH use	Never—2 Past or current—6
Smoker	Never—2 Past—1 Current—2
Pertinent PMH [†]	Alcoholism (3) Anemia (5) CAD (7) Cirrhosis (1) CVA (1) Diabetes (6) Diverticulitis (1) Esophageal varices (1) Factor V def (1)

Drug	Celebrex (Celecoxib)
	Gastrectomy (1) Gastritis (2) GI AVM (2) Hx PUD (11) Hx GI bleed (6) Malignancy (4) Thrombocytopenia (1)
Major systemic illness preceding bleed†	12 Liver failure (2) Metastatic ca (2) Multiple myeloma (1) Recent surgery (2) Recent admission for CP & anemia (1) Exacerbation of asthma, inc in steroid dose (1) Pneumonia (1) TEN (1) Pancreatitis (1)
Concomitant H2 blocker, antacid, or PPI	8
Bleeding other than GI	1
Diagnosis confirmed by diagnostic procedure	11 CT scan (1) EGD (6) Flex sig (1) Surgery (2) Autopsy (1)
Pos Dechallenge	1
Pos Rechallenge	1
Reviewer impression of quality of report	Good—3 Adequate—24 Poor—9

† more than one possible per case

Drug	Vioxx (Rofecoxib)
Total cases	37
Mean age Median age range	76 80 28 – 93
Gender	M—14 F—22 Unk—1
Event date	1999—3 2000—34
Indication	Osteoarthritis—14 Acute pain—6 Unspecified arthritis—6 Other—6 Unknown—5
Mean onset Median onset range	43 days 21 days 0 – 131 days
Dose at or below labeled range	Yes—24 No—1 Unk—12
GI event [†]	Hemorrhage—23 Perforation—7 Melena—4 Hematemesis—6 Erosions—1 Stenosis/obstr—1 Other—10
Location of GI event	Gastric—13 Duodenal—5 Large intestine—2 Other—2 Unknown—15
Mean nadir Hgb and Hct	Hgb 8.7 (range, 6 – 13.8) Hct 18 & 29.6 (Hct values reported in 2 cases)
Concomitant NSAID	
Concomitant warfarin	6
Concomitant corticosteroid	2
Concomitant antiplatelet	2 (clopidogril)
Concomitant ASA	8 80 mg—2 325 mg—1 Yes, dose unk—5
Concomitant alendronate	
ETOH use	Never—3 Past or current—2
Smoker	Never—2 Past—2
Pertinent PMH [†]	Anemia (1) ASA, sulfa allergy (2) Crohn's disease (1) CVA (1) Diabetes (1) Diverticulitis (1) Functional intestinal disorder (1) Gastrostomy (1)

Drug	Vioxx (Rofecoxib)
	Irritable bowel syndrome (1) Hepatic dysfunction (1) Hx PUD (4) Hx GI bleed (1)
Major systemic illness preceding bleed [†]	6 Metastatic gastric cancer (1) Pancreatitis, hepatitis (1) Shock (1) Recent surgery (3)
Concomitant H2 blocker, antacid, or PPI	4
Bleeding other than GI	2
Diagnosis confirmed by diagnostic procedure	18 EGD (5) Surgery (4) Autopsy (4) GI series X-ray (2) Not specified (3)
Pos Dechallenge	2
Pos Rechallenge	
Reviewer impression of quality of report	Good—6 Adequate—13 Poor—18

[†] more than one possible per case