

MEMORANDUM

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

DATE: April 17, 2002

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SUBJECT: Office of Drug Safety Postmarketing Safety Review (PID # D020154)
Drugs—Over-the-counter nonsteroidal anti-inflammatory drugs:
ibuprofen (numerous NDAs)
ketoprofen (NDA# N020429)
naproxen (NDA# N020204, N021076, N018164)
Reaction: Gastrointestinal hemorrhage, ulceration, or perforation

INTRODUCTION/ EXECUTIVE SUMMARY

Gastrointestinal (GI) toxicity is a major limiting factor for the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Risk factors have been identified that increase the risk of GI complications. These factors include age over 65 years, prior GI ulcer or bleeding, use of high doses or multiple NSAIDs, concomitant use of corticosteroids, concomitant use of anticoagulants, consumption of ethanol, cigarette smoking, presence of *Helicobacter pylori*, and serious systemic disease.^{1,2,3} However, no subgroup of patients is totally free of risk of NSAID-associated GI injury. Events resulting in morbidity and mortality occur in patients without apparent risk factors. Epidemiological studies have established that the incidence of significant GI complication (bleeding, perforation or obstruction) among patients on chronic NSAID therapy is 1-4% per year.³ However, when NSAID-induced GI injury occurs, it often occurs early in the course of NSAID therapy.²

Our objective was to review the recent postmarketing experience of over-the-counter (OTC) ibuprofen, ketoprofen, and naproxen relating to GI hemorrhage, ulceration, or perforation to determine the circumstances that may result in these events. We limited our review to events reported to the FDA from January 1, 1998 through December 31, 2001.

We reviewed 105 cases of GI hemorrhage, ulceration, or perforation reported for OTC ibuprofen, 3 cases for ketoprofen, and 89 cases for naproxen. Most of the reports did not contain complete information about the patients' prior medical history, medication use,

and course of the GI complication. Most patients were adults using an OTC NSAID to treat musculoskeletal pain (including the pain of arthritis), unspecified pain, and “aches and pains.” Most of the patients used daily doses of the NSAID at or below the maximum dose recommended in the OTC labeling. However, about 67% of the patients may have been at increased risk of GI bleeding because they had one or more of the risk factors listed above. Most of the patients were hospitalized and then subsequently recovered; however, ten patients in the case series died.

DRUG INFORMATION/LABELING

NSAIDs are available OTC for the temporary relief of headache, muscular aches, the minor pain of arthritis, toothache, backache, minor aches and pains associated with the common cold, the pain of menstrual cramps, and for reduction of fever. Ibuprofen is available OTC for use in pediatric patients 6 months of age and older for the temporary relief of fever and minor aches and pains due to the common cold, flu, sore throat, headaches and toothaches. Ketoprofen and naproxen are not approved for use in pediatric patients younger than 12 years of age.

Ibuprofen is available OTC generically and under several brand names, including Advil®, Motrin®, and Nuprin®. Ibuprofen is available in 100-mg and 200-mg tablets, 200-mg capsules, 50-mg and 100-mg chewable tablets, and 20-mg/mL and 40-mg/mL suspensions. Ibuprofen 200 mg is also available OTC in combination with pseudoephedrine 30 mg in a tablet. Ketoprofen is available in 12.5-mg tablets under the brand name Orudis-KT®. Naproxen is available OTC generically and under the brand name Aleve® in 200-mg (naproxen) or 220-mg (naproxen sodium). Naproxen 200 mg is also available OTC in combination with pseudoephedrine 120 mg in a tablet.

The OTC NSAID labeling contains a warning about the concomitant use of ethanol.

Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take naproxen sodium or other pain relievers/fever reducers. [NSAID brand name] may cause stomach bleeding.

The OTC NSAID labeling contains a warning regarding use with other analgesics/antipyretics, and all contain a warning regarding the length of time the OTC NSAID should be used. The following excerpt is contained in the labeling for Aleve®.

Do not use:

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- with any other pain reliever/fever reducer
- for more than 10 days for pain
- for more than 3 days for fever

The OTC NSAID labeling contains a warning regarding use by patients with medical conditions and by patients using other medications. This warning is general in nature, and does not specifically address the risk factors listed above. The following excerpt is contained in the labeling for Aleve®.

Ask a doctor before use if:

- the painful area is red or swollen
- you take other drugs on a regular basis
- you are under a doctor's care for any continuing condition
- you have had serious side effects from any pain reliever

The OTC NSAID labeling contains warnings regarding when to stop using the NSAID and seek medical attention. The following excerpt is contained in the labeling for Aleve®.

Stop use and ask a doctor if:

- an allergic reaction occurs, seek medical help right away
- any new or unexpected symptoms occur
- symptoms continue or worsen
- you have difficulty swallowing
- it feels like the pill is stuck in your throat
- you develop heartburn
- stomach pain occurs with use of this product or if even mild symptoms persist

The maximum OTC daily doses for the NSAIDS are listed below:

- ibuprofen—1200 mg;
- ketoprofen—75 mg; and
- naproxen sodium—660 mg.

SELECTION OF CASE SERIES

On March 11, 2002, we searched the AERS database for domestic cases of GI hemorrhage, ulceration, or perforation related to use of OTC ibuprofen, naproxen, and ketoprofen. The cases were identified using the higher level group terms (HLGTs) *Gastrointestinal Haemorrhages NEC*, and *Gastrointestinal Ulceration and Perforation*. We searched for cases received by the FDA from January 1, 1998 through December 31, 2001.

AERS contained 368 cases for ibuprofen, 22 cases for ketoprofen, and 315 cases for naproxen. We screened the cases to determine whether the use of ibuprofen was prescribed or self-administered using an OTC product. Cases were excluded if the use of the suspect product was by prescription, or if it could not be determined whether or not the use was by prescription. In reports in which the type of use was not stated, OTC use was assumed if an OTC product was used. Additionally, duplicate cases were combined. The following summarizes the exclusion and inclusion criteria.

Cases excluded from case series:

- Cases reported for patients using a prescription product as the suspect product
- Cases containing no strength or product name to allow identification of OTC use
- Duplicate cases
- Acute intentional overdoses
- Non-US cases

Cases included in case series:

- Cases reporting use of an OTC product as a suspect agent, such as
Advil®
Aleve®
Ibuprofen 200 mg
Motrin® 200 mg
Naproxen 200mg
Naproxen sodium 220mg
Nuprin®
Orudis® 12.5mg
Orudis KT®
- Cases reporting GI events that were temporally related to the use of these products
- Acute unintentional overdoses
- US cases

Two hundred sixty-three cases for ibuprofen, 225 cases for naproxen and 19 cases for ketoprofen were excluded from review for the reasons listed above. Ultimately, we included 105 cases for ibuprofen, 89 cases for naproxen and 3 cases for ketoprofen in this case series. In reviewing the cases, we defined “acute use” as use of the drug 7 days or less, and “chronic use” as use exceeding 7 days.

SUMMARY OF CASES

Ibuprofen

One hundred five cases of GI bleeding in connection with OTC ibuprofen were reported to AERS between January 1, 1998 and December 31, 2001. The mean age of the patients was 55.9 years. Seven patients experiencing GI bleeding were younger than 16 years of age (range, 1 to 15). Fifty-five percent (52/94) of the patients were male. Ibuprofen was used most often to treat the pain of arthritis (18), unspecified pain, or “aches and pains” (17), back, neck, or shoulder pain (12), fever (10), headache (9), and hip, knee, ankle, foot, and unspecified joint pain (8). The time to onset ranged from less than 1 day (after one dose) to 10 years, with a median time to onset of 7 days. The median daily dose was 800 mg. The patients recovered after discontinuation of ibuprofen in 57 cases (positive dechallenge); in 25 of these cases additional treatment (histamine H₂-receptor antagonists, proton pump inhibitors [PPIs], blood transfusions, surgery, or endoscopic cauterization) was administered in addition to discontinuing the ibuprofen.

Demographic data, outcomes, and some summary information from the 105 cases are provided below.

Age in years (n=90)	Mean-55.9, median-56, range 1 to 99
Gender	Male-52, Female-42, Unknown-11
Indication*	Unspecified pain, “aches and pains”-17

	Back, neck, or shoulder pain-12 Arthritis, type not specified-10 Fever-10 Headache-9 Hip, knee, ankle, foot, unspecified joint pain-8 Osteoarthritis-8 Flu symptoms-3 Dental pain-2 Migraine headache-2 Unspecified injury-1 Allergies-1 Osteoporotic pain-1 Pain associated with below-the-knee amputation-1 Prophylaxis prior to athletic practice-1 Stomach pain-1 Unknown-18
Time to onset (n=50)	Median-7 days (range, 1 dose to 10 years)
Acute vs chronic use (use 1 week or less vs use longer than 1 week)	Acute-29; chronic-32; intermittent-1; unknown-43
Daily dose (adult patients; n=59)	Mean-964 mg; median-800 mg (range 200-3000 mg) Daily dose > 1200 mg-16 cases
Report type	Direct-64; Periodic-21; Expedited-19; unk-1
Reporter	Healthcare practitioner-83 Consumer-17 Attorney-2 Unknown-3
Dechallenge	Positive dechallenge-57 (25/57 treated with H ₂ -blockers, PPI, blood, surgery, or cauterization in addition to discontinuing ibuprofen)
Serious Outcomes*	Death-5; hospitalization-79; life-threatening-12
*more than 1/case possible	

Most of the patients were hospitalized and then subsequently recovered. Five patients died. Daily dose was known in two of the cases resulting in death (1200 and 2400 mg). Two of the five patients who died had known risk factors. One was a 39-year-old alcoholic man who took ibuprofen 2400 mg daily to treat chronic low back pain. In addition, he took an unknown dose of aspirin daily. Another patient who died smoked an unknown number of cigarettes daily. Brief summaries of the five patients who died are presented in Attachment 1.

Sixteen patients were taking daily doses in excess of the maximum OTC labeled dose (1200 mg). There is no indication in the reports for these cases that a healthcare practitioner had suggested using a dose higher than the labeled OTC dose. One patient

was taking 3000 mg a day, a dose exceeding the labeled prescription dose for all indications except for rheumatoid arthritis (3200 mg). Seventy-one of the patients either used doses higher than labeled OTC doses (16), had a significant GI medical history (15), had significant non-GI medical histories or intercurrent illnesses (21), had a history of smoking or drinking that may have increased risk (19), used a medication concomitantly that may have increased their risk for a GI bleed (39), or were 65 years of age or older (37). Thirty-nine patients had more than one risk factor. In 32% of the cases (34/105) no risk factors are apparent in the cases except for the use of ibuprofen at or below the labeled OTC dose. Eight patients bled despite receiving a GI protectant medication concomitantly (H₂-blocker-6, PPI-2).

The table below shows the significant medical histories, social histories, and concomitant medications of the patients in the case series.

Significant GI medical history*	Previous GI ulceration-10 Previous GI bleed-6 Esophageal varices-2 Mallory-Weiss tear-1 <i>H. pylori</i> +-4
Significant social history*	ETOH abuse-9 Moderate ETOH use-3 Unspecified ETOH use-4 Tobacco (smoking) use-6
Concomitant medications possibly contributing to bleed*	Aspirin-20 COX-2 inhibitor-6 Other prescription NSAID-3 OTC NSAID-3 NSAID, OTC/Rx not specified-3 Warfarin-4 Clopidogrel-2 Heparin-1 Corticosteroids-3 Alendronate-1 TPa-1
Significant intercurrent illness or prior medical history*	Acute renal failure-1 Advanced small cell lung cancer-1 Anemia-4 Cerebrovascular accident-2 Cirrhosis-3 Congestive heart failure-3 Coronary artery disease-4 Diabetes mellitus-5 Systemic lupus erythematosus-1 Pancytopenia-1
Other	Age ≥ 65 years-37

	Dose > 1200 mg daily-16
*more than 1/case possible	

In one-half of the cases, the site of the GI bleed was not reported. In most of the cases in which the site of the GI bleed was known, the bleeding occurred in the stomach. In 40 cases, the report stated a study, most often esophagogastroduodenoscopy (EGD), was done to confirm the diagnosis.

Table 3. Location of GI Bleed and GI Studies Conducted	
Location of GI event* (n=52)	Stomach-28 Duodenum-11 Unspecified upper GI bleed-10 Esophagus-3 Colon-1 Unspecified lower GI bleed-1 Unknown-53
Study confirming diagnosis (n=40)	EGD-27 Surgery-4 Colonoscopy-2 Upper GI series-2 Autopsy-1 CT scan-1 Unspecified study-3
*more than 1/case possible	

Two representative cases are presented below.

AERS ISR # 3057641-5, 1998, Direct report

An 88-year-old woman presented to a hospital emergency room with bleeding from her rectum after using 400 to 600 mg of ibuprofen daily for one to two months to treat arthritis pain. She had a history of a previous gastric antral ulcer, insulin-dependent diabetes, chronic atrial fibrillation, and recent respiratory and urinary tract infections. Her hemoglobin on admission was 6.3 g/dL. She was treated with vitamin K, iron, epoetin alfa, and an H₂-receptor antagonist. The site of the bleeding was not determined. The woman was discharged after 8 days of hospitalization.

AERS ISR # 3507379-3, 2000, Direct report

A 36-year-old woman was hospitalized with a gastric ulcer after using aspirin and ibuprofen for 5 years to treat migraine headaches. The patient had increased her intake of aspirin and ibuprofen for a short, unspecified, period of time prior to admission. The patient's hemoglobin on admission was 4.4 g/dL. Endoscopy showed a 1.2-cm prepyloric ulcer. She was treated with omeprazole and 4 units of packed red blood cells. She was discharged after 2 days.

Ketoprofen

There were three cases of GI bleeding temporally associated with the use of an OTC ketoprofen product (Orudis-KT® or ketoprofen-OTC). Two patients were females and one patient was male. One patient was 76 years old and the age was unknown in the other two cases. One patient reported using the drug “as directed” for non-specified pain. The second used an unknown dose of ketoprofen for minor arthritic pain. The third patient did not report the dose, duration or the indication. The onset of event from the start of ketoprofen use was several days (unspecified) in one patient, 3 years in the second patient, and unknown in the third patient. The patients presented with one or more of the following symptoms: coffee ground emesis, epigastric pain, flank pain, abdominal cramping and rectal bleeding after starting ketoprofen.

The location of the GI bleed was reported in all cases (gastric-1; gastric/colon-1; rectum-1). One patient who presented with coffee ground emesis and epigastric pain had a positive EGD study confirming gastric ulcers and Barrett’s esophagus (peptic ulcer of lower esophagus). A second patient who presented with rectal bleeding and flank pain underwent colon resection and the pathology report stated that “the resected colonic segment shows necrotizing ulcerative lesions of rather nonspecific character. Such lesions have been described in association with non-steroidal anti-inflammatory drugs, as this patient has been reported to have taken”. The patient used ketoprofen as instructed on the product label for several days (exact duration and exact dose were unspecified). The third patient who presented with abdominal cramping and rectal bleeding had a h/o diverticulitis. Other than one patient being >65 years of age, none of the patients reported known risk factors for GI bleeding such as concurrent aspirin, NSAID, warfarin or prednisone use. All three cases were medically serious resulting in hospitalization. There were no fatalities.

Naproxen

There were 89 cases of GI hemorrhage that were temporally associated with the use of OTC naproxen products. In 73 of the cases, OTC naproxen was the primary suspect agent. In the remaining 16 cases, OTC naproxen was a co-suspect agent. There were 46 females and 38 males (gender unknown in 5 cases). The average age of the patients was 62 years. Thirty-one patients used naproxen 7 days or less (acute use), 33 patients used the drug longer than 7 days (chronic use), 3 used the drug intermittently, and the duration was unknown in 22 cases. The median time to onset from start of naproxen therapy to the GI bleed was 7 days. The patients recovered after discontinuation of naproxen in 53 cases (positive dechallenge). Sixty-eight percent (36/53) received H₂-blockers, PPI, blood transfusion or surgery in addition to discontinuing naproxen.

Demographic data, outcomes, and some summary information from the 89 cases are provided below.

Age in years (n=80)	Mean-62, median-68, range 23 to 87
Gender	Male-38, Female-46, Unknown-5
Indication*	Unspecified pain, "aches and pains"-37 Arthritis, type not specified-11 Hip, knee pain-5 Back pain-3 Cancer pain-1 Headache-3 Dental pain-2 Osteoarthritis-2 Fever-1 Flu symptoms-1 Migraine headache-1 Nerve pain-1 Sleep aid-1 Stomach pain-1 Unknown-20
Time to onset (n=51)	Median-7 days (range, 1 dose to 2 years)
Acute vs. chronic use	Acute-31; chronic-33; intermittent-3; unknown-22
Daily dose (n=59)	Daily dose: 200 to 600 mg-48 Daily dose > 600 mg-11
Report type	Direct-35; Periodic-31; Expedited-23
Reporter	Healthcare practitioner-42; Consumer-46; Attorney-1
Dechallenge	Positive dechallenge-53 (36 /53 treated with H ₂ -blockers, PPI, blood transfusion, and surgery in addition to discontinuing naproxen)
Serious Outcomes*	Death-5; hospitalization-62; life-threatening-1
*more than 1/case possible	

Sixty-two patients were hospitalized. Five patients died, and one additional case was categorized as life-threatening by the reporter. In the remaining cases, the outcome was unspecified.

The five cases resulting in death involved 4 males and 1 female aged 36, 42, 67, 81, and 81 years. Duration of therapy in cases resulting in death ranged from 15 to 30 days. Acetaminophen, ketoprofen, lorazepam, and coumadin were the primary suspect medications in four of the deaths. Naproxen was the primary suspect in one death. Known risk factors for GI bleeding were apparent in four of the five death cases and include advanced age, multiple NSAIDs, serious systemic disorder (renal failure), and use of an anticoagulant. One patient developed a GI bleed possibly as a result of coagulopathy associated with acetaminophen-induced hepatic failure, which was the primary adverse event. NSAID induced GI bleed may have directly or indirectly lead to death in the other four patients. Brief summaries of the five patients who died are presented in Attachment 2.

Sixty of the 89 patients had one or more known risk factors. Ten patients had a significant GI history including previous GI bleeding, or ulcer. Eight patients had serious pre-existing systemic illness (diabetes mellitus, myocardial infarction, cirrhosis, chronic renal insufficiency, and chronic myelogenous leukemia). Thirty percent (27/89) of the patients used one or more of the following agents concomitantly that might have contributed to the GI event: NSAIDs (celecoxib-1, etodolac-1, ibuprofen-3, meloxicam-1 and rofecoxib-2), aspirin (11), warfarin (8) or prednisone (3). Eight patients had a history of smoking or drinking that may have increased risk. Three patients reported more than one concomitant drug. About one-third of the patients had used naproxen 7 days or less before experiencing GI hemorrhage. Dosing information was available in 59 cases; in 80% of these cases patients used a recommended OTC dose. In 32% of the cases (29/89) no risk factors are apparent in the cases except for the use of naproxen at or below the labeled OTC dose. Seven patients bled despite receiving a concomitant GI protective medication (H₂-blocker-2, PPI-5).

The table below shows the significant GI medical histories, social histories, and concomitant medications of the patients in the case series.

Table 5. Potential Risk Factors Identified in 60 Naproxen Cases	
Significant GI medical history	Previous GI ulceration-5 Previous GI bleed-4 Esophageal varices-1
Other pertinent medical history*	Diabetes mellitus-3 Chronic renal insufficiency-1 Cirrhosis/liver disorder-2 Chronic myelogenous leukemia; s/p stem cell transplant-1 Myocardial infarction-1
Significant social history*	Alcohol consumption-7 Cigarette smoking-6
Concomitant medications possibly contributing to bleed	Aspirin-11 Warfarin-8 Other NSAIDs-5 COX-2 inhibitor-3 Corticosteroids-3
Other	Age ≥ 65 years-48 Dose > labeled OTC dose-11
*more than 1/case possible	

In 49 cases the site of the GI bleeding was not specified. In most of the cases in which the site of the GI bleed was known, the bleeding occurred in the stomach. In 36 cases upper GI bleeding was reported, and in 7 cases lower GI bleeding was reported. Most cases reported only one site of GI hemorrhage.

In 31 cases, the diagnosis was confirmed with positive EGD, colonoscopy, sigmoidoscopy, or autopsy.

The locations of the bleeding, the GI events, and the studies used to confirm the diagnosis are presented in the table below.

Table 6. Location of GI Bleed and GI Studies Conducted	
Location of GI event* (n=40)	Gastric-21 Duodenum-8 Esophagus-7 Small bowel-1 Colon-2 Rectal-4
Study confirming diagnosis (n=31)	EGD-23 Colonoscopy-6 Sigmoidoscopy-1 Autopsy-1
*more than 1/case possible	

Two representative cases are presented below:

AERS ISR # 3475354-3, 2000, Periodic report

A 69-year-old male with a h/o back pain and arthritis took 1-2 tablets of naproxen sodium daily for 5 days to treat sciatic pain. Concomitant medications included amlodipine, losartan potassium and hydrochlorothiazide (Hyzaar®), and pravastatin. Six days after starting naproxen sodium, he passed a bloody stool. On admission, his hemoglobin was 7.8 g/dL. Endoscopy revealed esophageal and stomach ulcers. He was transfused with 6 units of blood and treated with lansoprazole. The patient recovered and he was discharged after 5 days.

AERS ISR# 3694936-7, 2000, Periodic report

An 88-year-old female with a h/o HTN and MI took one naproxen sodium tablet twice daily for 52 days to treat shoulder pain. She took atenolol concomitantly. Approximately 2 months later, she developed melena and stomach pain. After 6 days of hospitalization, she recovered, and she was told that naproxen was responsible for the problem.

CONCLUSION

We reviewed 197 domestic cases of GI hemorrhage, ulceration, or perforation reported for OTC NSAIDs from January 1, 1998 through December 31, 2001. This included 105 cases reported for ibuprofen, 3 cases reported for ketoprofen, and 89 cases reported for naproxen. Most of the patients were hospitalized and then subsequently recovered. About 5% (10/197) of the patients in the case series died. Most patients were adults using an OTC NSAID to treat musculoskeletal pain, unspecified pain, and “aches and pains.” Most of the patients used daily doses of the NSAID at or below the maximum dose recommended in the OTC labeling.

Many patients were at increased risk for GI bleeding because of a past GI event, other significant intercurrent illness or past medical history, consumption of ethanol, tobacco use, or use of another OTC or prescription medication concomitantly that can increase risk of GI bleeding. In about 37% (72/197) of the cases, more than one risk factor was present. This suggests that some patients who should not use an OTC NSAID because they are at increased risk of GI complications are using these products and experiencing serious adverse events.

The product labeling advises patients to consult a healthcare practitioner if they are under a doctor's care for any condition, and if they are taking any other drugs. Although this addresses some of the risk factors, the labeling addresses most risk factors in an oblique, general manner. Only ethanol use is addressed in a direct manner in the OTC labeling. The OTC consumer is not fully informed of the risk factors from the OTC labeling; however, it is not known if providing more specific information in the OTC labeling would reduce the OTC use of these drugs in high-risk patients.

It should be noted that in 33% of the cases no risk factors are apparent in the cases except for the use of the NSAID, and there is no suggestion in the report that the NSAID was used in doses in excess of the OTC labeling. These data support the conclusions that no subgroup of patients is completely free of the risk of NSAID-induced injury.

References:

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Attachment 1—Ibuprofen-induced GI Hemorrhage Cases Resulting in Death

1. AERS ISR # 3778270-2, 2001, Direct report

A 94-year-old patient of unknown gender with COPD died after experiencing a GI bleed. Concomitant medications, additional prior medical history, dose of ibuprofen, and the course of the patient's illness were not reported.

2. AERS ISR # 3825072-4, 2001, Periodic report

An 82-year-old woman with a prior medical history of hypertension, chronic renal failure, angina, renal artery stenosis, mild congestive heart failure, and gout osteoarthritis experienced a GI bleed after taking 1200 mg of ibuprofen daily for 10 days to treat flu-related aches and pains. Concomitant medications were unknown. Her hemoglobin on admission was 6.5 g/dL. She was transfused with four units of blood, and she was treated with a PPI. An EGD showed hemorrhagic duodenitis. She experienced melena, and her hemoglobin dropped to 5.8 g/dL. She went into shock and died despite receiving additional transfusions of blood products and inotropic support.

3. AERS ISR # 3029915-6, 1998, Expedited report

An attorney reported that a man of unknown age was hospitalized and died after experiencing gastric ulcers and GI bleeding. He had received an unknown dose of ibuprofen for an unknown period of time to treat an unspecified injury. Concomitant medications, additional prior medical history, and the course of the patient's illness were not reported.

4. AERS ISR # 3749073-X, 2001, Expedited report

A 39-year-old alcoholic man took ibuprofen 2400 mg daily to treat chronic low back pain. In addition, he took an unknown dose of aspirin daily. Concomitant medications included famotidine, calcium carbonate, magnesium carbonate, and magnesium trisilicate (Tums®), and aspirin. The day after admission, the patient went into respiratory arrest. He was stabilized and underwent emergency exploratory surgery. A right retroperitoneal hematoma extending from the duodenum to the pelvis was discovered. Additional exploration was not performed. After return to the ICU, multi-organ system and bleeding from the mouth and anus occurred. The patient died despite receiving many units of platelets, blood, and fresh frozen plasma.

5. AERS ISR # 3581490-3, 2000, Direct report

A 40-year-old woman left work complaining of flu-like symptoms. She smoked an unknown number of cigarettes daily. Two days later the woman was found dead at home surrounded by coffee-ground emesis. She had used ibuprofen for an unknown

indication for at least 2 years. She used famotidine concomitantly. An autopsy concluded that she died of acute peritonitis from a perforated duodenal ulcer, and vomitus aspiration.

Attachment 2 — Naproxen-induced GI Hemorrhage Cases Resulting in Death

1. AERS ISR # 3414568-5, 1999, Expedited report

A 42-year-old male with a prior history of alcoholic cirrhosis (portocaval shunt in 1996), intractable ascites, thrombocytopenia, convulsions, depression, tobacco use and constipation experienced GI bleeding after taking naproxen sodium 400 mg to 1320 mg daily for 2 to 4 weeks. Concomitant medications included lactulose, spironolactone, fluoxetine, trazodone, phenytoin and aspirin. Within a month of using naproxen sodium, he developed severe abdominal pain and diagnosed with perforated duodenal ulcer and underwent emergency surgery to repair the perforation. Following an unremarkable hospital course for several days, he developed MRSA pneumonia, ARDS, and multiorgan failure, and he died. The cause of death was hepatorenal syndrome due to ARDS following a repair of perforated duodenal ulcer.

2. AERS ISR # 3458030-2, 2000, Direct report

An 81-year-old female with a h/o lorazepam, beta-blocker allergy and NSAID gastritis was admitted with melena, coffee ground emesis and acute renal insufficiency after receiving OTC naproxen and ibuprofen for 3-4 weeks. Concomitant medications include calcium supplements, quinidine, quinapril, digoxin, furosemide, potassium supplement, intranasal fluticasone, inhaled fluticasone, theophylline, iron, propoxyphene and acetaminophen (Darvocet®), clonazepam, albuterol, ipratropium, and prednisolone eye drops. Prior to the EGD, she received lorazepam (the allergy was not well documented in the chart) for agitation. Subsequently, the patient's oxygen saturation dropped, and she developed a decreased level of consciousness. Despite the adverse reaction to lorazepam, the EGD was performed. It was positive for a deep gastric ulcer. The patient's GI bleeding slowly improved, but her condition worsened. Ultimately, she developed respiratory failure and died.

3. AERS ISR # 3243548-8, 1999, Direct report

A 67-year-old female with history of COPD, smoking, pulmonary hypertension, hypertension and morbid obesity received naproxen sodium (unknown dose), ketoprofen 200 mg, and acetaminophen (unknown dose and duration) for chronic back pain for about one month. She was brought to the ER with increased shortness of breath, fever, hyperkalemia (5.8), weakness, renal failure (BUN/SrCr: 75/4.9), chills and productive cough. Her medications included potassium, ipratropium, inhaled fluticasone, theophylline, atenolol, amlodipine, alprazolam and a diuretic. A CT of abdomen showed perforated sigmoid diverticulum. She was admitted to an ICU to stabilize the patient for surgery, but she became combative and confused. Despite receiving antibiotics, vasopressors, urgent dialysis, and cardiac support, she developed an arrhythmia, and she died.

4. AERS ISR # 3130899-0, 1998, Direct report

An 81-year-old male presented to the ER with hemoptysis and hypotension after receiving coumadin (unknown dose and duration) for atrial fibrillation and OTC naproxen for 2 weeks for knee pain. Past medical history was significant for CHF, COPD, and atrial fibrillation. Concomitant medications were digoxin and furosemide. Patient declined EGD on admission. The laboratory values were: hemoglobin-8, hematocrit-26, INR-5.1, PTT-39, digoxin-1.3. His stools were heme-positive. Despite receiving fluids, fresh frozen plasma, packed red blood cells, and vitamin K, the patient expired. An autopsy result revealed massive GI mucosal hemorrhage.

5. AERS ISR # 3806866-8, 2001, Expedited report

A 36-year-old woman ingested 32 acetaminophen 500 mg and 10 naproxen 220 mg tablets over 23 hours for tooth pain. She complained of abdominal pain on presentation and was treated with N-acetylcysteine. Initial laboratory findings were: APAP-83.2mcg/ml, AST-540 U/L, ALT-3,415 U/L; total bilirubin-18 mg/dl; and PT greater than 100 seconds. Complications included GI bleeding and hypotension. Transaminases peaked at an AST of 19,000 U/L and an ALT of 8,000 U/L. The patient expired five days after the ingestion. The autopsy revealed hepatic necrosis due to acetaminophen.