

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

**DATE:** July 15, 2002

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**SUBJECT:** Office of Drug Safety Postmarketing Safety Review (PID # D020293)  
Drugs—Aspirin-Containing Products  
Reaction: Gastrointestinal hemorrhage, ulceration, or perforation

**INTRODUCTION/ EXECUTIVE SUMMARY**

Gastrointestinal (GI) toxicity is a major limiting factor for the use of products containing aspirin. Aside from its analgesic, anti-inflammatory, and antipyretic properties, aspirin has a number of vascular indications.<sup>1</sup> A review of randomized trials of aspirin found that GI toxicity was dose related, nonetheless trials of low-dose aspirin therapy have also shown a possible increased risk of GI bleeding.<sup>2-5</sup> 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.<sup>6-8</sup>

Our objective was to review the recent postmarketing experience of aspirin-containing products 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 541 cases of GI hemorrhage, ulceration, or perforation reported for aspirin-containing products. 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 aspirin product for cardiac or cerebrovascular indications. Most of the patients were taking aspirin at doses of less than or equal to 325mg per day. However, about 90% of the patients may have been at increased risk of GI bleeding because they had one or more of the risk factors listed above. The most significant risk

factors identified were concomitant use of medications that might have increased the risk of GI bleeding and advanced age. It should be noted that use of multiple medications containing aspirin was reported in only 10 cases (1.9%). Most of the patients were hospitalized and then subsequently recovered; however, 29 (5%) patients in the case series died.

## **DRUG INFORMATION/LABELING**

Numerous single ingredient and combination products are available OTC and by prescription. The internal analgesic, antipyretic, and antirheumatic drug product monograph lists the following indications for aspirin use:

- **Rheumatologic Disease Indications:** Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.
- **Vascular Indications:**
  - To reduce the risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli,
  - to reduce the risk of vascular mortality in patients with a suspected acute MI,
  - to reduce the combined risk of death and nonfatal MI in patients with previous MI or unstable angina pectoris,
  - to reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.
- **Revascularization Procedures:** Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

Dosing varies by indication, however the OTC Aspirin Regimen Bayer Adult low strength 81mg® product states the following regarding the dosage:

**Directions:** For nonprescription analgesic indications: Adults & children 12 years and older: Take one or two 325 mg caplets or four to eight 81 mg tablets every 4 hours with water. Do not exceed 4000 mg in 24 hours. Dosage may be modified as directed by a doctor.

This particular product also contains the following warnings and safety of enteric-coated products relative to plain aspirin products.

**Warnings:** Children and teenagers should not use this medicine for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin. Do not take for pain for more than 10 days or for fever for more than 3 days unless directed by a doctor. If pain or fever persists or gets worse, if new symptoms occur, or if redness or swelling is present, consult a doctor because these could be signs of a serious condition. Do not take this product if you are allergic to aspirin, have asthma, ulcers, or stomach problems (such as heartburn, upset stomach or stomach pain) that persist or recur, gastric ulcers or bleeding problems unless directed by a doctor. If ringing in the ears or loss of hearing occurs, consult a doctor before taking any more of this product. Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. **IT IS ESPECIALLY IMPORTANT**

**NOT TO USE ASPIRIN DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.**

**Safety:** The safety of enteric-coated aspirin has been demonstrated in a number of endoscopic studies comparing enteric-coated aspirin and plain aspirin, as well as buffered aspirin and "arthritis strength" doses. In these studies, endoscopies were performed in healthy volunteers either before and/or during, and/or after administration of various aspirin doses. Compared to all the other preparations, the enteric-coated aspirin produced significantly less damage to the gastric mucosa.

The 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 aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.

### **SELECTION OF CASE SERIES**

We searched the AERS database for domestic cases of GI hemorrhage, ulceration, or perforation related to use of aspirin or products containing aspirin. 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 629 cases, of which 19 were duplicates for a total of 610 cases. Sixty-nine cases were excluded for the following reasons:

Cases excluded from series:

- Not spontaneous case reports - cases were from a published epidemiological study examining whether GI bleeds were higher in individuals on calcium channel blockers<sup>9</sup> (58)
- Acute intentional overdoses (5)
- Non-US cases (1)
- Reports were not legible (2)
- Study comparing ticlodipine to aspirin, not clear which product patient received when they experienced their GI event (2)
- No adverse GI event (1)

### **SUMMARY OF CASES**

We reviewed 541 US cases of GI bleeding, ulceration, or perforation in connection with aspirin-containing products between 1998 and 2001. The mean age of the patients was 69.3 years. Two patients were younger than 16 years of age (age's 14 months and 11 years). Where gender was known, 63% (319/503) of the patients were male. Aspirin-containing products were used most often for cardiac or cerebrovascular indications. The duration of aspirin use was not reported in the majority of the cases. Of those that reported duration, it ranged from less than 1 day (after one dose) to 25 years, with a median duration of 42 days. The median daily dose and the dose most often reported was 325mg per day. There was only one case that reported a daily dose that averaged greater than 4gm per day.

Eighty-six percent of the patients required hospitalization and 5% died. Treatment generally consisted of discontinuation of the offending agent(s), use of proton pump inhibitors, histamine H2 blockers, transfusion therapy, coagulation by heat, electricity or laser, or endoscopic injection of epinephrine. Twenty-four patients reportedly required surgical intervention.

Demographic data, outcomes, and some summary information from the 541 cases are provided below.

<b>Table 1. Demographic Data and General Summary Information</b>	
Age in years (n=491)	Mean-69.3, median-71, range 1.2 to 100
Gender	Male-319, Female-184, Unknown-38
Indication*	Heart disease or CAD (includes AMI, after revascularization, and primary & secondary prevention)-121 Cerebrovascular disease (includes acute therapy, primary & secondary prevention)-60 Pain (GI, foot, back, pain not specified)-38 Non-cardiac vascular thrombosis, occlusion, or stent placement (also includes unspec antiplatelet indication)-29 Miscellaneous-24 Headache/Migraine-24 Arthritis (OA, RA, or type not specified)-18 Flu/fever symptoms-2 Unknown-236
GI Events or Findings*	Bleed-361 Ulceration-197 Perforation-9 Melena-101 Hematemesis-52 Gastritis-29 Hematochezia-20 Erosion-10 Duodenitis-6 Esophagitis-5 Colitis-3 Necrotic bowel, obstruction, stenosis, hemoptysis-1 each
Duration (n=145)	Median-42 days, mean 1.5 years (range, 1 dose to 25 years)
Acute vs chronic use (use ≤1 week vs >1 week)	Acute-28; chronic-117; unknown-396
Daily dose (adult patients; n=338)	Mean-423 mg; median-325 mg (range 75-6825 mg) (≤ 81mg-93; > 81 to < 325mg-12; 325mg-177; > 325mg-56)
Reporter	Healthcare practitioner-510 Consumer-21 Study-9 Unknown-1
Serious Outcomes*	Death-29; hospitalization-468; life-threatening-78; disability-9
FDA received date	1998-99, 1999-102, 2000-158, 2001-182

Event date	1979-1, 1990-1, 1994-1, 1995-1, 1996-11, 1997-34, 1998-88, 1999-126, 2000-146, 2001-103, unknown-29
*more than 1/case possible	

Four hundred eight-five patients (~90%) had one or more known risk factors or other possible causes for their GI event. Risk factors included a significant GI medical history (111 cases), a concurrent smoking or drinking history that may have increased risk (75 cases), concomitant medication that may have increased their risk for a GI bleed (366 cases), or were 65 years of age or older (347 cases). Sixty-seven of the 347 patients listed age  $\geq$  65 years old as the only risk factor. Sixty-one percent of all patients in this case series had more than one risk factor. Additionally, a large number of patients had significant underlying or intercurrent illness, but because of the large case series this number was difficult to quantify. Use of multiple medications containing aspirin was reported in only 10 cases (1.9%). Sixty-four patients experienced their GI event despite receiving a GI protectant medication concomitantly (H<sub>2</sub>-blocker-35, PPI-28, misoprostil-3).

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

<b>Table 2. Potential Risk Factors Identified</b>	
Significant GI medical history*	Previous GI ulceration-59 Previous GI bleed (includes UGIB, LGIB, and rectal bleed)-40 Esophageal varices-5 Mallory-Weiss tear-4 <i>H. pylori</i> +-21
Significant social history*	ETOH use-53 Tobacco (smoking) use-29
Concomitant medications possibly contributing to bleed*	Other NSAID-218; includes COX inhibitors-97 (Celecoxib-44, Rofecoxib-53) OTC-24, RX-155, both-3, unknown-36 Warfarin-67 Clopidogrel-49 Heparin-37 Low-molecular weight heparin-17 Corticosteroids-22 Alendronate-13 Eptifibatide-12 Tirofiban-8 Abciximab-5 Thrombolytics-5 Pentoxylline-4 Cilostazol-2 Anagrelide-1 Lepirudin-1
Other	Age 65 years-347
*more than 1/case possible	

In almost one-half of the cases, the site of the GI event was not reported. In most of the cases in which the site was known, the bleeding occurred in the stomach. In 231 cases, the report stated a study, most often esophagogastroduodenoscopy (EGD), was done to confirm the diagnosis.

Location of GI event*	Stomach-131 Duodenum-75 Unspecified upper GI bleed-44 Esophagus-15 Colon-17 Unspecified lower GI bleed-13 Rectal-12 GE junction-2 Unknown-264
Study confirming diagnosis* (n=231)	EGD-131 Unspecified endoscopy-60 Colonoscopy-38 Gastroscopy-11 Surgery-10 Upper GI or small bowel series-5 Autopsy-2 Tagged RBC scan-1
*more than 1/case possible	

### **CONCLUSION**

We reviewed 541 domestic cases of GI hemorrhage, ulceration, or perforation reported for aspirin-containing products from January 1, 1998 through December 31, 2001. 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 aspirin at less than or equal to 325mg for cardiac or cerebrovascular indications. Eighty percent of cases that reported duration reported chronic use defined as use for greater than 1 week.

Most patients were at increased risk for GI bleeding because of a past GI event, advanced age, consumption of ethanol, tobacco use, or use of another medication concomitantly that can increase risk of GI bleeding. Additionally, although not quantified many patients had other significant intercurrent illness or past medical history that might have put them at increased risk of a GI event. Greater than 60% of the patients had more than one risk factor present. It should be noted that use of multiple medications containing aspirin did not appear to be a factor in most of these cases.

### **References:**

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