

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-998/s-009

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Generally, the labeling for celecoxib and rofecoxib reflects the risk of fatal gastrointestinal bleeding, obstruction, perforation, and stenosis observed in postmarketing experience. However, because in 12 fatal cases the patient bled and died despite taking a drug concomitantly to protect the gastrointestinal tract, we recommend adding

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 review 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)
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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/RECOMMENDATION

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.

For the most part, the labeling for celecoxib and rofecoxib regarding gastrointestinal bleeding, obstruction, perforation, and stenosis adequately reflects the data in the AERS database. The *Warnings* sections for both celecoxib and rofecoxib state, in part, "NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population." The cases in the AERS database generally involve elderly and debilitated patients, and in 21% (15/73) of the cases a past history of peptic ulcer disease was reported. We thought it noteworthy that in 16% (12/73) of the celecoxib and rofecoxib cases the patient bled and died despite taking a drug to protect the gastrointestinal tract. We recommend adding information in the product labeling regarding the occurrence of fatal gastrointestinal bleeding despite the attempts of the clinicians to prevent bleeding by prescribing a gastrointestinal-protectant drug concomitantly. Additionally, although the *Drug*

Interactions sections for both celecoxib and rofecoxib state there may be an increased rate of GI ulceration or other complications with the concomitant use of aspirin or warfarin, the possibility of fatal outcomes from the concomitant use of aspirin or warfarin is not mentioned. We recommend _____

Signed 12-29-00 by

Joyce Weaver, Pharm.D., Safety Evaluator

Concur:

Signed 12-29-00 by

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

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

Drug	Lodine (Etodolac)	Celebrex (Celecoxib)	Vioxx (Rofecoxib)
Total cases	9	36	37
Mean age	79	77	76
Median age	78	78.5	80
age range	69 – 94	46 – 99	28 – 93
Gender	M—5 F—3 Unk—1	M—12 F—22 Unk—2	M—14 F—22 Unk—1
Event date	1991—2 1992—4 1993—1 1994—1 1996—1	1999—30 2000—6	1999—3 2000—34
Indication	Osteoarthritis—2 Gouty arthritis—1 Unknown—6	RA—4 Osteoarthritis—12 Acute pain—3 Unspecified arthritis—3 Other—5 Unknown—9	Osteoarthritis—14 Acute pain—6 Unspecified arthritis—6 Other—6 Unknown—5
Mean onset	35.7 days	25.7 days	43 days
Median onset	30 days	14 days	21 days
range	17 – 60 days (Onset data available for 3 cases)	1 – 115 days	0 – 131 days
Dose at or below labeled range	Yes—3 Unk—6	Yes—18 No—2 Unk—16	Yes—24 No—1 Unk—12
GI event ¹	Hemorrhage—6 Perforation—2 Melena—1 Hematemesis—1 Stenosis/obstr—1	Hemorrhage—22 Perforation—2 Melena—8 Hematemesis—10	Hemorrhage—23 Perforation—7 Melena—4 Hematemesis—6 Erosions—1 Stenosis/obstr—1 Other—10
Location of GI event	Esophageal—1 Gastric—2 Duodenal—1 Large intestine—1 Unknown—4	Gastric—3 Duodenal—5 Rectal—2 Small intestine—1 Unknown—25	Gastric—13 Duodenal—5 Large intestine—2 Other—2 Unknown—15
Mean nadir Hgb and Hct	Hgb 5.8 Hct 16.6 (Info from 1 case)	Hgb 8 (range, 6 – 10.8) Hct 26.1 (range, 20.1 – 31.8)	Hgb 8.7 (range, 6 – 13.8) Hct 18 & 29.6 (Hct values reported in 2 cases)
Concomitant NSAID		4 Ibuprofen (1) Nabumetone (2) Naproxen (1)	
Concomitant warfarin	1	5	6
Concomitant corticosteroid		5	2
Concomitant antiplatelet			2 (clopidogril)
Concomitant ASA		8 80 mg—1 325 mg—1 Yes, dose unk—6	8 80 mg—2 325 mg—1 Yes, dose unk—5
Concomitant alendronate		1	
ETOH use		Never—2	Never—3

Drug	Lodine (Etodolac)	Celebrex (Celecoxib)	Vioxx (Rofecoxib)
		Past or current—6	Past or current—2
Smoker		Never—2 Past—1 Current—2	Never—2 Past—2
Pertinent PMH†	Diabetic gastroparesis (1) Bowel obstruction (1) CAD (3)	Alcoholism (3) Anemia (5) CAD (7) Cirrhosis (1) CVA (1) Diabetes (6) Diverticulitis (1) Esophageal varices (1) Factor V def (1) Gastrectomy (1) Gastritis (2) GI AVM (2) Hx PUD (11) Hx GI bleed (6) Malignancy (4) Thrombocytopenia (1)	Anemia (1) ASA, sulfa allergy (2) Crohn's disease (1) CVA (1) Diabetes (1) Diverticulitis (1) Functional intestinal disorder (1) Gastrostomy (1) Irritable bowel syndrome (1) Hepatic dysfunction (1) Hx PUD (4) Hx GI bleed (1)
Major systemic illness preceding bleed†	CABG (1)	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)	6 Metastatic gastric cancer (1) Pancreatitis, hepatitis (1) Shock (1) Recent surgery (3)
Concomitant H2 blocker, antacid, or PPI		8	4
Bleeding other than GI		1	2
Diagnosis confirmed by diagnostic procedure	4 Surgery (2) CT scan (1) EGD (1)	11 CT scan (1) EGD (6) Flex sig (1) Surgery (2) Autopsy (1)	18 EGD (5) Surgery (4) Autopsy (4) GI series X-ray (2) Not specified (3)
Pos Dechallenge		1	2
Pos Rechallenge		1	
Reviewer impression of quality of report	Good—0 Adequate—2 Poor—7	Good—3 Adequate—24 Poor—9	Good—6 Adequate—13 Poor—18

† more than one possible per case

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/s/

Joyce Weaver
1/4/01 03:39:31 PM
PHARMACIST

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OPDRA REVIEW

Colitis with COX-2
agents compared to 3
Non-selective
NSAIDs

Number of Pages

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Commercial Information

OPDRA REVIEW

Thrombotic Vascular
Events

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

DATE: February 6, 2001

FROM: Renan Bonnel, Pharm. D., M.P.H, Safety Evaluator
 Claudia B. Karwoski, Pharm.D., Team Leader
 Allen Brinker, M.D., Epidemiologist
 Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director
 Division of Drug Risk Evaluation I, HFD-430

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

SUBJECT: OPDRA Postmarketing Safety Review
 Drugs: Rofecoxib (Vioxx®, NDA 21-042, 21-052),
 Celecoxib (Celebrex®, NDA 20-998, 21-156)
 Etodolac (Lodine®, NDA 18-922, 20-584)
 Reaction: Thrombotic Vascular Events

Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.

EXECUTIVE SUMMARY

This document summarizes our evaluation of 223 US cases of thrombotic or embolic events possibly associated with rofecoxib (99), celecoxib (102), and etodolac (22). These events include myocardial infarction (MI), cerebrovascular events, pulmonary embolism (PE) and deep venous thrombosis (DVT), and miscellaneous thrombotic events. Etodolac, a non-selective NSAID, was chosen for review because it is a relatively new antiinflammatory agent with similar indications.

These summaries provide qualitative and descriptive information about case reports in the FDA's spontaneous Adverse Event Reporting System (AERS) that have been received for the individual drugs. These summaries should not be interpreted as supporting conclusions about the comparative safety of the different drugs. Variations in adverse event reporting practices make quantitative safety comparisons of different drugs problematic. Sources of variation may include manufacturer reporting practices, time on market, calendar year, and publicity. These and other factors may result in substantial variations in the types and numbers of reports for individual drugs in AERS.

There were several common characteristics in these cases noted for all three products. In general, the patients were elderly and the mean ages for rofecoxib, celecoxib and etodolac were 67, 69, and 65 years old, respectively. For all three products, females made up slightly greater than 65% of the cases. Most cases reported a dose within the recommended labeled range. This

information, however, was not always consistently reported. Risk factors or precipitating factors such as past medical history, underlying disease, concomitant medications, or acute concurrent adverse events were present in many of the cases.

Rofecoxib

There were a total of 99 cases reviewed that were possibly associated with the use of rofecoxib. These events include 26 of MI, 19 of PE or DVT, 43 cerebrovascular events, and 14 miscellaneous thrombotic vascular events. The numbers of events (102) slightly exceed the number of cases because one case reported both MI and a PE and two cases reported PE/DVT and CVA. Seven of the 26 patients who experienced an MI did not have apparent precipitating factors or cardiovascular risk factors. Two of the seven were greater than 65 years of age, and in three cases there was extremely poor documentation. Of the 19 patients who were possibly at an increased risk, two had a single cardiovascular risk factor and 17 had at least two cardiovascular risk factors, past medical history, and/or a major concurrent event that may have contributed to the MI.

Ten of the 19 patients who experienced a PE or DVT may have been at increased risk. Risk factors noted include obesity, history of DVT/PE, concurrent CHF or MI, and/or concomitant suspect medications labeled for thromboembolic events (including hormone replacement therapy (HRT) and oral contraceptives (OC)). There were no apparent risk factors in the remaining nine patients. Twenty-six of the 43 patients who experienced a cerebrovascular event had precipitating risk factors or concurrent medical conditions that may have contributed to the cerebrovascular event. Hypertension was the most frequently reported underlying medical condition. The remaining 17 cases lacked detailed clinical information. We reviewed 14 miscellaneous thrombotic or embolic vascular events possibly related to the use of rofecoxib. The events include arterial thrombosis (1), portal vein thrombosis (1), ocular vascular occlusion/embolism/clot (4), and intestinal vascular insufficiency/ischemic colitis (8).

Celecoxib

There were a total of 102 cases reviewed that were temporally associated with the use of celecoxib. These events include 37 of MI, 27 of PE or DVT, 31 cerebrovascular events, and 10 miscellaneous thrombotic vascular events. The numbers of events (105) slightly exceed the number of cases because two cases reported both MI and a CVA and one case reported PE/DVT and CVA. Six of the 37 patients who experienced an MI did not appear to have precipitating factors or cardiovascular risk factors for MI. Two of the six were greater than 65 years of age and the other four were poorly documented. Of the 31 patients who were possibly at an increased risk, three had a single cardiovascular risk factor and 28 had at least two cardiovascular risk factors, past medical history, and/or a major concurrent event that may have contributed to the MI.

Seventeen of the 27 patients who experienced a PE or DVT may have been at increased risk. Risk factors noted include obesity, history of thrombosis, anticardiolipin antibody, malignancy, SLE, recent surgery, concurrent events (SBO, ARDS, and CHF), and/or concomitant suspect medications labeled for thromboembolic events (including HRT). There were no apparent risk

factors in the remaining 10 patients. None of the 10 cases were very well documented. Twenty-five of the 31 patients who experienced a cerebrovascular event had precipitating risk factors or concurrent medical conditions that may have contributed to the cerebrovascular event. Hypertension was the most frequently reported underlying medical condition. The remaining six cases lacked detailed clinical information. We reviewed 10 miscellaneous thrombotic vascular events possibly related to the use of celecoxib. The events were ocular vein occlusion (3), digital ischemia /occlusive thrombosis/limb embolism (5), and ischemic colitis (2).

Etodolac

There were a total of 22 cases reviewed that were temporally associated with the use of etodolac. These include seven cases of MI, six cases of PE or DVT, seven cases involving cerebrovascular events, and two miscellaneous thrombotic vascular events. Only one of the seven patients who experienced an MI did not have apparent precipitating factors or cardiovascular risk factors for an MI. The age and past medical history of this patient was not reported. Of the six patients at an increased risk, one had a single cardiovascular risk factor, two had no risk factors but a single concurrent event, and the remaining three had at least two risk factors, past medical history, and/or a major concurrent event that may have contributed to the MI.

Four of the six patients who experienced a PE or DVT may have been at increased risk. Risk factors noted include HRT use, history of CHF, probable immobility secondary to hospitalization, and concurrent eosinophilic pneumonia and interstitial nephritis. There were no apparent risk factors in the remaining two patients, however these two cases were not well documented. We reviewed seven cases of cerebrovascular events possibly related to the use of etodolac. Four of the seven patients had possible predisposing factors (hypertension- 4, DM-2, smoker-1, and HRT-1) for the cerebrovascular events. Two patients had more than one risk factor. We reviewed two miscellaneous thrombotic vascular events possibly related to the use of etodolac. The events were retinal vein thrombosis (1) and digital thrombosis (1).

In conclusion, this document describes the US cases of thrombotic vascular events possibly related to rofecoxib, celecoxib, and etodolac use. Because many of these patients were older and/or had possible predisposing factors or underlying disease, it is difficult to determine the role of each of the products in causing the event. Although certain thrombotic events are mentioned in the product labeling, the continued existence of the thrombotic events particularly in high-risk populations is an important finding since the actual number of cases may in fact be higher due to the underreporting of adverse events in passive surveillance systems.

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INTRODUCTION

Reports of serious thrombotic vascular events with the use of rofecoxib and celecoxib were noted during the routine postmarketing surveillance of these products. Simultaneously, a written consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products requested a review of serious thrombotic cardiovascular adverse events associated with celecoxib and rofecoxib since their approval. This consult request prompted a review of all thrombotic and embolic vascular events for these products in the Adverse Event Reporting System (AERS) database.

Rofecoxib was approved in 1999 for the treatment of osteoarthritis, management of acute pain, and treatment of primary dysmenorrhea. Celecoxib was approved in 1998 for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis in adults and to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care. Etodolac was approved in 1991 for acute and long-term use in the management of signs and symptoms of osteoarthritis and pain.

Nonselective NSAIDs (such as etodolac) and the COX-2 selective NSAIDs (celecoxib and rofecoxib) induce potent analgesic and anti-inflammatory effects via the inhibition of cyclooxygenase (COX) enzymes in arthritic patients. The inhibition of COX enzymes decreases the production of prostaglandins and thromboxane. COX-2 (the inducible form) is primarily found in inflamed tissue, brain, reproductive organs, and the kidney; very little COX-2 is found in normal tissue. COX-1 (the constitutive form) is expressed in most tissues, primarily in GI tract, kidney, and platelets. It is involved in the production of protective prostaglandins that are responsible for the maintenance of normal GI mucosa, and the production of thromboxane A₂, which promotes platelet aggregation. Because selective COX-2 inhibitors (rofecoxib and celecoxib) do not block COX-1 mediated platelet aggregation, there is a theoretical increased risk of thrombotic vascular events in certain patients at risk for such events.

LABELING

The current labeling contains the following information regarding thrombotic events:

Rofecoxib (Vioxx®)

ADVERSE REACTIONS (Cardiovascular): In the osteoarthritis studies, the following events occurred in >0.1% to 1.9% of patients treated with Vioxx regardless of causality: cerebrovascular accident, deep venous thrombosis, myocardial infarction, pulmonary embolism, transient ischemic attacks, and unstable angina.

DRUG INTERACTIONS: Aspirin - At steady-state, Vioxx 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by *ex vivo* platelet aggregation and serum TBX₂ generation in clotting blood. Vioxx is not substituted for aspirin for cardiovascular prophylaxis.

Celecoxib (Celebrex®)

ADVERSE REACTIONS (Cardiovascular): Angina pectoris, coronary artery disorder, myocardial infarction, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis.

DRUG INTERACTIONS: Aspirin - Because of its lack of platelet effects, Celebrex is not a substitute for aspirin for cardiovascular prophylaxis. Celebrex can be used with low dose aspirin.

Etodolac (Lodine®)

ADVERSE REACTIONS (Cardiovascular): Myocardial infarction, cerebrovascular accident.

DRUG USE

The following table summarizes projected total prescriptions of Vioxx, Celebrex, and Lodine dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S from initial marketing through August 2000. This information is not to be used outside of the FDA without prior clearance by _____

Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Vioxx®	1	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Celebrex		_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____
Lodine		_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____

The numbers in the table represent total number of prescriptions in thousands; add three 0's to each figure. The cumulative total prescriptions since approval is provided below:

Total Rx - Vioxx: 1 _____
Total Rx - Celebrex: _____
Total Rx - Lodine: _____

MEDICAL LITERATURE

A MEDLINE search of the medical literature for thrombotic adverse event case reports was performed using the MESH terms rofecoxib, celecoxib, etodolac, cardiovascular adverse events, myocardial infarction, pulmonary embolism, cerebrovascular accident, and thrombosis. The search resulted in one relevant article of interest⁶. The article reported thrombosis occurring during celecoxib therapy in four female patients. All four cases were submitted to the FDA and all are summarized with the other cases in the document.

SELECTION OF CASES

An October 12, 2000 AERS search was conducted for rofecoxib, celecoxib, and etodolac utilizing the following MedDRA Terms: central nervous system hemorrhages and cerebral accidents (HLT), coronary artery occlusion (PT), coronary artery embolism (PT), myocardial infarction (PT), gastrointestinal occlusion and infarction (HLT), and embolism, thrombosis, and stenosis (HLGT). The AERS search was limited to US cases only. The search resulted in 144 unduplicated cases for celecoxib, 159 for rofecoxib, and 25 for etodolac.

Cases Excluded from Review

Forty-two celecoxib cases, 60 rofecoxib cases, and three etodolac cases were excluded from review for one or more of the following reasons:

- No systemic thrombotic or embolic adverse event reported – These include reports of superficial phlebitis, GI bleeds with mucosal blood clot formation, hematoma, epistaxis, hemorrhagic colitis, aortic valve regurgitation, retrobulbar hemorrhage, and reports of patients that ruled out for thrombotic or embolic events.

- Hemorrhagic strokes in cases with an INR, PT, or PTT above the upper limit of normal range. The therapeutic INR for most conditions is 2 to 3. In individuals with a mechanical valve or recurrent systemic embolism, the recommended INR is 3-4.5. So based on the upper limit of 4.5, we excluded cases with INRs above this value. If the INR value was not available then those with a PT or PTT value greater than 2 times of control were excluded.
- Events not included in this review – Thrombocytopenic Purpura, DIC, mediastinal tumor with superior vena cava syndrome, and temporal arteritis.
- Consumer or second hand reports with no confirmed diagnosis of a thrombotic event – These reports refer to consumer or “hearsay” reports with no medical confirmation of diagnosis. An example includes the following:
 - By HCP - A pharmacist reported that another pharmacist told her that his mother-in-law was taking Celebrex for a couple of weeks before she died. The reporting pharmacist knew nothing further about the Celebrex case. She did not know the prescribing physician or the patient.
 - By consumer – Unnamed consumer reports that a female patient started on Celebrex and developed severe intestinal cramps and then had a heart attack.
- No actual adverse event report – just request for information, initially interpreted by company as an ADR
- Not clear if the patient was receiving the product (celecoxib, rofecoxib, or etodolac) or the thrombotic event was not temporally related to product – in these cases, the use of either celecoxib or rofecoxib prior to the event was questionable.
- No actual patient – physician reported that an unspecified number of patients (NOS) experienced DVT and MI.
- Study reports

Cases Included in Review

- Cases with events that were temporally related to the use of the product – Cases lacking this information were excluded.
- Cases with reported diagnosis of a systemic thrombotic or embolic event – these events include myocardial infarction (MI), pulmonary embolism (PE), deep vein thrombosis (DVT), cerebrovascular accidents (CVA), and other miscellaneous systemic thrombotic or embolic events. This review did not include cases of varying degrees of angina or chest pain. Cases were included in the following two circumstances:
 - If a HCP reported a diagnosis of any of the above events with no supporting clinical data, the diagnosis was taken at face value.
 - If a consumer (patient or family member) reported the event with enough specific details regarding the event, these were taken at face value.
- Cases that met the following clinical definitions^{4,5} – but did not provide a diagnosis were included if the following case definitions were met:
 - Myocardial infarction (MI) - The presence of two of the following criteria was used to identify MI cases: (1) a history of prolonged chest discomfort or anginal equivalent, (2) ECG changes consistent with ischemia or necrosis, (3) elevated cardiac enzymes, or (4) serious outcome attributed to MI in the report. Cases with a diagnosis of myocardial ischemia or angina were not included in this review unless they met the criteria above.

- Pulmonary embolism (PE) - The presence of two or more of the following criteria was used to identify PE cases: (1) clinical symptoms including dyspnea, pleuritic chest pain, apprehension, cough, tachypnea, and tachycardia, (2) antecedent or concurrent DVT, (3) positive ventilation-perfusion (V/Q) lung scan, (4) positive pulmonary angiography (5) serious outcome attributed to PE in the report, and (5) PE on autopsy. If a case reported a diagnosis of PE with no supporting clinical data, the diagnosis was taken at face value.
- Cerebrovascular Events - The presence of one of the following criteria was used to identify cerebrovascular events: (1) clinical symptoms and functional deficits confirmed by neurologic examination (2) positive diagnostic tests including MRI, CT Scan, Carotid Doppler, and Transthoracic Two-dimensional Echocardiography (TTE) to confirm the cerebrovascular event or, (3) serious outcome attributed to “stroke” in the report. If a case reported a diagnosis of cerebrovascular accident, stroke, or transient ischemic attack with no supporting clinical data, the diagnosis was taken at face value.

SUMMARY OF CASES

We reviewed the thrombotic vascular events for rofecoxib, celecoxib, and etodolac. These events include myocardial infarction, cerebrovascular events, pulmonary embolism and deep venous thrombosis, and miscellaneous thrombotic events. The cerebrovascular events include the following events or reported terms: stroke, cerebrovascular accident (CVA), transient ischemic attacks (TIA), and cerebrovascular hemorrhage. The miscellaneous thrombotic events involved ocular, gastrointestinal, and peripheral circulatory systems.

1. ROFECOXIB

There were a total of 99 cases reviewed that were temporally associated with the use of rofecoxib. These events include 26 of MI, 19 of PE or DVT, 43 cerebrovascular events, and 14 other thrombotic vascular events. The numbers of events (102) slightly exceed the number of cases (99) because one case reported both MI and a PE and two cases reported PE/DVT and CVA.

	Rofecoxib (N=99)
Event	Myocardial Infarction-26, PE/DVT-19, Cerebrovascular Events-43 Miscellaneous thrombotic events-14 (arterial thrombosis-1, portal vein thrombosis-1, ocular events-4, ischemic colitis-8)
Age	Range 19-91 years, mean-67.1, median-69 (unknown in 17)
Gender	Female-59, Male-35, (unknown in 5)
Outcome *	Death-15, Hospitalization-64, Disability-10, Outcome not specified-22
Time to onset	Range 1-300 days, mean-44, median-22 (n=58)
Dose	At labeled range-59, outside of labeled range-2 (unknown in 38)
Event year	1999-27, 2000-54, unknown-18
Report type	15 day (expedited)-78, periodic-11, direct-10
Reporter	HCP-75, Non-HCP-24

* A case may have more than one reported outcome.

Myocardial Infarction

We reviewed 26 cases of myocardial infarction (MI) possibly related to the use of rofecoxib. In one case, there was also a diagnosis of pulmonary embolism so this case is also summarized in that section of the document. The cases involved 11 females, 11 males, and four whose gender was not specified. The patients' ages ranged from 50 to 87 years of age with a mean and median of 71 and 73 years, respectively. Sixteen patients were > 65 years of age. The mean and median time to onset (n= 16) was 42 and 13 days, respectively with a range of 1 day to 5 months. The dose of rofecoxib was within the recommended range in 14 patients and not reported in the remaining 12 patients. Twenty patients required hospitalization, and six patients eventually died. The outcome in five cases was not reported.

In 19 of the 26 cases, the patients may have been at increased risk for an MI because of past medical history, the presence of cardiovascular risk factors, and/or a recent major concurrent event. Six patients had a prior history of coronary heart disease as evidenced by past history of previous MI (2), coronary artery bypass graft (CABG) (3), percutaneous coronary angioplasty (1), and/or history of coronary artery disease (4). One or more cardiovascular risk factors were reported in 13 patients and include hypertension (9), diabetes (6), hyperlipidemia (7), obesity (2), hormone replacement therapy (3), and smoking (2). Additionally, the MI in 11 patients may have been precipitated by a major concurrent event. The major events included gastrointestinal hemorrhage (4), recent surgery (2), renal failure (2), congestive heart failure (3), and unspecified hemorrhage (1).

A total of six patients were on ASA therapy at the time of the MI. One of the six was also on Advil. Of the five patients with a prior history of coronary heart disease, only one was receiving ASA. Neither of the two patients with a previous MI was on ASA, however one was on concomitant warfarin for an unknown indication.

Overall, only 7 of the 26 patients did not have apparent precipitating factors or cardiovascular risk factors for a MI. Two of the seven were greater than 65 years of age, and in three cases there was extremely poor documentation including no information regarding a past medical history or risk factors. Of the 19 patients previously mentioned at an increased risk, two had a single cardiovascular risk factor (diabetes-1, hypertension-1). The remaining 17 had at least two risk factors, past medical history, and/or a major concurrent event that may have contributed to the MI.

Pulmonary Embolism and Deep Venous Thrombosis

We reviewed 19 cases of pulmonary embolism (PE) and deep venous thrombosis (DVT) possibly related to the use of rofecoxib. In three cases, there was also a diagnosis of cerebrovascular accident (2) and myocardial infarction (1) and these cases are again summarized in those respective sections of this document. Rofecoxib was the only suspect medication in 14 cases. In five cases, Enbrel (1), estrogen (2), celecoxib (1), and olanzapine (1) were listed as co-suspect and were temporally associated with the event.

The cases involved 11 females, seven males, and one whose gender was not specified. The mean and median ages were 51 and 54, respectively with a range of 19 to 74 years old. Five patients were ≥ 65 years of age. For rofecoxib therapy, the mean and median time to onset (n= 14) was 40 and 15.5 days, respectively with a range of 5 to 165 days. The dose of rofecoxib was within the recommended range in 15 patients and not reported in the remaining four patients. Eleven patients required hospitalization, and four patients died. The death in two patients was secondary to PE, in the third patient was secondary to endocarditis (diagnosed after PE), and in the fourth is not clear but may have been secondary to PE.

Because of the complexity and range of severity of these cases, brief descriptions of these events are presented below to hopefully provide more clarity.

- Seven patients suffered lower extremity (6) or upper extremity (1) DVTs.
- Three patients developed lower extremity DVT that progressed to PE.
- One patient suffered lower extremity DVT that was felt by the reporting physician to have embolized in her right middle cerebral artery and caused a stroke.
- Four patients presented with PE with no mention of DVT.
- Two patients were diagnosed with PE at autopsy (one also diagnosed with subarachnoid hemorrhage at autopsy).
- One patient presented with MI, possibly anaphylaxis, and PE that might have been diagnosed on autopsy. The specific time course of these events is not clear.
- One patient presented with PE and CHF.

In 10 of the 19 cases, the patients may have been at increased risk of PE or DVT. The following risk factors were noted in six patients: obesity (4) and history of DVT/PE (2). Two patients reported concurrent events (CHF-1, MI-1) however it is not clear if these events may have precipitated a PE. Two of the 10 patients were on chronic warfarin at the time they experienced their PE, although it is not clear if they had a therapeutic INR. One was on warfarin for chronic atrial fibrillation and the other patient had a history of DVT and PE and was positive for anticardiolipin antibodies. Seven patients were on concomitant or co-suspect medications labeled for thromboembolic diseases. These medications include HRT or OC use (5), Enbrel (1), and paroxetine (1) listed as co-suspect and were temporally associated with the event. There were no apparent risk factors in the remaining nine patients. Two representative cases are presented below:

ISR 3396968, MFR# WAES 99102156, NC, 1999

A 50-year-old male physician with no significant medical history or concomitant medication began to experience right leg pain approximately five days after starting rofecoxib 25mg per day for chronic back pain. An unspecified flow study revealed a right DVT and he was subsequently hospitalized and treated with heparin and warfarin. He did not receive rofecoxib during hospitalization, but was restarted on rofecoxib on discharge. Two days after discharge, he began to experience similar symptoms in his left leg. He underwent another flow study, which revealed a DVT in his left leg. He was readmitted and treated with heparin. He was also treated for a petechial rash felt to be related to rofecoxib. He was eventually discharged home on warfarin and enoxaparin.

ISR 3595541, direct, KY, 2000

A 30-year-old female with no significant medical history died of multiple pulmonary emboli approximately one month after starting rofecoxib 50mg daily for knee pain. Concomitant medication included Estrosten Fe (an oral contraceptive) for 10 months. She had previously used other oral contraceptives without problems. One month after initiation of rofecoxib, she experienced severe dyspnea and agitation. She was admitted to the ER in respiratory arrest and expired after 2 hours of cardiopulmonary resuscitation. The autopsy findings were as follows: bilateral multiple pulmonary emboli, subarachnoid hemorrhage, and negative post-mortem blood toxicology.

Cerebrovascular Events

We reviewed 43 cases of cerebrovascular events possibly related to the use of rofecoxib. Rofecoxib was the primary suspect drug in 41 cases and the secondary suspect in two cases. In two cases, there was a diagnosis of pulmonary embolism so these cases are also summarized in that section of the document. Celecoxib, aspirin, warfarin, Premarin, Naprosyn, captopril, Estrogen Fe, and Kenalog injection were co-suspect medications in eight cases. The quality of data in the reports varied from good (7) to adequate (17), and poor (19). The majority of the reports lacked detailed clinical information.

The cases involved 27 females and 16 males. The mean age was 71 years old (n=32) with a range of 30 to 91 years. The mean and median time of onset (n=21) was 44 and 18 days, respectively with a range of 1 to 300 days after starting rofecoxib therapy. The dose was within the recommended range in 26 patients, outside of the recommended range in one patient, and not reported in 16 patients. Twenty-eight patients were hospitalized, seven reported disability, and 15 reported the event as life threatening. Seven cases had a reported positive dechallenge and six had a reported negative dechallenge upon discontinuation of the drug. There were six fatalities. The cause of death was secondary to cerebral hemorrhage in three patients, possible acute renal failure in one patient, PE and subarachnoid hemorrhage in one patient, and was undetermined in one patient.

Twenty-six cases had one or more possible predisposing factors for stroke (hypertension-18, hormone replacement therapy (HRT)-7, hyperlipidemia-6, diabetes mellitus (DM)-3, malignancy-2, obesity-2, smoking-1, and illicit drug use-1). There were four patients who suffered hemorrhagic stroke that were receiving warfarin at the time. In addition, 11 of the 26 patients had concurrent medical conditions such as immobility/paraplegia, deep vein thrombosis, gram negative sepsis, severe migraine, severe epistaxis, atherosclerosis, acute GI bleeding with severe blood loss, multiorgan failure, carotid artery disease, and cardiac valve replacement that may have played a contributory role in the events. Many patients had more than one risk factor. Two patients had an indication for cardioprotective aspirin therapy (h/o TIA and CVA) and neither was receiving chronic aspirin therapy. Eighteen patients had diagnostic work-ups including neuroimaging (MRI or CT scan) studies in 13 patients to confirm the diagnosis of the cerebrovascular event.

The types of stroke were thrombotic (2), embolic (2), hemorrhagic (9) and indeterminate (30). The case involving the thrombotic event was reported as "blood clot in the brain" and cerebral

thrombosis. This case was poorly documented. A CT scan confirmed the second thrombotic stroke case. The patient was an 84-year-old female with a previous history of HTN, MI, and obesity that may have contributed to the event. She suffered left-sided hemiplegia. There were two well-documented cases involving embolic events. One of the patients, with hypercholesterolemia, small vessel disease, and mild hypertension, presented with a TIA. The small vessel disease and mild hypertension were thought to be contributory to the event. The second patient had concurrent deep vein thrombosis and hypertension that resulted in right middle cerebral artery stroke and persistent severe hemiparesis.

There were 30 cases that merely included the terms “stroke”, CVA or infarcts. These cases were classified as “indeterminate” because they lacked specific information regarding the type of lesion (hemorrhagic vs ischemic). Fifteen of the 30 cases were confounded by risk factors for stroke such as hypertension (12), hyperlipidemia (5), HRT (5), DM(2), or malignancy (1) at the time of the event. Nine patients had more than one risk factor.

There were nine cases involving hemorrhagic cerebrovascular events. The majority of the cases were well documented and had neuroimaging (CT or MRI) studies or an autopsy to confirm the location of the hemorrhage. Five patients may have had an increased risk for the event. Uncontrolled hypertension was a possible contributory risk factor in three patients. Other risk factors include HRT/OC use (2), obesity (1), and DM (1). Concomitant aspirin (325 mg) and warfarin use was reported in four patients. However, normal or slightly elevated (3.9) INR lab values did not support the role of warfarin in these cases. Although cerebral hemorrhages may have resulted from rupture of an arteriosclerotic vessel by uncontrolled arterial hypertension, the possibility of local thrombus formation and ischemia prior to cerebral hemorrhage cannot be excluded.

Overall, in 26 of the 43 cases, the patients had precipitating risk factors or concurrent medical conditions that may have contributed to the cerebrovascular event. Hypertension was the most frequently reported underlying medical condition. The remaining 17 cases lacked detailed clinical information. The following are representative cases of thrombotic cerebrovascular events:

ISR # 3483702 (MFG # WAES 00031937) (US, 2000)

A 75-year-old female with a history of hyperlipidemia, GERD, osteoporosis, DJD, compression fractures and s/p bilateral knee replacement, suffered a stroke during treatment with rofecoxib 25mg daily for osteoarthritis. Other than hyperlipidemia, the patient had no other known risk factors. The patient’s blood pressure had always been within the normal range. Concomitant medications included baby aspirin and vitamins. Two days after initiation of rofecoxib, she developed blurred vision, dizziness, and vertigo and rofecoxib was discontinued. The symptoms cleared and the family suspected a stroke at the time of this event. Three weeks after discontinuation of rofecoxib, she presented with left lower leg weakness, facial droop, mild left-sided paresis and another episode of blurred vision. She was hospitalized and CT scan showed enlarging lacunar infarcts. The carotid studies were unremarkable and EKG was negative for left atrial enlargement or left ventricular hypertrophy. The patient has not fully recovered as of the time of the report. Presently, she is being treated in a rehabilitation hospital and has a persistent left hemiparesis.

ISR # 3530025 (MFG # WAES 00050833) (US, 2000)

A 59-year-old male with a history of hypercholesterolemia, mild hypertension, BPH, and bilateral knee replacement, suffered a TIA during treatment with rofecoxib 25 mg daily for arthritis. Concomitant therapy included finasteride and doxazosin (dose and duration unknown). Six weeks after initiating rofecoxib, he noted acute onset of weakness in his right hand, numbness, and clumsiness of the hand while golfing. He was admitted to the ER. On admission his BP was 155/90 and physical examination was unremarkable other than his neurologic symptoms, which disappeared after 2 –1/2 hours. A CT scan (without contrast) showed abnormal appearance of both orbits and densities were present anteriorly. No previous scan was available for comparison. The carotids, EKG, lab values were normal. The diagnosis of transient ischemic attack was made and he was placed on therapy with Aggrenox.

Miscellaneous Thrombotic Vascular Events

We reviewed 14 other or miscellaneous thrombotic or embolic vascular events possibly related to the use of rofecoxib. The events include arterial thrombosis (1), portal vein thrombosis (1), ocular vascular occlusion/embolism/clot (4), and intestinal vascular insufficiency/ischemic colitis (8).

Arterial Thrombosis/Digital Ischemia

A case of arterial thrombosis (MFR # WAES 99070971) was temporally related to rofecoxib therapy. The patient was a 51-year-old female who developed severe digital vasospasm of all five fingers on the left hand and acrocyanosis after four days of rofecoxib (unknown dose) therapy for arthritis. Her past medical history was unknown. Concomitant medications included Premarin, Prozac, and Ritalin. Therapy with rofecoxib was immediately discontinued. She was found to have a thrombosis of the proximal ulnar artery. The patient was hospitalized and treated with t-PA and surgical measures. At the time of the report, the patient remained hospitalized and continued to have digital ischemia in two fingers.

Portal Vein Thrombosis

One case of (ISR# 3576870) portal vein thrombosis involved a 59-year-old male patient who developed portal vein thrombosis while using rofecoxib on an “as needed” basis. The patient had concurrent pancreatic neoplasm, hepatic veno-occlusive disease, and portal hypertension that may have contributed to the event. Rofecoxib use was deemed unlikely to be the etiology for the event.

Ocular Vascular Events

There were four cases of ocular vascular occlusion, embolism, or clot formation temporally associated with rofecoxib therapy. All four patients were elderly females. Two of the patients had hypertension or concurrent essential thrombocythemia that might have contributed to ophthalmic thrombotic events. These cases are described below.

- (ISR#3557980) A 72-year-old female with a history of retinal hemorrhage (1998) who developed “a second episode of retinal vein thrombosis” of the left eye about one month after starting rofecoxib 25 mg daily for osteoarthritis. The patient had a history of hemorrhagic gastric ulcer and was on concurrent lansoprazole. She had no history of hypertension, glaucoma, or other systemic coagulopathies. Other concomitant meds

included alendronate and hormone replacement therapy. Rofecoxib was discontinued. No further information was expected.

- (ISR# 3535108) A 70-year-old female developed retinal vein branch occlusion after receiving rofecoxib (unknown dose and duration). Concomitant therapy included levothyroxine, Dyazide, raloxifene and atorvastatin. The report was lacking clinical detailed information.
- (ISR #3536521) A 76-year-old female with a history of hypertension developed an ophthalmic vascular disorder, loss of blood pressure control, “clot”, blind spot and visual loss five days after starting rofecoxib 12.5 mg daily.
- (ISR# 3548936) A 72-year-old female developed essential thrombocythemia (platelet count 926,000) and thrombocyte embolus of the eye five weeks after starting rofecoxib. Her baseline thrombocyte count was 283,000. Upon discontinuation of rofecoxib, the platelet count normalized. The patient was treated with anagrelide.

Intestinal Vascular Insufficiency or Ischemic Colitis

We reviewed eight cases of intestinal vascular insufficiency or ischemic colitis with rofecoxib use. The patients’ ages ranged from 49 to 86 years with a mean of 67 years old. Five patients received the recommended dose for 7 days to 5 months. The onset of the event was 4 to 106 days after initiation of therapy. Three cases may have been confounded by recent major multiple illness, aspirin use, erosive esophagitis, previous history of gastrointestinal distress, and concomitant ibuprofen (1800 mg daily) therapy. One patient reported a history of colectomy for an unspecified reason. Five cases reported positive dechallenge upon discontinuation of therapy. Six patients reported recovery, one patient remained in the hospital at the time of the report and one patient died as a result of GI hemorrhage with ischemic bowel disease. There was one compelling case (MFR# WAES 00010660) involving a 53-year-old female with no known predisposing factors who developed intestinal vascular insufficiency, colitis, and intestinal ischemia while on rofecoxib therapy. An extensive evaluation did not reveal predisposing factors or an underlying process promoting ischemia or any evidence of ischemic arterial disease. She was hospitalized, had a bowel resection, and recovered.

2. CELECOXIB

There were a total of 102 cases reviewed that were temporally associated with the use of celecoxib. These events include 37 of MI, 27 of PE or DVT, 31 cerebrovascular events, and 10 other thrombotic vascular events. The numbers of events (105) slightly exceed the number of cases (102) because two cases reported both MI and a CVA and one case reported PE/DVT and CVA.

Celecoxib (N=102)	
Event	Myocardial Infarction-37, PE/DVT- 27, Cerebrovascular Events-31 Miscellaneous thrombotic events-10 (ocular events-3, digital ischemia-5, ischemic colitis-2)
Age	Range 24-95 years , mean-69, median-74 (unknown in 17)
Gender	Female-64, Male-31 (unknown in 7)

Outcome *	Death-15, Hospitalization-78, Disability-7, Outcome not specified-17
Time to onset	Range 1-565 days, mean-55, median-27.5 (n=76)
Dose	At labeled range-81 (unknown in 21)
Event year	1998-1, 1999-66, 2000-17, unknown-18
Report type	15 day (expedited)-43, periodic-33, direct-26
Reporter	HCP-78, Non-HCP-18 (unknown in 6)

* A case may have more than one reported outcome.

Myocardial Infarction

We reviewed 37 cases of MI possibly related to the use of celecoxib. In two cases, there was also a diagnosis of cerebrovascular accident and these are again summarized in the cerebrovascular events section of this document. The cases involved 19 females, 17 males, and one whose gender was not specified. The mean and median ages were 73 and 75, respectively with a range of 39 to 92 years old. Twenty-seven patients were ≥ 65 years of age. The mean and median time to onset (n= 32) was 53 and 24 days, respectively with a range of 1 day to 1.5 years. The dose of celecoxib was within the recommended range in 32 patients and not reported in the remaining five patients. Thirty-one patients required hospitalization, and nine patients died. The outcome in four cases was not reported.

In 31 of the 37 cases, the patients may have been at increased risk for an MI because of past medical history, the presence of cardiovascular risk factors, and/or a recent major concurrent event. Eleven patients had prior history of coronary heart disease as evidenced by past history of previous MI (3), percutaneous coronary angioplasty (1), and/or history of coronary artery disease, angina, or chest pain (9). One or more cardiovascular risk factors were reported in 24 patients and include hypertension (14), diabetes (7), hyperlipidemia (5), obesity (6), hormone replacement therapy (3), and smoking (2). Additionally, the myocardial infarction in 16 patients may have been precipitated by a major concurrent event. The major events include gastrointestinal hemorrhage (9), renal failure (1), congestive heart failure (3), hemolytic anemia (1), pericarditis (1), and pancreatitis (1).

A total of eight patients were on ASA therapy at the time of the MI. Of the eight patients with a prior history of coronary heart disease, three were receiving ASA. Two of the three patients with a previous MI were on ASA.

Overall, six of the 37 patients did not appear to have precipitating factors or cardiovascular risk factors for MI. Two of the six were greater than 65 years of age (70 and 90yo). Four of the six were also poorly documented cases. Of the 31 patients previously mentioned at an increased risk, three had a single cardiovascular risk factor (hypercholesteremia-1, diabetes-1, hormone replacement therapy-1). The remaining 28 had at least two risk factors, past medical history, and/or a major concurrent event that may have contributed to the MI.

There was one profound case involving a 39-year-old female on long term estrogen and methyltestosterone who suffered a "massive" MI approximately three weeks after initiating therapy with celecoxib. She was put on celecoxib 200mg per day for anterior cruciate joint inflammation of her shoulder. About one week after starting therapy she developed nausea and

vomiting and temporarily stopped celecoxib for four days, but she suffered the MI about 10 days after restarting it. Other than hormone replacement therapy she had no other risks for heart disease.

Pulmonary Embolism and Deep Venous Thrombosis

We reviewed 27 cases of pulmonary embolism (PE) and deep venous thrombosis (DVT) possibly related to the use of celecoxib. In one case, there was also a diagnosis of cerebrovascular accident and this case is again summarized in the cerebrovascular event section of this document. Celecoxib was the only suspect medication in 23 cases. In four cases, heparin (1), warfarin (1), and aspirin (2) were listed as co-suspect. Three of these listed a concurrent hemorrhagic adverse event.

The cases involved 19 females, five males, and three whose gender was not specified. The mean and median ages were 65 and 64, respectively with a range of 39 to 95 years old. Ten patients were ≥ 65 years of age. The mean and median time to onset (n=21) was 56 and 25 days, respectively with a range of 2 to 565 days. The dose of celecoxib was within the recommended range in 23 patients and not reported in the remaining three patients. Twenty-four patients required hospitalization, and one patient died. The cause of death was unknown in an elderly patient who experienced a DVT two weeks prior.

Because of the complexity and range of severity of these cases, brief descriptions of these events are presented below to hopefully provide more clarity.

- Eleven patients suffered lower extremity (5) or unspecified (6) DVTs.
- Two patients developed lower extremity DVT that progressed to PE.
- Two patients developed PE during hospitalization for GI hemorrhage.
- Two patients were diagnosed with subclavian thrombosis.
- Seven patients were diagnosed with PE with no mention of prior DVT.
- One patient developed CVA and DVT during admission for GI hemorrhage.
- One patient developed hemolytic anemia, DIC, and PE felt to be related to gallbladder CA.
- One patient on chronic warfarin developed an extension of her DVT while on celecoxib.

In 17 of the 27 cases, the patients may have been at increased risk of PE or DVT. The following possible risk factors were noted in 12 patients: obesity (3), history of DVT (1), history of ulnar artery thrombosis (1), history of carotid artery occlusion (1), anticardiolipin antibody (2), malignancy (3), SLE (1), unspecified circulatory problems (1), recent surgery (2), total knee replacement (1), and bedridden (1). Four of the 16 also reported concurrent events (CHF-1, hemolytic anemia and DIC -1, Small bowel obstruction and ARDS-1, GI bleed and CVA-1) however it is not clear if these events may have precipitated the thromboembolic event. Five patients were on concomitant medications labeled for thromboembolic disease. These medications include HRT (3), tamoxifen (1), gabapentin (1), methotrexate (1), and fluoxetine (1). None of these medications were listed as co-suspect.

Two patients were on warfarin at the time they experienced their event. One was receiving warfarin for a DVT and had an INR of 6.48. She developed progression of her DVT despite a

supratherapeutic INR. Another patient was on warfarin for anticardiolipin syndrome and previous ulnar artery thrombus. Her INR was maintained between 2 to 2.5. There were another four cases with warfarin listed as a concomitant but the indications were not specified.

There were no apparent risk factors in the remaining 10 patients. None of these cases were very well documented. One physician reported four cases of DVT occurring in elderly nursing home patients who were on celecoxib from 1 to 3 months. The patients past medical history and concomitant medications were not reported

Cerebrovascular Events

We reviewed 31 cases of cerebrovascular events possibly related to the use of celecoxib. In three cases, there was also a diagnosis of MI (2) and PE/DVT (1) these are summarized in those sections of the document. Celecoxib was the primary suspect in 27 cases and methotrexate, warfarin (5), metaxalone, and hydrochlorothiazide were co-suspect in eight cases. In the majority of the cases, the quality of data was adequate for evaluation, but 11 cases were poorly documented.

The cases involved 19 females, 10 males, and two whose gender was not specified. The mean age (n=24) was 75 years old with a range of 24 to 92 years. The mean time of onset (n=20) was 53 days with a range of 1 to 300 days after starting celecoxib therapy. The dose was within the recommended range in 22 cases and not reported in nine cases. Twenty-three patients were hospitalized, six reported disability, and seven reported the event as life threatening. Seven patients reported positive dechallenges and two patients reported negative dechallenge upon discontinuation of the drug. There were six fatalities. The cause of death was secondary to cerebral hemorrhage in two patients, multiorgan failure in two patients, and myocardial infarction in two patients.

Seventeen cases had one or more predisposing factors (hypertension-14, HRT-4, hyperlipidemia-3, DM-6, obesity-1) that might have contributed to the cerebrovascular event. In addition, five patients had concurrent medical conditions such as chronic renal failure with dialysis, carotid endarterectomy, cardiomyopathy/mitral valve regurgitation/sepsis, pancytopenia, severe vascular disease, and GI bleeding that might have played a contributory role in the cerebrovascular event. As with the rofecoxib cases, many patients had more than one risk factor. Five patients had an indication for cardioprotective aspirin therapy (h/o TIA and CVA) and only one was receiving chronic aspirin therapy. Ten patients had a diagnostic work-up, including a CT scan in six to confirm the diagnosis of the cerebrovascular events.

The types of stroke were thrombotic (1), hemorrhagic (13) and indeterminate (17). The case involving the thrombotic event was reported as "thrombotic infarction-stroke" and affected the left middle cerebral artery. The event occurred six weeks after starting celecoxib therapy and left the patient with aphagia and hemiplegia. This obese patient had hyperlipidemia and hypertension that might have contributed to the event.

There were 17 reports of "stroke" and CVA that lacked the specific information to determine the type of the lesion. They were classified as "indeterminate" for the purpose of this evaluation.

Eight of the patients had hypertension, one had hyperlipidemia, and two were on hormone replacement therapy at the time of the event that might have contributed to events.

There were 13 cases involving hemorrhagic cerebrovascular events. The majority of the reports had adequate information and four cases had CT scans to confirm the intracranial hemorrhage. Five patients were receiving warfarin at the time of the event, however the INR was within the normal range in one patient and was unknown in the other four. Five patients had hypertension that might have contributed to event. Although the cerebral hemorrhages may have resulted from rupture of an arteriosclerotic vessel by uncontrolled arterial hypertension, the possibility of local thrombus formation and ischemia prior to cerebral hemorrhage cannot be excluded.

Overall, 25 of 31 patients had precipitating factors or concurrent medical conditions that may have contributed to the cerebrovascular event. Hypertension was the most frequently reported medical condition. The remaining six cases lacked detailed clinical information. The following are representative cases of the cerebrovascular events:

ISR # 3274994, Direct, US, 1999

A 77-year-old female in excellent health received celecoxib 200 mg daily for arthritic trigger finger. After two doses, she experienced rash and increased temperature followed by a right-sided deficit that included speech impairment and inability to walk and use her hand. She discontinued celecoxib without clinical improvement. In the ER, she was diagnosed with "stroke" in progress. The patient was hospitalized and required long-term rehabilitation. Although progress was being made, she had not fully recovered at the time of this report.

ISR #3358036, MFG # SKEL0319990003, US, 1999

A 92-year-old female started taking celecoxib 100 mg twice a day in 1999 for osteoarthritis of the neck. On 7/1/1999 after 2-3 doses of celecoxib, she suffered an acute left-sided cerebrovascular accident while attending mass. She presented with right-sided weakness, and aphagia. Concomitant medications included Skelexin ½ tab (strength unknown) twice daily, nitroglycerin, digoxin, potassium supplement, paroxetine, quinine, klonopin, VitE, Cozaar, and Ca supplement. The strength and the duration of all concomitant medications were unknown. A CT scan was negative for hemorrhage. The rheumatologist indicated celecoxib and Skelaxin as suspect medications

Miscellaneous Thrombotic Vascular Events

We reviewed 10 miscellaneous thrombotic vascular events possibly related to the use of celecoxib. The events were ocular vein occlusion (3), digital ischemia /occlusive thrombosis/limb embolism (5), and ischemic colitis (2).

Ocular Vein Occlusion

There were three cases of ocular vein occlusion with celecoxib therapy. These cases included two females, both 50 years of age, and one male whose age was not reported. Two patients received a recommended dose of celecoxib, and one patient received an unspecified dose. The three patients developed ocular vein occlusion 2 days, 3 months, and 6 months after initiation of celecoxib therapy. One patient had a sulfa allergy and she developed hives, pruritus, facial

swelling, and retinal occlusion within two days of celecoxib therapy. None of the patients had documented hypertension, elevated intraocular pressure, carotid occlusive disease, retinal vasculitis, or systemic coagulopathies. One patient had a history of deep vein thrombosis and one patient had a history of cataract surgery. Concomitant medications included HRT therapy (2), torsemide (1) and unspecified herbal extracts (1). It is unclear what if any role these concomitant medications might have had in this event. One patient reported a positive dechallenge.

Digital ischemia, occlusive thrombosis, or limb embolism

There were five cases of digital ischemia, occlusive thrombosis, or limb embolism temporally associated with celecoxib therapy. Three cases were interesting and are described in the literature⁶. These three events occurred during celecoxib therapy in women aged 37, 41, and 42. All patients received celecoxib \leq 400mg/day as required for arthritis. All of the women had a history of, or had conditions that predisposed them to thrombosis including Raynaud's phenomenon (RP), previous history of thrombosis, systemic lupus erythematosus (SLE), and lupus anticoagulant (LAC). These cases are described below:

- A 42-year-old female with RP began developing acute ischemic changes to the left foot after 2 doses of celecoxib. The angiography confirmed thromboembolic disease. Her concomitant medications were prednisone and hydroxychloroquine. She was treated with methylprednisolone and heparin. Two weeks after starting celecoxib, she was hospitalized with diminished posterior tibial and dorsalis pedis pulses. Thrombolytic therapy failed and she underwent an embolectomy. Her arterial blood flow was partially restored and warfarin therapy was started. One month later, the arterial flow to her foot remained reduced and she developed gangrene in her left great toe and the dorsum of her foot.
- A 37-year-old female with a history of SLE, cerebritis, Raynaud's and Sjogren's syndrome developed pain, cyanosis, swelling of her toes within 2 weeks of celecoxib use. She discontinued celecoxib and was hospitalized and treated with methylprednisolone and aspirin. After she failed to improve clinically she was treated with a single dose of cyclophosphamide. Her ulceration had improved 2 weeks later, but digital ischemia persisted.
- A 41-year-old female with a history of SLE, RP and LAC developed occlusive thrombosis involving the proximal right anterior tibial, proximal peroneal, and proximal posterior tibial arteries 5 months after starting celecoxib. Symptoms of pain, discoloration, and ulcer formation attributed to vasculitis 2 months after initiation of therapy in this patient may, in retrospect, have been due to thrombosis. There was no evidence of atherosclerotic disease. Concomitant medications included methotrexate and prednisone. She received thrombolytic infusion therapy resulting in some improvement. An embolectomy was performed to restore blood flow and she was discharged on warfarin therapy.

The remaining two cases had minimal information stating that the patients developed emboli in the toes or the feet after starting celecoxib. One patient was a 79-year-old female who developed thromboembolism of the toes after two weeks of celecoxib use. The event occurred two weeks after stopping the drug and the hematologist in the case felt the event was unrelated to celecoxib.

Ischemic colitis

There were two cases of ischemic colitis in two females, ages 64 and 77 years old. One patient had a history of diverticulitis and developed ischemic colitis (per reporter) while on celecoxib. The dose and duration of celecoxib was unknown. She was hospitalized and a colonoscopy was positive for GI hemorrhage. The second patient had no significant GI history but developed ischemic colitis after taking celecoxib for one day. She presented with rectal hemorrhage and leukocytosis. Aspirin and estrogen were co-suspect medications. A colonoscopy confirmed the diagnosis of severe colitis. The patient recovered and was discharged. Both cases were confounded by the past medical history or concomitant NSAID use.

C. ETODOLAC

There were a total of 22 cases reviewed that were temporally associated with the use of etodolac. These include seven cases of MI, six cases of PE or DVT, seven cases involving cerebrovascular events, and two other thrombotic vascular events.

	Etodolac (N=22)
Event	Myocardial Infarction-7, PE/DVT-6, Cerebrovascular Events-7, Miscellaneous thrombotic events-2 (Retinal Vein thrombosis-1, Digital thrombosis-1)
Age	Range 24-81 years , mean-65, median-70 (unknown in 4)
Gender	Female-15, Male-7
Outcome *	Death-6, Hospitalization-17, Disability-2
Time to onset	Range 1-210 days, mean-36.5, median-13 (n=14)
Dose	At labeled range-17, (unknown in 5)
Event year	1991-1, 1992-5, 1993-3, 1994-1, 1006-2, 1999-1, 2000-2, unknown-7
Report type	15 day (expedited)-17, periodic-5
Reporter	HCP-17, Non-HCP-5

* A case may have more than one reported outcome.

Myocardial Infarction

We reviewed seven cases of MI possibly related to the use of etodolac. The cases involved four females and three males. The patient’s ages ranged from 50 to 81 years of age with a mean and median of 69 and 70 years, respectively. Five patients were > 65 years of age. The time to onset (n= 4) ranged from 1 to 28 days. The dose of etodolac was within the recommended range in five patients and not reported in the remaining two patients. Five patients required hospitalization, and two patients died.

In 6 of the 7 cases, the patients may have been at increased risk of MI because of past medical history, the presence of cardiovascular risk factors, and/or a recent major concurrent event. One patient had a history of previous MI. One or more cardiovascular risk factors were reported in four patients and include hypertension (2), diabetes (1), hormone replacement therapy (1), and smoking (2). Additionally, the MI in four patients may have been precipitated by a major

concurrent event. The major events include gastrointestinal hemorrhage and ventricular thrombus (1), anaphylaxis (1), anemia (1), and aortic valve disorder (1). No patients were on ASA at the time of the MI, however there was one patient who had years of Naprosyn treatment prior to switching to etodolac.

Overall, only 1 of the 7 patients did not have apparent precipitating factors or cardiovascular risk factors for an MI. The age and past medical history of this patient was not reported. Of the six patients previously mentioned at an increased risk, one had a single cardiovascular risk factor (smoking-1), and two only had the concurrent event (anemia-1, aortic valve disorder-1) but no reported risk factors or past coronary disease. The remaining three patients had at least two risk factors, past medical history, and/or a major concurrent event that may have contributed to the MI.

Pulmonary Embolism and Deep Venous Thrombosis

We reviewed six cases of pulmonary embolism (PE) and deep venous thrombosis (DVT) possibly related to the use of etodolac. The cases involved four females and two males. The mean and median ages were 52 and 70, respectively with a range of 24 to 77 years old. Four patients were ≥ 65 years of age. The time to onset reported in four cases was 11 days, 1, 2, and 7 months. The dose of etodolac was within the recommended range in all six patients. Five patients required hospitalization, and three patients died. The death was secondary to right heart thromboembolism in one patient, adult respiratory distress syndrome in the second patient, and PE in the third patient. Brief descriptions of these events are presented below.

- One patient was diagnosed with right heart thromboembolism on autopsy.
- Three patients developed lower extremity DVT.
- One patient was diagnosed with PE.
- One patient was diagnosed with eosinophilic pneumonia, multifocal thromboemboli, and microinfarction of the lung.

In four of the six cases, the patients may have been at increased risk of PE or DVT. The following risk factors were noted in four patients: HRT or OC use (2), congestive heart failure (1), and probable immobility secondary to hospitalization (1). Two patients reported concurrent acute events (eosinophilic pneumonia-1, interstitial nephritis-1) however it is not clear if these events may have precipitated a PE. There were no apparent risk factors in the remaining two patients, however these two cases were not well documented.

Cerebrovascular Events

We reviewed seven cases of cerebrovascular events possibly related to the use of etodolac. The reports dated back to the early 1990's and in general lacked detailed clinical information. The cases involved five females and two males. The mean age (n=24) was 75 years old with a range of 24 to 92 years. The mean age was 64 with a range of 47 to 74 years. The time of onset (n=4) was 38.5 days with a range of 3 to 120 days. The dose of etodolac was within the recommended range in four patients and was not reported in three.

Four patients had possible predisposing factors (hypertension- 4, DM-2, smoker-1, and HRT-1)

for the cerebrovascular events. Two patients had more than one risk factor. Three patients had imaging (MRI or CT scan) studies and two had confirmed middle artery occlusion and lacunar infarct. All patients were hospitalized and one reported disability as an outcome. There were no reported deaths. The following is a representative case of thrombotic cerebrovascular event:

ISR #936131, MFG # 8-93062-001S, US, 1993

A 73-year-old female with a history of Bell's Palsy presented with stroke-like symptoms while receiving etodolac 900 mg for DJD for unspecified length of time. Concomitant medications included lisinopril, amoxicillin, and Trental. During hospitalization, she developed acute renal failure (BUN/SCr: 135/5.3) in addition to stroke. A CT scan revealed middle cerebral occlusion. Etodolac was discontinued. The patient's clinical condition improved. The adverse events resulted in prolonged hospitalization.

Miscellaneous Thrombotic Vascular Events

We reviewed two miscellaneous thrombotic vascular events possibly related to the use of etodolac. The events were retinal vein thrombosis (1) and digital thrombosis (1).

The case (MFR#8-96239-007S, 1996) of retinal vein thrombosis occurred after five days of etodolac at 300mg twice daily. Six days after discontinuation of etodolac therapy, a female (age unknown) presented with foot pain, swelling, red-purple rash on her lower extremities, headache, and blurred vision. The diagnosis of cryoglobulinemia associated with leukocytoclastic vasculitis was made. The patient suffered permanent damage to her eye due to retinal vein thrombosis. The reporter stated that the ocular event resulted from leukocytoclastic vasculitis and cryoglobulinemia.

The case of digital thrombosis (MFR# 8-92120-0110A, 1992) occurred in a female patient who developed hypersensitivity vasculitis with necrosis and thrombosis of fingertips after taking etodolac for two weeks. The patient was thought to have lupus and a coagulopathy was felt to represent evidence of anticardiolipin antibodies as a manifestation of lupus erythematosus.

EPIDEMIOLOGY

REPORTING RATES: INTRODUCTION, METHODS, RESULTS

Reporting rate comparisons can be used to support a potential safety signal. Background rates can be used to compare an *expected rate* and to an *observed rate* calculated for a specific drug product; these comparisons are usually based on incidence density as the reference rate is given as person-time. Alternatively, if the number of days of drug supplied per prescription is comparable for 2 drugs, reporting rates can be expressed more simply as the total number of cases divided by the total number of prescriptions. Reporting rates in this case are usually presented as cases per 1,000,000 Rx or 10,000,000 Rx.

In general, direct comparisons of reporting rates of different drugs are problematic given differential reporting between drug products. Known causes of differential reporting include secular trends (older versus newer drug product), different sponsors, different prescribers and populations, and varying notoriety in the disease or drug-event association. Notwithstanding these limitations, very large differences (say, greater than 10-fold) in reporting rates between

Risk factors or precipitating factors such as past cardiovascular medical history, underlying disease, concomitant medications, or acute concurrent adverse events were present in many of the cases. It is plausible that the elderly, particularly those with preexisting cardiovascular risk factors would be more susceptible to developing thrombotic vascular events. The thrombotic events did not appear to be dose related as the majority of the patients received the recommended daily dose. The quality of the reports was overall adequate but some cases lacked detailed clinical information and many were potentially confounded.

Although, certain thrombotic events such as CVA, MI, PE, venous thrombosis, and TIA are mentioned in the product labeling, the continued existence of thrombotic events in high-risk population in post-marketing phase is an important finding. The actual number of thrombotic adverse events may in fact be higher due to the underreporting of adverse events in passive surveillance systems.

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**APPEARS THIS WAY
ON ORIGINAL**

OPDRA
REVIEW
Renal Failure

MEMORANDUM

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

DATE: February 14, 2001

FROM: Syed Rizwanuddin Ahmad, M.D., M.P.H., Epidemiologist
Allen Brinker, M.D., M.S., Epidemiologist
Cindy Kortepeter, Pharm.D., Safety Evaluator
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Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation I, HFD-430

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

SUBJECT: OPDRA Postmarketing Safety Review:
Drugs : Etodolac (Lodine, NDA 18-922, 20-584)
Celecoxib (Celebrex, NDA 20-998)
Rofecoxib (Vioxx, NDA 21-042, 21-052)
Reaction: Renal Failure

EXECUTIVE SUMMARY

This review of U.S. postmarketing reports of renal failure associated with the use of celecoxib and rofecoxib is provided in response to your request and in preparation for the Advisory Committee meeting on February 7-8, 2001. We also summarized reports of renal failure for an anti-inflammatory drug, etodolac, for your information.

Renal concerns are addressed in the labeling under the *Clinical Pharmacology*, *Warnings*, *Precautions*, and *Adverse Reactions* sections, with some variation in wording and emphasis, for all three drugs. As stated in the labeling, patients at greatest risk of renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. We evaluated a total of 277 U.S. cases of renal failure possibly associated with etodolac (13), celecoxib (122) and rofecoxib (142). Generally, the cases occurred in high-risk elderly patients with a mean age of 70-77 and mostly in females (62-77%). Almost all of the cases occurred within recommended doses. The mean time to onset of adverse renal symptoms leading to renal failure occurred between 27-42 days (median 10-28 days). Of interest, 32 (32%) of the 100 cases that reported time to onset of rofecoxib associated renal failure occurred acutely within 3 days of starting therapy, and 65 cases (65%) occurred within 14 days. For celecoxib, 4 (5%) of the 81 cases that reported time to onset occurred within 3 days and

33 (41%) occurred within two weeks of starting therapy. The mean creatinine changes (peak SCr minus baseline SCr) when reported ranged from 2.7 to 4.0 mg/dL. Over 70% of cases were hospitalized for treatment, some of which included need for dialysis or death as outcomes.

Common multiple risk factors in these cases included concurrent/underlying medical diseases such as hypertension, diabetes mellitus, congestive heart failure, or pre-existing renal disease; and/or concomitant use of medications such as diuretics and ACE inhibitors, or other NSAIDs.

In conclusion, cases of serious or life threatening renal failure, some leading to fatalities, have been reported in association with etodolac, celecoxib and rofecoxib based on postmarketing data. Renal failure mostly occurred at recommended doses and in some cases, shortly after drug treatment in patients with or without risk factors. Labeling revisions for each drug reflecting the postmarketing experience should be considered. They are listed by drug as follows:

Etodolac

Celecoxib

Rofecoxib

This summary document provides qualitative and descriptive information about reports that have been received for individual drugs from the postmarketing Adverse Event Reporting System (AERS). The data should not be interpreted as supporting conclusions about the comparative safety of the different drugs. Variations in adverse event reporting practices make quantitative safety comparisons of different drugs problematic. Sources of variations may include manufacturer reporting and marketing practices, time on market, different prescribers and treating population, and publicity. These and other factors may result in substantial variations in the types and numbers of reports for individual drugs in the spontaneous Adverse Event Reporting System.

DRUG INFORMATION and LABELING

Etodolac (Lodine®), celecoxib (Celebrex®), and rofecoxib (Vioxx®) are nonsteroidal anti-inflammatory drugs (NSAIDs) that were approved by the FDA in January 1991, December 1998, and May 1999, respectively. The mechanism of action of NSAIDs is primarily by interfering with the enzymatic activity of cyclooxygenase (COX), thereby inhibiting the production of prostaglandins from arachidonic acid. Prostaglandins in the kidney regulate intrarenal blood flow and electrolyte balance.

Two COX isoenzymes have been identified: COX-1 and COX-2. Hypotheses that prostaglandins produced by the COX-2 dependent pathway result in pain, inflammation, and tissue destruction led to the development of agents that selectively inhibit the COX-2 isoform. To date, two agents are commercially available in the U.S. that mainly inhibit the COX-2 but not the COX-1 isoenzyme at recommended doses: celecoxib and rofecoxib. Etodolac is a nonspecific NSAID that inhibits both COX-1 and COX-2.

Lodine is indicated for acute and long-term management of signs and symptoms of rheumatoid and osteoarthritis, as well as for pain management. Celebrex is indicated for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis in adults. It is also indicated to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis, as an adjunct to standard therapy. Vioxx is indicated for the relief of signs and symptoms of osteoarthritis,

management of acute pain in adults, and treatment of primary dysmenorrhea.

Labeling for Vioxx is shown below and is similar for all three products with regard to renal concerns. The information is found under the *Clinical Pharmacology, Warnings, Precautions,* and *Adverse Reactions* sections of the current label.

Clinical Pharmacology, Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended at present because no safety information is available regarding the use of VIOXX in these patients.

Warnings, Advanced Renal Disease

No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore, treatment with VIOXX is not recommended in these patients. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable.

Precautions, Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range.

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease.

Adverse Reactions

Urogenital System: acute renal failure, breast malignant neoplasm, interstitial nephritis, prostatic malignant neoplasm, urolithiasis, worsening chronic renal failure.

The patient package insert of Vioxx advises the patient to inform the physician of kidney disease and mentions the following in the section titled, *What are the possible side effects of VIOXX?*: serious kidney problems occur rarely, including acute kidney failure and worsening of chronic kidney failure.

	Lodine (etodolac)	Celebrex (celecoxib)	Vioxx (rofecoxib)
Initial marketing			
Rx year 1			
Rx year 2*			
Rx year 3			
Total			

*includes data through Q1R3 2000 for both celecoxib and rofecoxib

Selected patient specific data derived from the _____ are shown in the following table. [These data should be considered *qualitative* given the sample size and underlying methodology of the NDTI.]

	Lodine (etodolac)	Celebrex (celecoxib)	Vioxx (rofecoxib)
Time interval	Jan – Dec 1994	Jan – Sept 2000	Jan – Sept 2000
Attribute			
Sex (%)			
Female	58.9	58.7	59.7
Male	37.1	37.7	36.1
Unspecified	3.9	3.6	4.3
Age distribution (%)			
3-9	0.2	0.0	0.0
10-19	2.5	1.3	1.2
20-39	25.8	12.5	17.1
40-59	31.7	33.0	33.9
60-64	7.8	8.3	8.2
65-74	15.8	19.5	18.3
75-84	8.7	16.8	11.9
85+	2.3	3.4	4.4
Unspecified	5.2	5.2	5.0
Dosing strengths	---	200 mg – 75%	25mg – 73.5%
most frequent sig	---	1 per day – 70.1%	1 per day – 85.9%
	---	2 per day – 24.5%	2 per day – 5.5%
	---	100 mg – 22%	12.5 mg – 16.4%
	---	2 per day – 66.9%	1 per day – 78.2%
	---	1 per day – 26.7%	2 per day – 11.7%
	---	---	50 mg – 7.1%
	---	---	1 per day – 87.4%
	---	unspecified – 3%	unspecified – 3%

The labeling for celecoxib is similar to rofecoxib as stated above. However, in the *Adverse Reactions* section, renal toxicity is mentioned under two subheadings as stated below:

Metabolic and nutritional: BUN increased... creatinine increased...

Renal: Acute renal failure, interstitial nephritis.

We note that there is no patient package insert for Celebrex.

The labeling differs between Lodine Tablets and Capsules and Lodine XL Extended Release Tablets. Unlike Lodine XL Extended Release Tablets, the labeling for Lodine Tablets and Capsules does not contain the following: (1) a cautionary statement in the *Clinical Pharmacology* section about use of Lodine in patients with severe renal impairment; (2) advising against use of Lodine in patients with advanced renal disease in the *Warnings* section, and (3) cautioning about use of etodolac in patients with considerable dehydration in the *Precautions* section. Worsening chronic renal failure is not mentioned in the *Adverse Reactions* section for any etodolac product.

Finally, we note that the *Information for Patients* section does not mention the occurrence of renal failure for any etodolac product, or for celecoxib or rofecoxib.

LITERATURE

Reports of renal failure have been described in the medical literature with the COX-2 inhibitors¹⁻⁶. Perazella et al¹ hypothesized that, in patients with prostaglandin-dependent disease states such as volume depletion, cirrhosis, CHF, nephrosis, and CRF, the COX-2 enzyme may have an important role in prostaglandin production. Thus, in selected individuals, inhibition of COX-2 could lead to deterioration of renal function through elimination of COX-2-dependent prostaglandins.

A case report from Germany described a 49-year-old patient who had undergone a kidney transplant 9 years ago.⁵ He had good renal function 4 weeks prior to admission. During the 4 weeks when he received rofecoxib 50 mg daily, his SCr progressively increased from 1.3 to 4.0 mg/dL and recovered to 1.2 mg/dL three days after discontinuation of rofecoxib. The authors referenced an abstract⁶ in which preliminary data suggested that the drug has no detrimental effects on renal function in 3,595 study patients.

DRUG USE

RENAL FAILURE CASE DEFINITION

To accommodate the various ways in which renal failure was annotated in the reports, we defined renal failure in this review as:

- A rise in serum creatinine of ≥ 0.5 mg/dL, if the baseline serum creatinine is ≤ 3.0 mg/dL or
- A rise in serum creatinine of ≥ 1.0 mg/dL, if the baseline serum creatinine is ≥ 3.0 mg/dL or
- A $\geq 20\%$ decline in recovery serum creatinine from peak serum creatinine or
- A peak serum creatinine of ≥ 2 mg/dL and one or more events from the sign/symptom list is mentioned (see below for sign/symptom list) or
- A rise in BUN (> 25 mg/dL) and one or more events from the sign/symptom list is mentioned (see below for sign/symptom list) or
- Any case requiring phosphate binders (i.e., calcium, aluminum) or potassium-binding resins (i.e., Kayexalate) or sodium bicarbonate (to correct acidosis) or
- Any case requiring dialysis or kidney transplant or
- Any case with a reported diagnosis of renal failure or acute renal failure.

"Sign/Symptom" List

↓ UOP (urinary output), ↑ blood pressure, ↑ potassium (serum $K^+ > 5.1$ mmol/L), ↓ sodium (serum $Na^+ < 135$ mmol/L), hyperphosphatemia, metabolic acidosis (serum $HCO_3^- < 20$ mmol/L), anemia (Hct $< 30\%$), azotemia, uremia, edema, symptoms of CHF

METHOD OF SELECTION OF AERS CASES

To capture all possible cases of renal failure, acute renal failure, renal insufficiency, renal vascular related renal disorder, renal tubular disorder, and hypersensitivity related nephropathies, we searched in AERS under the following MedDRA midlevel terms:

- Renal failure and impairment (High Level Term)
- Renal vascular and ischaemic conditions (High Level Term)
- Nephropathies (High Level Group Term)

We reviewed a total of 695 reports from the searches and eliminated duplicates and reports that were miscoded or did not have the events of interest. Most of the cases were renal failure-related events with a few cases of nephritis and renal necrosis. Due to their small numbers, we did not review the cases of nephritis and renal necrosis and only focused on cases of renal failure.

Renal failure cases included reports of renal failure, acute renal failure, or renal insufficiency with data consistent with the above case definition. We used the general criteria outlined in Appendix 1 to exclude cases that were not associated with the drug. The remaining cases can be further classified as either probably or possibly associated with the drug using the criteria outlined in Appendix 2. For the purpose of this review, all probable and possible cases were grouped together for analysis.