1. Gehan's Large-sample Formula *1969 J. Chron. Dis. 21, 629-644*
2. SAS: PROC LIFETEST Program

Figures 1 and 2 are also included as power point documents

Figure 1: Plot of the Cumulative Hazard Function
-Log(Survival Function) Estimates
Cardiovascular Events Only (A, 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B= ——→ 1000 mg/day)

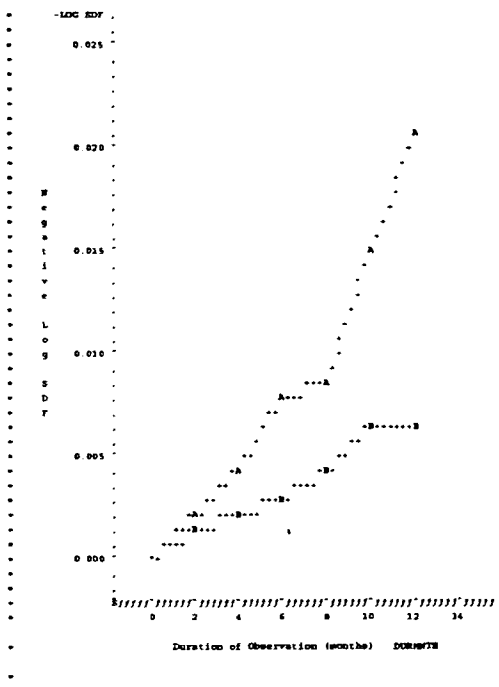

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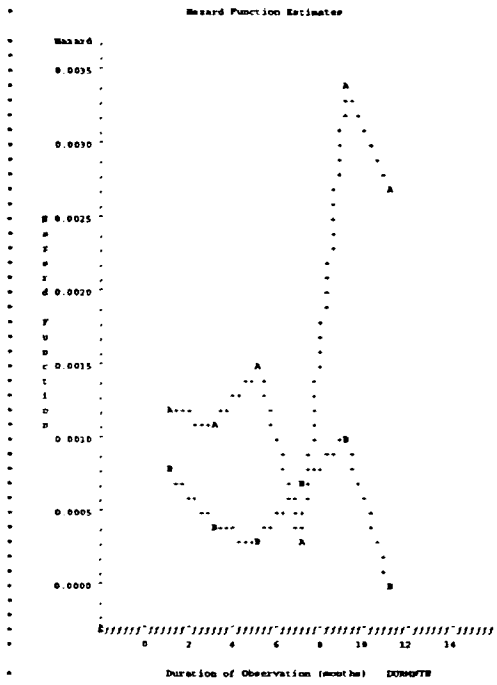
Figure 2:
Hazard Function Estimates

Cardiovascular Events Only (A, 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B= [redacted] 1000 mg/day)
(Note: The hazard rate in the [redacted] needs to be multiplied by 12 for the rate per year)



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MEMORANDUM OF CONSULTATION (Addendum to the Memorandum of March 14, 2002)

DATE: March 20, 2002

FROM: M. F. Huque, Ph.D.
Division of Biometrics III/OB/OPSS/CDER/
HFD-725

TO: Lawrence Goldkind, M.D.
Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products/
HFD-550

SUBJECT: Memorandum of March 14, 2002/
NDA 21-042/ Rofecoxib Labeling Comments

Documents Reviewed: 1) Merck draft of 15 Feb 2002
2) Merck "VIGOR Cardiovascular Hazard Rates Analysis"

This memorandum corrects a few typographical errors that were found in column (2) and (4) of Table 1 of the Naproxen group. This table was sent to you as an attachment of the memorandum of March 14, 2002. The new revised table is labeled as "Table 1 (Revised)" to distinguish it from the old table "Table 1". The old table however had correct hazard rate estimates, standard error of the estimates and confidence intervals for drawing statistical conclusions.

All my earlier comments and suggestions included in the March 14 memorandum hold and do not change.

Attachment:
Table 1 (Revised) gives hazard rate estimates for every 4-month intervals and confidence intervals for the cardiovascular events only, total 45 CV events for the Rofecoxib group and total 19 CV events for the Naproxen group.

cc:
HFD-550
HFD-550/Ms. Gould
HFD-550/Dr. Goldkind
HFD-725/Dr. Stan Lin
HFD-725/Dr. Qian Li
HFD-725/Dr. Huque
HFD-700/Dr. O'Neill
HFD-700/Dr. Anello

***Table 1 (REVISED) :* Hazard Rate Estimates**
Cardiovascular Events Only (Rofecoxib 45 versus Naproxen 19)
(Data extracted from the sponsor's electronic data file)

Rofecoxib Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
0-4	17	625	3734.5	1245	1.36%	0.3324	(0.69, 2.02)
4-8	12	587	3111.5	1037	1.16	0.3348	(0.49, 1.83)
8-12	16	2733	1439.5	480	3.35	0.8388	(1.67, 5.03)

Total 45 Events

Naproxen Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4	9	625	3716.5	1239	0.73%	0.2424	(0.25, 1.21)
4-8	6	591	3099.5	1033	0.58	0.2376	(0.10, 1.06)
8-12	4	2734	1431.0	477	0.84	0.4200	(0.00, 1.68)

Total 19 Events

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Goldkind
4/18/02 09:52:01 AM

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TELECON MINUTES

MEETING DATE: February 08, 2002 **TIME:** 1:30 P.M. **LOCATION:** Corp S300

NDA 21-042/S-007, 012
NDA 21-052/S-004, 007

DRUG: Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, 50 mg
Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25mg/5 mL

SPONSOR/APPLICANT: Merck Research Laboratories

TYPE of TELECON: Labeling Negotiations

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthalmic Drug Product**
Jonca C. Bull, MD	Acting Director, Deputy Director, Office of Drug Evaluation V
Larry Goldkind, MD	Deputy Division Director
James Witter, MD, Ph.D.	Acting Medical Team Leader
Maria L. Villalba, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
Lisa Hubbard, RPh.	Labeling Reviewer
Barbara Gould	Project Manager

INDUSTRY PARTICIPANTS:	**Merck Research Laboratories**
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Robert Silverman	Regulatory Affairs
Dr. Ned Braunstein	Regulatory Affairs
Dr. Diane Benezra	Regulatory Affairs
Ms. Dawn Chitty	Regulatory Affairs
Dr. Alise Reicin	Clinical Research and Sciences
Dr. Kenneth Truitt	Clinical Research and Sciences
Dr. Thomas Simon	Clinical Research and Sciences
Dr. Barry Gertz	Clinical Research and Sciences
Dr. Deborah Shapiro	Clinical Biostatistics
Mr. James Bolognese	Clinical Biostatistics
Dr. Leonard Oppenheimer	Clinical Biostatistics
Dr. Douglas Watson	Epidemiology
Dr. Harry Guess	Epidemiology
Dr. Thomas Bold	Worldwide Product Safety and Epidemiology
Ms. Linda Hostelley	Worldwide Product Safety and Epidemiology
Dr. Douglas Greene	Clinical Scientific and Product Development
Dr. Peter Kim	Research & Development
Mr. Thomas Casola	Office of Medical/Legal

DISCUSSION:

For NDA s 21-042 and 21-052

Advantage study

1. In your June 29, 2001 correspondence you state that the correct number for Table 10 of the Advantage CSR is 352 and 367 low dose-aspirin users in the rofecoxib and naproxen arm, respectively. Please provide corrected Tables 68, 69 and 70 (Serious Clinical AE by aspirin use).

2. Advantage: In addition to the 27 cases referred for adjudication, two additional cases [AN 1867 and 1477] were referred for adjudication making a total of 29 cases evaluated by the CV Adjudication committee. Clarify who decided that those two additional patients were appropriate for adjudication and when the referral for adjudication occurred. Also explain the process that led to not referring AN 065 5005 for adjudication (a cardiac patient who experienced shortness of breath before experiencing "sudden death").

3. Advantage: Approximately 470 patients in each arm took ASA within 30 days prior to study entry. Only approximately 360 in each arm took ASA during the study. Did any of those patients who discontinued ASA present with serious CV thrombotic events during the study?

4. Advantage: Approximately 20 patients in each arm received anti-thrombotic therapy within 30 days prior to study entry. However, as per protocol, anti-thrombotic therapy was not allowed during the study. Did any of the patients who discontinued anti-thrombotic therapy present with serious CV thrombotic events during the study?

Rheumatoid Arthritis Supplement

Regarding RA safety update (S012, submitted 6/27/01)
Please provide treatment allocation for those patients with serious cardiovascular events presented in table 66 of the RA SUR. That information is essential for a complete evaluation of the long-term cardiovascular safety of rofecoxib.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Jane Walling
7/13/01 02:47:14 PM
CSO

Mary Jane Walling
7/13/01 02:49:09 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 28-Nov-01

Re: NDA 21-042/S-012 Clinical Information Request

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

For the sNDA 21-042 please provide an analysis pertaining to the number of subjects who are ACR 50 responders and responders and completers. Please do the same for ACR70.

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 28-September-01
Re: NDA 21-042/S-012 (RA)	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the following information for review for NDA 21042/S-012 (RA):

Please provide summary tables and analyses of mean and median changes in systolic and diastolic blood pressure at 6 and 12 weeks for each dataset in the RA database.

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 18-September-01
Re: NDA 21-042/S012 CV Adjudication	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

● Comments:

Please provide all adjudication packages of patients referred for evaluation to the CV adjudication committee for the RA efficacy supplement (012).

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** July 18, 2001
Re: NDA 21-042 S-012 Clinical Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the following clinical information for review for NDA 21-042 S-012:

1. Please provide where in the RA submission the cardiovascular adjudication packages are located?

2. Table 65 of the RA SUR provides an analysis of confirmed adjudicated or APTC events combined. This analysis is inadequate. Please provide analyses of investigator reported, serious cardiovascular thrombotic adjudicated events and APTC events from RA studies 96, 97, 98 and 103. (Since study 068 did not use the adjudication process do not include study 068 in this analysis.)

3. Please clarify how the calculation of patient years at risk was made. Please provide the number of patients randomized to each treatment group (placebo, rofecoxib 12.5, 25, 50 mg and naproxen) regardless of exposure.

Please call if you have any questions.

Thanks,

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 2 (including cover)	**Date:** 08-August-01
Re: NDA 21-042 Clinical Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Please provide the following clinical information for review for NDA 21-042 S-012:

1. In your June 29, 2001 correspondence you state that the correct number for Table 10 of the Advantage CSR is 352 and 367 low dose-aspirin users in the rofecoxib and naproxen arm, respectively. Please provide corrected Tables 68, 69 and 70 (Serious Clinical AE by aspirin use).

2. Advantage: In addition to the 27 cases referred for adjudication, two additional cases [AN 1867 and 1477] were referred for adjudication making a total of 29 cases evaluated by the CV Adjudication committee. Clarify who decided that those two additional patients needed evaluation and when the referral for adjudication occurred. Also provide rationale for not referring AN 065 5005 for evaluation.

3. Advantage: Approximately 470 patients in each arm took ASA within 30 days prior to study entry. Only approximately 360 in each arm took ASA during the study. Did any of those patients who discontinued ASA present with serious CV thrombotic events during the study?

4. Advantage: Approximately 20 patients in each arm received antithrombotic therapy within 30 days prior to study entry. However, as per protocol, antithrombotic therapy was not allowed during the study. Did any of the patients who discontinued antithrombotic therapy present with serious CV thrombotic events during the study?

5. Regarding RA safety update (S012, submitted 6/27/01)
   Please provide treatment allocation for those patients with serious cardiovascular events presented in table 66 of the RA SUR. That information is essential for a complete evaluation of the long-term cardiovascular safety of rofecoxib

Please call if you have any questions.

Thanks,

BJ Gould

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 610 397-2516	**Fax:** 301 827-2531
Phone: 610 397-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** June 19, 2001
Re: NDA 21-042	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Studies 096 and 097

In regards to the supplemental New Drug Application NDA 21-042/S-102: VIOXX for Rheumatoid Arthritis, we request that Merck and Co. submit to the FDA an efficacy analysis of all randomized subjects and all randomized subjects who took at least one dose of the drug, for the ACR 20 efficacy endpoint.

Please call if you have any questions.

APPEARS THIS WAY
ON ORIGINAL

(B4)

69 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

MEMORANDUM

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

DATE: December 29, 2000

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

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

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

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

INTRODUCTION/ EXECUTIVE SUMMARY

Our objective was to review the postmarketing experience of celecoxib and rofecoxib relating to gastrointestinal bleeding, obstruction, perforation, or stenosis. Although it may not be appropriate to directly compare postmarketing adverse event data for celecoxib and rofecoxib with older data for nonselective nonsteroidal anti-inflammatory drugs, a review of similar events for etodolac was done to provide perspective. We concentrated on the most serious gastrointestinal events, those resulting in death.

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

Generally, the labeling for celecoxib and rofecoxib reflects the risk of fatal gastrointestinal bleeding, obstruction, perforation, and stenosis observed in postmarketing experience.

[ ]

DRUG INFORMATION/LABELING

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

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

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

MEDICAL LITERATURE SUMMARY

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

SELECTION OF CASE SERIES

On October 25, 2000 we searched the AERS database for cases of gastrointestinal bleeding, perforation, obstruction, or stenosis related to etodolac, celecoxib, and rofecoxib. The cases were identified using the higher level group terms (HLGTs) *Gastrointestinal Haemorrhages NOS, Gastrointestinal Stenosis and Obstruction,* and *Gastrointestinal Ulceration and Perforation.* AERS contained 214 reports (190 domestic) linked to etodolac, 744 (705 domestic) linked to celecoxib, and 829 (613 domestic) linked to rofecoxib. We limited our 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 prescibed 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 H_2-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 H_2-receptor antagonist or proton pump inhibitor concomitantly with celecoxib.

Two cases are presented below.

AERS 3305112, MFR 990709-SK489, US (MD), 1999
An 87-year-old woman with past medical history of peptic ulcer disease, arteriosclerotic heart disease, aortic valve disorder, and diabetes was prescribed an unknown dose of celecoxib to treat osteoarthritis. Her concomitant medications included warfarin. After 37 days of therapy with celecoxib, the patient presented to the emergency room with gastrointestinal bleeding. She died in the emergency room.

AERS 3472602, US (NC), 2000
A 92-year-old female nursing home resident with past medical history of hypertension, chronic obstructive pulmonary disease, glaucoma, parkinsonism, and arteriosclerotic heart disease, but with no history of peptic ulcer disease, was prescribed celecoxib 100 mg twice a day for an unknown reason. After receiving celecoxib for an unknown period of time, she was transferred to the hospital with lethargy, nausea, diarrhea, and abdominal pain. Her hemoglobin and hematocrit dropped from 12 g/dL and 36%, respectively, on admission to 10.7 g/dL and 31.7%, respectively, after one day of hospitalization. Esophagogastroduodenoscopy (EGD) revealed a one-centimeter bleeding ulcer. Epinephrine was injected in an attempt to stop the bleeding. The patient's condition deteriorated, a do-not-resuscitate (DNR) order followed, and the patient died.

Rofecoxib

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

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

Significant concomitant medications	ASA (8), Clopidogril (2), Corticosteroid (2), Warfarin (6) Antacid, H2 blocker, or PPI (4)

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

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

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

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

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

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

Two cases are presented below.

AERS 3397744, WAES 99111907, US (FL), 1999
An 87-year-old female independent retirement village resident with a past medical history of irritable bowel syndrome, paroxysmal atrial tachycardia, hypertension, and spastic colon, but no history of peptic ulcer disease, was prescribed rofecoxib 25 mg a day for sciatic neuralgia. Five days later she presented to the emergency room via ambulance with diaphoresis, weakness, and hypotension. The diagnosis on admission was septic or cardiogenic shock. An exploratory laparotomy revealed a perforated

duodenal ulcer. Two liters of dark grayish fluid were removed from the peritoneal cavity, and the perforated ulcer was repaired. The patient was transferred to the post-anesthesia care unit on vasopressor support with a blood pressure of 80/30 mm Hg, a heart rate of 60 beats per minute, and respiratory rate of 13 per minute. She went into cardiac arrest and died despite attempts to resuscitate her.

AERS 3424661, WAES 00010945, US (SC), 2000
An 85-year-old man with a history of atrial fibrillation, and an unspecified vascular disorder was prescribed rofecoxib to treat back pain. Concomitant medications included clopidogril and warfarin. Six days later the patient was hospitalized with unspecified gastrointestinal bleeding confirmed by endoscopy. On admission, the patient's hemoglobin was 5-7 g/dL. Rofecoxib and warfarin were discontinued. Vitamin K and 4 units of packed red blood cells were administered, and the patient stabilized. However, 3 days later the patient developed an arrhythmia and died suddenly. The attending physician believed the patient might have had a cerebrovascular accident caused by discontinuation of warfarin.

CONCLUSION/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

[ ]

[ ]

Signed 12-29-00 by

Joyce Weaver, Pharm.D., Safety Evaluator

Concur:

Signed 12-29-00 by

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

APPEARS THIS WAY
ON ORIGINAL

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 Median age range	79 78 69 – 94	77 78.5 46 – 99	76 80 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 Median onset range	35.7 days 30 days 17 – 60 days (Onset data available for 3 cases)	25.7 days 14 days 1 – 115 days	43 days 21 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†	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

APPEARS THIS WAY
ON ORIGINAL

/s/

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

Julie Beitz
1/5/01 09:04:02 AM
DIRECTOR

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
Joyce Weaver, Pharm.D., Safety Evaluator
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 rofexocib 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

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.

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:

[ ]

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 ——— in the *Precautions* section. Worsening chronic renal failure is not mentioned ———

Finally, we note that the *Information for Patients* section does not mention ——— 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 inhibiors[1-6]. Perazella et al[1] 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 abstract[6] in which preliminary data suggested that the drug has no detrimental effects on renal function in 3,595 study patients.

DRUG USE

Total prescriptions for the first three years of marketing, as well as information on patient gender, race and dosing strengths administered will be presented for Lodine, Celebrex and Vioxx. ———) total prescriptions for the first three years of marketing are presented in the following table. [These totals are used to calculate reporting rates (Under EPIDEMIOLOGY).]

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

*includes data through QTR3 2000 for both celecoxib and rofecoxib

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

	Lodine (etodolac)	Celebrex (celecoxib)	Vioxx (rofecoxib)
Time interval	Jan – Dec 1994	Jan – Sept 2000	Jan – Sept 2000
Attribute			
Sex (%)			
Female			
Male			
Unspecified			
Age distribution (%)			
3-9			
10-19			
20-39			
40-59			
60-64			
65-74			
75-84			
85+			
Unspecified			
Dosing strengths	---	**200 mg –** [redacted]	**25mg –** [redacted]
most frequent sig	---	1 per day – [redacted]	1 per day – [redacted]
	---	2 per day – [redacted]	2 per day – [redacted]
	---	**100 mg –** [redacted]	**12.5 mg –** [redacted]
	---	2 per day – [redacted]	1 per day – [redacted]
	---	1 per day – [redacted]	2 per day – [redacted]
	---	---	**50 mg –** [redacted]
	---	---	1 per day – [redacted]
	---	**unspecified –** [redacted]	**unspecified –** [redacted]

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 ≥ 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.

RESULT OF SELECTION OF CASE SERIES

Etodolac

A search of the AERS database on October 26, 2000 for renal cases based on the search strategy (see Method of Selection of Cases) captured a total of 65 cases for etodolac. A hands-on review of the cases resulted in the exclusion of 52 cases primarily due to duplication, erroneous drug, renal failure exacerbated by concomitant acute disease states (for example, GI bleed, sepsis), nonspecific renal disorder, or failure to meet the case definition. The remaining 13 cases matched our case definition for renal failure and are included in the case series for further analysis.

Celecoxib

A search in AERS through October 26, 2000 identified 256 reports of renal events for celecoxib based on our search strategy. A hands-on review of these reports identified 122 unduplicated reports of renal failure which met our case definition. Reports of abnormal kidney function, fluid retention, oliguria, renal insufficiency not meeting the case definition (with available lab data), hepatorenal syndrome, and renal failure precipitated by concomitant rhabdomyolysis or GI bleed were excluded.

Rofecoxib

A search of the AERS database on October 26, 2000 captured a total of 374 cases for Vioxx. A hands-on review of the cases resulted in the exclusion of 232 cases primarily due to duplication, erroneous drug, renal failure exacerbated by concomitant acute disease states (i.e., GI bleed, rhabdomyolysis, sepsis), nonspecific renal disorder, failure to meet the case definition, or isolated oliguria or fluid retention with no indication of renal failure. The remaining 142 cases matched our case definition for renal failure and are included in the case series for further analysis.

We noted that the original searches for renal events revealed 92 reports of fluid retention without mention of renal failure. Most cases were associated with weight gain, edema, dyspnea, or congestive heart failure.

The number of domestic cases suggesting renal failure, in association with each of the three drugs, that were analyzed in our final case series are as follows:

Etodolac	13
Celecoxib	122
Rofecoxib	142

SUMMARY OF CASES

Descriptive statistics for the 3 renal failure case series are provided in the attached Table 1. A summary of cases for each drug case series follows:

Etodolac (13)

Additional demographics:	
Daily dose (based on 8 cases):	Range 400-900 mg, median 600 mg, mean 611 mg
Indication:	Osteoarthritis-6, rheumatoid arthritis-1, unspecified arthritis-3, lumbosacral sprain-1, unknown-3
Dechallenge:	positive- 8
Rechallenge:	no patient was rechallenged
Report year:	1991-4, 1992-2, 1993-4, 1996-1, 1998-2
Report type:	15-day-6, periodic-5, direct-2

The mean age of the patients was 77.3 years. The mean onset was 26.6 days after instituting therapy with etodolac. Seven cases reported time to onset. There was a 3.3:1 predominance of females. The dose of etodolac was within labeled dosing in all cases in which the dose was reported. Based on the 4 cases in which an increase from baseline serum creatinine was reported, the mean increase in serum creatinine was 2.7 mg/dL (range 2-3.9 mg/dL). The data were not sufficient to support a finding of a dose-response effect on serum creatinine. In 3 of the 4 cases in which a change in serum creatinine from baseline was reported, the patient was receiving 600 mg of etodolac a day.

Eleven of the 13 patients who developed renal failure had risk factors for acute renal failure in addition to taking etodolac. These additional risk factors included baseline chronic renal insufficiency, concomitant angiotensin converting enzyme inhibitor, concomitant diuretics, concomitant methotrexate, concomitant NSAIDs, congestive heart failure, hypercalcemia, hypertension, hypotension, and metastatic malignancy. Many patients had more than one risk factor. Three patients had chronic renal insufficiency before beginning etodolac.

Three patients died, and in another case the reporter considered the episode life-threatening. Two of the deaths appear to be directly attributable to renal failure. In the third case resulting in death, renal failure apparently resulted in decreased methotrexate excretion and an increased methotrexate plasma concentration. Pancytopenia related to increased methotrexate plasma concentration resulted in the death of the patient.

Eight patients recovered after the drug was discontinued. In the three cases in which timeframes are provided on recovery to baseline serum creatinine, recovery occurred in three days, three weeks, and two months. In another case a drop in serum creatinine from 3.1 to 2.1 mg/dL occurred within two days of discontinuation of etodolac. However, information on further recovery is not known, and the patient's baseline serum creatinine was not provided. Nonspecific qualitative statements regarding recovery were provided in four cases; for example, the reports described the patients' conditions after discontinuation of the etodolac as "subsequently

recovered," "slowly recovered," "subsequent improvement," and "recovered."

Two cases are presented below.

1. ISR# 5004660, MFR# 893146009S, US (ME), 1993
A 78-year-old woman with a prior medical history of hypertension, arteriosclerotic heart disease, and cerebral vascular accident, but no prior history of renal function impairment, was prescribed etodolac 600 mg a day for osteoarthritis. Concomitant medications included atenolol and chlorthalidone. After an unknown period of time, the dose of etodolac was increased to 900 mg a day because the patient was not receiving sufficient effect with the dose initially prescribed. After a "short" but unspecified period of time, the patient was admitted to the hospital with a 3-to-4-day history of progressive shortness of breath and weakness. Scattered rales were noted in the lower lung fields on examination. A chest x-ray was consistent with congestive heart failure. Blood urea nitrogen was 123 mg/dL, and serum creatinine was 9.8 mg/dL. The patient did not respond to treatment with fluid challenge, intravenous furosemide and dopamine, and she died after 8 days of hospitalization.

2. ISR# 48039048, Direct, US (GA), 1991
A 75-year-old woman with a prior medical history of hypertension, hypertrophic cardiomyopathy, tachyarrhythmias, and noninsulin dependent diabetes mellitus was prescribed etodolac for osteoarthritis and back pain. Concomitant medications included digoxin and furosemide. After taking etodolac for 4 days, she presented to the emergency room with severe fatigue and confusion. She was diagnosed with renal failure and digoxin toxicity, and she was admitted to the hospital. Serum creatinine on admission was 5.9 mg/dL, up from her baseline of 2 mg/dL. Etodolac was discontinued, and the patient recovered.

Celecoxib (122)
Additional demographics include:

Daily dose:	Range 100-800 mg, median 200 mg, mean 224 mg (n=88)
Dechallenge:	Positive-55
Rechallenge:	Positive-2
Report type:	15-day-20, periodic-59, direct-43

The median age was 72 years (see Table 1). Age and gender were not stated in 18 and 14 reports respectively. Among the cases where gender was reported, there was a preponderance of females. Eighty-one (66%) cases mentioned time of onset of adverse renal symptoms from the start of Celebrex therapy, and the median time was 18 days. In 4 (5%) cases, the time of onset was less than or equal to 3 days and in 33 (41%) cases this was less than or equal to 14 days. Dose was mentioned in 88 (72%) reports and it was within the labeling recommendation in all patients except one. One patient received at least twice the recommended dose of Celebrex [400 mg twice a day (800 mg total daily dose)] for his unspecified backache (off-label indication) and osteoarthrosis. Serum creatinine (SCr) changes (peak SCr minus baseline SCr) were reported in 44 cases (36%). The mean SCr change was 2.9 mg/dL (range 0.5 – 7.6 mg/dL). In all 30 cases where SCr changes were reported as 2 mg/dL or above, the reported total daily dose of Celebrex

was within the recommended dosage. Those cases reporting a peak and recovery serum creatinine (37 cases, 30%) noted an average decline of 1.8 mg/dL (range = 0.5 – 4.5 mg/dL) to recovery. Positive dechallenge was noted in 55 (45%) cases and positive rechallenge in 2 of these cases which are described below. Sixty-four percent of the patients were hospitalized and 12 percent underwent dialysis. In nearly 20 percent of cases the reporter considered that the adverse renal event was life threatening. Eight (6%) patients died and these can be attributed to renal failure in association with Celebrex use.

Forty-five cases reported a baseline SCr. Of the 45 cases, 15 (33%) had a baseline SCr ≤ 1.0 mg/dL, 27 (60%) had a baseline SCr ≤ 1.2 mg/dL, and 32 (71%) had a baseline SCr ≤ 1.5 mg/dL. There were 2 cases with apparently normal kidney function and no history of a renal problem who experienced renal failure. In one of these two cases, the time of onset of renal failure was 4 days and 30 days in the other.

All cases presented with risk factors for renal failure aside from Celebrex use with the exception of 26 (21%) case reports, which did not state any risk factors. Of the 96 cases reporting risk factors, the most prevalent medical condition reported was hypertension (39%), followed by diabetes mellitus (29%), congestive heart failure (22%) and pre-existing or history of renal failure or renal insufficiency (21%). Among patients with pre-existing renal disease, worsening of the patient's renal status was observed. The most common medications reported were concomitant diuretics (39%), followed by concomitant ACE inhibitors (19%), and concomitant or recent use of other NSAIDs (5%).

Two representative cases follow:

1. ISR#3410368-0, Direct Report, US (MA), 1999
A 78-year-old female with a history of hypertension, coronary artery disease, diabetes mellitus, and peripheral neuropathy was started on celecoxib 200 mg (unspecified frequency) for osteoarthritis. Her baseline SCr was 1.1 and BUN 16. Approximately 120 days later her SCr increased to 3.1 and BUN to 40 and her medications namely Celebrex, captopril, HCTZ were discontinued. At that time she was also on sulfamethoxazole plus trimethoprim for her UTI and this combination was also discontinued. About 35 days later her SCr was 1.2 and BUN 20. Nearly two months later her SCr was 1.2 and BUN 29 and Celebrex 100mg QD was restarted. About 12 days later her SCr increased to 2.0 and BUN 42 and Celebrex was stopped. A week later her SCr was 1.4 and BUN was 30. Concomitant medications included atenolol, simvastatin, insulin and sertraline.

2. ISR# 3488770-0, Mfr# 991208-SK443, US (ND), 2000
A physician reported that an 88-year-old female under his care on celecoxib therapy for unspecified disease/dose/duration went into acute renal failure (ARF) for which she was hospitalized for 10 days. Per her physician the ARF resolved rapidly after unspecified therapy. Within a month the physician restarted her on celecoxib and she was hospitalized again with ARF and had to undergo dialysis. Her SCr rose to 4.3 and BUN to 58. Celecoxib was discontinued and she again responded to unspecified therapy. There is no mention of

concomitant illness or meds.

Rofecoxib (142)

Additional demographics:

Daily dose:	Range 12.5-50 mg, median 25 mg, mean 26.6 mg
Rechallenge:	Positive - 1; Negative - 1
Report type:	15-day-108, periodic-0, direct-34
Report year:	2000-114, 1999-28

The patients were predominantly female and the average age was 73 years (range = 33 - 101 years). Twenty-nine cases (20%) did not report age and 18 cases (13%) did not report gender. Among the cases where gender was reported, there was a preponderance of females. The dose of Vioxx was reported in 103 cases and fell within the recommended range of 12.5 to 50 mg once daily with a mean of 26.6 mg and a median of 25 mg per day. The onset of adverse renal symptoms was reported in 100 cases and occurred at an average of approximately 33 days after the initiation of Vioxx; however, the median was 10 days. Thirty-two (32%) cases occurred within 3 days and 65 (65%) cases occurred within 14 days. Fifty-two cases noted a baseline and peak serum creatinine which showed a mean creatinine change of 4.0 mg/dL (range = 0.4 - 12.9 mg/dL). Those cases reporting a peak and recovery serum creatinine (45 cases, 32%) noted an average decline of 2.8 mg/dL (range = 0.4 - 11.1 mg/dL) to recovery. There were only 2 rechallenge cases where one was positive and the other negative at the time of reporting. Nearly 70% of the cases required hospitalization and 15% reported the need for dialysis. Death attributed to Vioxx-initiated renal failure occurred in 6%.

Cases where patients were stable on multiple concomitant medications were included in the case series. Of the 142 cases, 12 reported normal kidney function or no history of renal dysfunction prior to initiating Vioxx. Fifty-four cases reported a baseline SCr. Of the 54 cases, 10 (19%) had a baseline SCr $\leq$ 1.0 mg/dL, 16 (30%) had a baseline SCr $\leq$ 1.2 mg/dL, and 30 (56%) had a baseline SCr $\leq$ 1.5 mg/dL.

Common risk factors consist of concomitant disease states and medications and were multiple for most patients. Of the 112 cases reporting risk factors, the most prevalent medical condition reported was hypertension (33%), followed by diabetes mellitus (27%), pre-existing or history of renal failure or renal insufficiency (25%), congestive heart failure (21%), and hyperuricemia - evidenced by gout or allopurinol use - (12%). The most common medications reported were concomitant diuretics (54%), followed by concomitant or recent history of selective or nonselective nonsteroidal anti-inflammatory agents (42%), and angiotensin converting enzyme inhibitors (36%).

Four representative cases follow:

1. ISR# 3498492-8, Direct Report, US (IN), 2000

A 79 year-old female with concurrent DM, lymph and peripheral edema, ASHD, and a prior

mastectomy was placed on Vioxx for osteoarthritis. Concomitant medications include Lasix, Zaroxolyn, potassium, and Zestril. The patient was admitted to the hospital 3 and 1/2 weeks later for edema. Laboratory tests showed a SCr = 4.3, BUN = 97, K^+ = 6.8, and Phosphorus = 7.2. The nephrologist diagnosed acute renal failure and hyperkalemia due to Lasix, Zestril, Vioxx, and potassium. Vioxx was discontinued and the patient was stabilized and discharged one week later. The patient restarted Vioxx without the physician's consent and, again, experienced acute renal failure (SCr = 8.3, BUN = 65, K^+ = 5.5, Phosphorus = 10.6).

2. ISR# 3351628-1, Mfr# WAES 99080373, US (MA), 1999
A 73 year-old female with multiple medical problems including osteoporosis, HTN, DM, COPD, atrial fibrillation, asthma, and angina, developed renal failure, CHF, digoxin toxicity, and thrombocytopenia after 1 week of Vioxx. Admission labs revealed SCr = 2.2, BUN = 50, pH = 7.1, K^+ = 7.0, and digoxin = 5.6 (baseline labs: SCr = 1.7, BUN = 25-28, and digoxin < 2.0). She experienced a cardiac arrest, was intubated, and revived. She also required hemodialysis.

3. ISR# 3460052-2, Direct Report, US (IL), 2000
A 78 year-old male with a SCr = 1.4 and digoxin = 1.9 five days prior to initiating Vioxx developed an elevated SCr of 3.7 and a digoxin level of 4.2 four days after beginning Vioxx. Vioxx was discontinued and Digibind was administered. His SCr was 2.5 six days after discontinuation.

4. ISR# 3490859-7, Direct Report, US (IA), 2000
An 84 year-old female with multiple medical problems including DJD, osteoporosis, and renal vascular disease was prescribed Vioxx 12.5mg daily. After 3 weeks, the dose was increased to 25mg daily and after 1 week, her SCr had increased from a baseline of 1.6 to 3.7 and her BUN increased from 33 to 81. Concomitant medications were glucosamine, meclizine, and levothyroxine.

EPIDEMIOLOGY

- **REPORTING RATE CALCULATIONS**

Reporting rate comparisons can be used to support a potential safety signal. Observed reporting rates for a specific drug product can be compared to expected or background rate of the event(s) of interest; these comparisons are usually based on incidence density since 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 ——— Rx or ——— Rx.

In general, direct comparisons of reporting rates of different drugs based on postmarketing spontaneous reporting data are problematic given variations in reporting between drug products. Known sources of variations in reporting include time on market or secular trends (older versus

newer drug product), different manufacturer reporting and marketing practices, different prescribers and treating populations, varying notoriety in the disease or drug-event association and publicity. These and other potential factors may result in substantial differences in the types and numbers of reports for individual drugs in the postmarketing Adverse Event Reporting System (AERS).

For the purposes of calculating reporting rates for this consult, time-on-market and numerous other factors preclude a meaningful comparison between Lodine and the COX-2-selective agents. Therefore, the following table is limited to Celebrex and Vioxx and contains the number of cases for each agent. Reporting rates were calculated using [redacted] total prescriptions for each product through QTR3 2000. The reporting rate ratio (Vioxx / Celebrex) is [redacted]

Cases for Celebrex	Rate for Celebrex (per [redacted] Rx)	Cases for Vioxx	Rate for Vioxx (per [redacted] Rx)	Reporting rate ratio
122	[redacted]	142	[redacted]	[redacted]

- **INTERPRETATION**

As noted in the preceding paragraph, there are many factors that can result in a difference in reporting rates. In addition to the ones mentioned, comparison of rates/Rx for Celebrex and Vioxx may overestimate differences between these drugs if the mean duration of Celebrex prescriptions is less than for Vioxx. [redacted] data indicate that about [redacted] of Celebrex users take 2 tablets/day versus [redacted] of Vioxx users, suggesting the possibility that a Celebrex prescription may run out faster than a Vioxx prescription.] Thus, finding approximately a 2-fold difference in the rate at which acute renal failure has been reported for these two drug products has questionable clinical significance.

It is interesting to note that the onset of acute renal failure was faster (median 10 versus 18 days) and the creatinine change higher (mean 4.0 versus 2.9 mg/dL) for Vioxx in comparison to Celebrex. Again, these findings cannot be used to make quantitative safety comparisons between Vioxx and Celebrex. But taken together with the qualitative comparison of the ARF reporting rates, they support a need for further clinical research into the different renal effects of COX-2 agents.

CONCLUSION/RECOMMENDATION

Etodolac

We evaluated 13 cases of renal failure in the AERS database temporally related to therapy with etodolac. Most of the cases occurred in high-risk elderly patients. Eighty-five percent of the patients in the case series had risk factors for renal failure in addition to taking etodolac. Many

patients had more than one risk factor for renal failure. Two patients in the series died due to renal failure.

The prevalence of risk factors in the patients in the case series suggests that patients at increased risk for renal function impairment should be monitored closely while taking etodolac. We recommend that the labeling for all etodolac products

[redacted]

Celecoxib

Serious or life threatening renal toxicity including acute renal failure leading to fatalities has been reported in association with Celebrex use. One hundred and twenty-two domestic cases of Celebrex-associated renal failure have been identified in the FDA's AERS database. The current labeling of Celebrex mentions acute renal failure, interstitial nephritis, increased BUN and creatinine under the *Adverse Reactions* section. Under the *Precautions* section, the *Renal effects* statements regarding renal decompensation indicate that patients at greatest risk of this reaction are those with impaired renal function and other diseases. While it is true that patients at greatest risk of renal failure are those with risk factors, there were cases of renal failure reported in

patients with apparently normal kidney function. Additionally, the *Precautions* section implies renal injuries occur from long-term administration of NSAIDs. Our review shows that 41% of the cases occurred within two weeks and 5% within 3 days of starting therapy. Finally, the labeling has no reference to renal toxicity in the *Information for Patients* section.

We recommend that the labeling of Celebrex be

Rofexocib

One hundred and forty-two cases of renal failure temporally associated with Vioxx were evaluated. The patients were mostly elderly females with multiple risk factors. Cases reporting risk factors commonly included pre-existing disease states: hypertension, diabetes mellitus, renal dysfunction, congestive heart failure, hyperuricemia, and/or medications: concomitant diuretics and/or angiotensin converting enzyme inhibitors, and concomitant or recent use of other NSAIDs.

It is interesting to note that of the 100 cases that reported a time to onset of adverse renal symptoms, 32 (32%) cases occurred within 3 days and 65 (65%) occurred within 14 days. The majority of patients recovered upon discontinuation of the medication; nevertheless, greater than 15% reported the need for dialysis, nearly 70% required hospitalization, and 6% attributed death due to Vioxx-initiated renal failure. The dose did not appear to be a factor as all dosing was within the recommended range. Pre-existing renal disease (chronic renal failure/insufficiency, or history of renal failure/insufficiency) was reported in 25% of the cases. Twelve reported normal kidney function or no history of renal dysfunction prior to initiating Vioxx.

Our findings are consistent with the current labeling under *Precautions* in that patients at greatest risk are those with impaired renal function, heart failure, those taking diuretics, ACE inhibitors, and the elderly. However, the labeling refers to long-term administration of NSAIDs and it was noted in the evaluation of our case series that nearly one-third of our cases reported an acute onset (0-3days).

We recommend that labeling be revised to

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2/12/2001/COX2RF2.12.doc

Table 1. Descriptive statistics for the renal failure case series. [Includes cases classified as "renal failure" or "acute renal failure". These aggregate statistics are based on cases with the selected data element; i.e. null values excluded.]

		Celebrex (celecoxib) (n=122)	Vioxx (rofecoxib) (n=142)	Lodine (etodolac) (n=13)
Age (years)	Median	72	75	77
	Mean	69.7	73.1	77.3
	Range	14-101	33-101	72-84
Sex	%Female	62.0	68.5	76.9
	%Male	38.0	31.5	23.1
Onset (days)	Median	18	10	28
	Mean	41.7	32.7	26.6
	Range	1-300	1-450	4-45
Cases with onset @ <=3 days		4	32	0
@ <=14 days		33	65	0
Creatinine change (baseline to peak, mg/dL)	Median	2.4	3.3	2.4
	Mean	2.9	4.0	2.7
	Range	0.5-7.6	0.4-12.9	2-3.9
Outcome (% appearance)		Hospitalized (64.0) Life threatening (19.7) Dialysis (12.3) Death (6.6)	Hospitalized (69.9) Life threatening (23.1) Dialysis (15.4) Death (6.3)	Hospitalized (69.2) Life threatening (7.7) Death (15.4)
Dose	Median	200	25	600
	Mean	224	26.6	611
	Range	100-800	12.5-50	400-900
Cases > recommended dose*		1	0	0
Reporting rate** (per ——— Rx)		—	—	—

* >400 mg per day for Celebrex; >50 mg per day for Vioxx; > 1,000 mg per day for Lodine

**Based on cases received through 10/26/2000 for Celebrex and Vioxx and through marketing year 3 for Lodine (10 of 13 cases)

Appendix 1

Criteria for excluding cases for further review or analysis

- Events not related to the drug administration, e.g., renal failure reported while patient had car accident and went into multi-organ failure
- Events resulting from the previously existing underlying renal disorder
- Events more related to (or confounded by) another suspect drug (2 suspects reported) or concomitant drug(s), based on their therapy dates, and the other drug(s) is labeled for renal failure
- Events for which causality cannot be assessed due to multiple suspect drugs (3 or more)
- No evidence that the patient received the drug, including unconfirmed second hand report
- No evidence that the event of interest occurred including unconfirmed second hand report (i.e., reporter was notified by competitor's drug representative)
- Evidence of hepatorenal syndrome (concomitant liver and renal failure)
- Renal failure precipitated by concomitant rhabdomyolysis, acute GI bleed, sepsis
- Fluid retention with no indication of renal failure
- Event did not meet the case definition for renal failure

Appendix 2

Criteria for Probable cases

- No past history of renal insufficiency or disorder, normal baseline serum creatinine/BUN, within a reasonable time after drug administration the patient developed diagnosed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition, events abated after drug discontinuation. No concomitant drugs reported.
- Patient with a past history of renal insufficiency, normal baseline serum creatinine/BUN, within a reasonable time after drug administration developed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition, events abated after drug discontinuation. No concomitant drugs reported.
- Patients with or without a past history of renal insufficiency or disorder, normal baseline serum creatinine/BUN, within a reasonable time after drug administration developed diagnosed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition. Events abated only after suspect drug discontinuation. Concomitant drugs, which were not labeled for renal failure, were continued.

Criteria for Possible cases

- Baseline serum creatinine/BUN were elevated possibly indicating a chronic renal disorder but the patient developed diagnosed renal failure/acute renal failure only after suspect drug administration supported by changes in serum creatinine/BUN meeting the case definition. The patient is at risk for developing renal failure due to the abnormal baseline.
- No history of renal insufficiency or disorder, normal baseline serum creatinine/BUN, within a reasonable time after drug administration developed diagnosed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition, events abated after drug discontinuation. There were standing concomitant drugs, which may or may not be labeled for renal failure.
- The patient is reported to have diagnosed renal failure but with insufficient lab data to support the diagnosis from a health care provider or consumer and can not exclude the possibility that the drug is associated with the events (e.g., because of drug therapy date).
- The patient is reported to require dialysis or kidney transplant while on drug with insufficient lab data and can not exclude the possibility that the drug is associated with the event, based on the drug therapy date.

/s/

Cindy Kortepeter
2/21/01 10:55:58 AM
PHARMACIST

Julie Beitz
2/22/01 07:38:22 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

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