

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. 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 osteoarthritis. Serum creatinine (SCr) changes (peak SCr minus baseline SCr) were reported in 44 cases (36%). The mean SCr change was 2.9 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 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 \leq 1.0 mg/dL, 27 (60%) had a baseline SCr \leq 1.2 mg/dL, and 32 (71%) had a baseline SCr \leq 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 (_____ mg/dL). Those cases reporting a peak and recovery serum creatinine (45 cases, 32%) noted an average decline of 2.8 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**

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).

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- **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. [NDTI data indicate that about 33% of Celebrex users take 2 tablets/day versus 6% 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 advise healthcare practitioners to closely monitor patients at increased risk for renal function impairment; for example, elderly patients, patients with cardiovascular disorders or diabetes, and/or in the setting of concomitant use of diuretics, ACE inhibitors or other NSAIDs.

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 strengthened to state that serious or life threatening renal failure can occur in patients with normal or impaired renal function and that it may be observed after short-term therapy. Kidney function should be monitored closely for any signs of potential renal injuries, especially for high-risk populations, such as the elderly and patients with cardiovascular disorders, diabetes mellitus, and/or in the setting of concomitant use of diuretics and ACE inhibitors or concomitant or recent use of other NSAIDs. Finally, the *Information for Patients* section should adequately warn about the signs and symptoms of serious renal toxicity, and about the need for patients to see their physician promptly if they occur. Consideration should be given to developing a patient package insert for Celebrex.

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

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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

Concur:

Min Chen, M.S., R.Ph., Team Leader

cc:

HFD-430/Beitz/Trontell/Chen/Weaver/Ahmad/Kortepeter/Brinker
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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 10,000,000 Rx)		38.3	82.4	7.1

* >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

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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**

OPDRA

REVIEW

Severe Hyponatremia
and the Syndrome of
Inappropriate
Antidiuretic Hormone
(SIADH)

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

DATE:

FROM: Renan Bonnel, Pharm. D., M.P.H, 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 Antiinflammatory and Ophthalmic Drug Products, HFD-550

SUBJECT: OPDRA Postmarketing Safety Review (PID # D010162)
 Drugs: Rofecoxib (Vioxx®, NDA 21-042, 21-052),
 Celecoxib (Celebrex®, NDA 20-998, 21-156)

 Reaction: Severe Hyponatremia and the Syndrome of Inappropriate
 Antidiuretic Hormone (SIADH)

EXECUTIVE SUMMARY

This document summarizes our evaluation of cases of hyponatremia and SIADH associated with rofecoxib and celecoxib, which were identified during the routine postmarketing surveillance of these products.

We evaluated 20 cases of hyponatremia that were possibly associated with the use of rofecoxib. All patients were greater than 65 years of age. Eleven patients developed various neurological symptoms, including seizures. Fourteen of the 20 patients did not have apparent precipitating factors. Six patients had precipitating factors such as thiazide therapy, intracranial hemorrhage, and sertraline use that may have contributed to the development of hyponatremia.

We evaluated 17 cases of hyponatremia that were possibly associated with the use of celecoxib. All patients were elderly with a mean age of 80 years old. Ten patients developed various neurological symptoms, including seizures. Ten of the 17 patients did not have apparent precipitating factors. Seven patients had precipitating factors such as thiazide therapy, recent stroke, malignancy and other medical conditions that may have contributed to the development of hyponatremia.

For both products females made up slightly greater than 50% of the cases. Most cases reported a dose within the recommended labeled range. Although baseline serum concentrations and urine osmolality were not reported in most cases, serum sodium concentrations were reported in 86%.

of the cases. Thiazide therapy was the most frequently mentioned confounding or precipitating factor in these cases (20%). In all of the cases, there was no obvious evidence of hypovolemia or hypervolemia. Additionally, these patients had no past history or concurrent medical conditions such as thyroid, renal, or adrenal dysfunction to contribute to the occurrence of hyponatremia.

Our findings suggest that the COX-2 inhibitors may be associated with isovolemic hyponatremia or SIADH. Elderly patients, particularly those exposed to thiazide diuretics may be at increased risk. Hyponatremia is not mentioned in either product labeling. Because these cases were serious and potentially life threatening, we recommend including hyponatremia in the labeling of both drugs.

INTRODUCTION

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.

It is known that nonsteroidal anti-inflammatory drugs (NSAIDs) can adversely affect the kidneys^{8,11} and the gastrointestinal tract causing fluid loss or fluid retention resulting in hypovolemic or hypervolemic hyponatremia.^{3,5,10} NSAIDs are also reported to cause SIADH.^{5,7}

Reports of hyponatremia (possibly isovolemic) with the use of rofecoxib and celecoxib were noted during the routine postmarketing surveillance of these products. The most common cause of *isovolemic hyponatremia* is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). SIADH occurs as a result of sustained or intermittently elevated levels of anti-diuretic hormone (ADH) without identifiable osmotic or volume stimuli, resulting in impaired renal free water excretion^{3,5}. Drugs that inhibit prostaglandin synthesis, such as nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated potentiation of ADH and thus are likely to contribute to isovolemic hyponatremia, particularly in the elderly or neonates.⁵ This document describes the cases of hyponatremia possibly due to SIADH after using the selective COX-2 inhibitors.

LABELING^{1,2}

The current labeling contains the following information regarding electrolyte imbalance:

Rofecoxib (Vioxx®)

ADVERSE REACTIONS: Under the metabolism and nutrition section - _____
and _____, are not mentioned.

DRUG INTERACTIONS: Furosemide- Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide

and thiazides in some patients. This response has been attributed to prostaglandin synthesis.

Celecoxib (Celebrex®)

ADVERSE REACTIONS: Under metabolic and nutritional- hypokalemia, hyperglycemia, hypoglycemia, BUN increased, and creatinine increased. ... are mentioned. There is no mention of _____

DRUG INTERACTIONS: Furosemide- Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to prostaglandin synthesis.

MEDICAL LITERATURE

A MEDLINE and EMBASE (International database) search of the medical literature was performed using the MESH terms *rofecoxib*, *celecoxib*, and *hyponatremia/chemically induced*. This search resulted in no relevant articles or case reports of interest. The MEDLINE search using MESH terms *hyponatremia/chemically induced*, *nonsteroidal anti-inflammatory drugs* and *prostaglandin antagonist* produced several relevant articles to support the electrolyte imbalance and renal dysfunction related to nonsteroidal anti-inflammatory drugs. There was one foreign abstract of interest featuring three cases of hyponatremia.⁶ All three cases were submitted to FDA along with this abstract as an attachment. This particular abstract was not identified in any of the above searches.

SELECTION OF CASES

On March 16, 2001, an AERS search was conducted for rofecoxib and celecoxib utilizing the following MedDRA terms: blood sodium decreased (PT), posterior pituitary disorders (HLT), and sodium decreased (hyponatremia) (HLT). Ninety-two reports representing 84 unique cases (rofecoxib-50; celecoxib-34) were retrieved. Forty-seven cases were excluded from further review.

Cases Excluded from Review (47 cases)^{3,5,10}

Seventeen celecoxib cases and 30 rofecoxib cases were excluded from review for one or more of the following reasons:

- Hyponatremia as a result of extracellular fluid (ECF) depletion (hypovolemic hyponatremia)
 1. Diarrhea/vomiting; (R-6; C-2)
 2. Third space accumulation (severe burn-like skin reactions and ascites); (R-1; C-1)
 3. GI hemorrhages (R-6; C-2)
- Hyponatremia as a result of ECF excess (hypervolemic hyponatremia)
 1. Acute renal failure (R-3; C-2)

2. Congestive heart failure (R-3; C-1)
 3. Hypoalbuminemia (e.g., hepatic cirrhosis) (R-3)
 4. Peripheral lower extremity edema (R-1)
- Hypertonic hyponatremia (e.g. hyperglycemia)(R-1)
 - Consumer or second hand reports with no confirmed diagnosis of hyponatremia (C-2)
 - Any case with a reported diagnosis of hyponatremia without supporting clinical data, including serum sodium concentration.(R-4; C-3)
 - The event was not temporally related to rofecoxib or celecoxib (R-1; C-2)
 - Metastatic carcinoma with pre-existing electrolyte disturbances (C-1)
 - No adverse event (hyponatremia) reported (C-1; R-1)

Cases Included in Review (37 cases)

- Any case with a reported diagnosis of SIADH.
- Cases that met the following clinical definition of isovolemic hyponatremia^{3,4}
 - Plasma sodium is less than 135 mmol/liter with one or more of the following signs or symptoms:
 - a. An inappropriately concentrated urine (urine osmolality > 100mOsm/kg)
 - b. Urine sodium > 20 mEq/L
 - c. Isovolemia (absence of edema, hypotension, tachycardia and absence of poor skin turgor)
 - d. Normal renal, adrenal and thyroid function.

SUMMARY OF CASES

We reviewed 37 cases of hyponatremia (possibly isovolemic) temporally associated with rofecoxib and celecoxib use.

ROFECOXIB

Twenty cases (US-14, foreign-6) met our clinical definition of hyponatremia or SIADH and were temporally associated with the use of rofecoxib. The cases involved 9 females, 6 males, and 5 whose gender was not specified. The patients' ages ranged from 70 to 102 years of age with a mean and median of 83 and 81 years, respectively. The mean and median time to onset (n= 14) was 37 and 28 days, respectively with a range of 1 day to 6 months. The dose of rofecoxib was within the recommended range in 13 patients and not reported in the remaining 7 patients. Eleven patients developed clinical manifestations of acute hyponatremia including seizures (1 patient), confusion (5 patients), unspecified neurological symptoms (2 patients), asthenia/anorexia (1 patient), weakness/dizziness (1 patient), and altered mental status (1 patient).

Seventeen of the 20 patients reported low serum sodium concentrations ranging from 110 to 133 mmol/liter (normal range: 136-148 mmol/liter). Seven patients had serum sodium concentrations <120mmol/L. The baseline serum sodium levels were available in five patients. One patient reported elevated urine sodium concentration (109 mEq/L). Two patients reported vasopressin

levels of 1.2 and 1.1 ng/L (normal range: 2.3-3.1 ng/L). Four cases reported a diagnosis of SIADH. None of the patients reported concurrent renal, adrenal, or thyroid dysfunction or signs and symptoms of volume depletion or fluid excess.

Thirteen patients required hospitalization, and one patient reported a life-threatening outcome. There were no reported fatalities. The outcome in 6 cases was not reported. Four patients received sodium replacement, in the form of tablets and hypertonic sodium chloride infusion, to correct the acute hyponatremia. Fourteen patients reported a positive dechallenge. There were no fatalities.

Fourteen of the 20 patients did not have apparent precipitating factors or concurrent medical conditions that may have contributed to the development of acute hyponatremia. In the remaining six patients, concomitant use of thiazide diuretics (4), sertraline use (1), and intracranial hemorrhage (1) might have contributed to acute isovolemic hyponatremia.

Two representative cases are presented below:

ISR# 3642661-0, MFR# WAES 00128238, Switzerland, 2000 15-day/Literature

An 86-year old patient received an unknown dose of rofecoxib for the treatment of arthritis pain for 30 days. The patient had no known significant medical conditions or medications. While on rofecoxib therapy, the patient developed unspecified neurological symptoms and hyponatremia. On admission the serum sodium was 114 mMol/L and the vasopressin level was 1.1 ng/L (normal range: 2.3-3.1ng/L). Rofecoxib was discontinued and the patient's neurological symptoms improved with correction of the hyponatremia.

ISR# 3616716-0, MFR# WAES 00086140, France, 2000 15-day/Literature

An 80-year old female patient received rofecoxib 12.5 mg daily for rheumatoid arthritis. Her past medical history was significant for arrhythmia and ischemic heart disease. She had no known history of renal, thyroid, or adrenal disease. Concomitant medications included hydrochloroquine, diltiazem, coumarol and omeprazole. Eighteen days after initiation of rofecoxib, she was hospitalized with worsening asthenia and anorexia. On admission, her serum sodium was 110 mMol/l, serum creatinine was 44 umol/L (normal range: 53-133 umol/L), and serum potassium was 3.9 umol/L (normal range: 3.5-5.0 umol/L). Rofecoxib was discontinued and she received unspecified therapy to improve her serum sodium concentration (122 mmol/L; 130 mmol/L). Two months later, she fully recovered and serum sodium levels were not measured.

CELECOXIB

Seventeen cases (US-16, foreign-1) met our clinical definition of hyponatremia or SIADH and were temporally associated with the use of celecoxib. The cases involved 13 females and 4 males. The patients' ages ranged from 57 to 92 years of age (n=14) with a mean and median of 80 and 82 years, respectively. The mean and median time to onset (n= 11) was 38 and 14 days, respectively with a range of 1 day to 5 months. The dose of celecoxib was within the

recommended range in 12 patients and not reported in the remaining 5 patients. Ten patients developed clinical manifestations of acute hyponatremia including seizure (1 patient), fatigue/weakness (3 patients), asthenia (1 patient), gait abnormality (2 patients), somnolence (1 patient), altered mental status (1 patient), and confusion (1 patient).

Fifteen of the 17 patients reported low serum sodium concentrations ranging from 109 to 126 mmol/liter. Twelve patients had a serum sodium <120mmol/L. The baseline serum sodium was available in one patient. Elevated urine osmolality and urine sodium was reported in two patients (urine osmolality: >300mOsm, high urine sodium (unspecified); urine osmolality:705 mmol/L/urine sodium:71mmol/L). Six patients had a reported the diagnosis of SIADH.

None of the patients reported concurrent renal, adrenal, thyroid disorders, or sign or symptoms of volume depletion or fluid excess as a cause of acute hyponatremia. Two patients had a history of hyperthyroidism and were stable at the time of the event. Twelve patients required hospitalization, one patient reported a life-threatening outcome, and one required an unspecified medical intervention. The outcome in 3 cases was not reported. Six patients received therapy to correct the acute hyponatremia, including fluid restriction, diuresis, salt tablets, or hypertonic sodium chloride infusion. Seven patients reported positive dechallenges and one had a positive rechallenge. There were no fatalities.

Ten of the 17 patients did not have apparent precipitating factors or concurrent medical conditions that may have contributed to the development of acute hyponatremia. In the remaining seven patients, recent stroke (1), lung cancer (1), concomitant thiazide diuretics (4), citalopram (1), sertraline (1), carbamazepine use (1), and chronic obstructive pulmonary disease (1) might have contributed to the development of hyponatremia. Two had more than one precipitating factor.

Three representative cases are presented below:

ISR# 3570308-0, MFR# 000721-SK709, IA, 2000

15-day

An 83-year old male was started on Celebrex 200mg daily for an unknown indication. He had a history of osteoporosis, osteoarthritis, glaucoma, and COPD. He had no known history of hypertension, diabetes, thyroid, adrenal, renal, or heart disease. Concomitant medications included docusate, casantranol, tamsulosin, dorzolamide and temazepam. Thirteen days after starting Celebrex, the patient had a sodium level of 133 (normal range 136-145 mmol/L) with a serum creatinine of 1 mg/dl. Two days later, he was admitted to hospital with a diagnosis of osteoporosis and compression fracture due to a fall. For the next several days his serum sodium continued to drop (127 mmol/L; 119 mmol/L; 118 mmol/L) and serum creatinine remained stable (0.6 / 0.5 mg/dl). Celebrex was discontinued. A week later, his serum sodium was back to 133 mmol/L and the patient was discharged from the hospital.

ISR# 3435467-9, MFR # WAES 99121619, Switzerland, 2000

15-day/Literature

A 67-year old male with a long-standing history of hypertension and thiazide diuretic therapy, received celecoxib for a recent episode of lumbo-ischelgia. The dose and duration of celecoxib was not reported. Ten days after starting celecoxib, he developed nausea, vomiting, gait

disturbance, and progressive disorientation. He subsequently fell and developed a “monocle” hematoma. On admission his serum sodium level was 109 mMol/L, urine sodium was 71 mMol/L, and the urine osmolality was 705 mMol/L. The diagnosis of SIADH was made and the patient received intravenous hypertonic saline infusion and oral fluid restriction. Diagnostic procedures during his hospitalization included chest X-ray, head CT, unspecified diagnostic tests, and serum, urine protein electrophoresis which were all negative for plasmacytoma, multiple myeloma, pathologic proteins, and tumors.

ISR# 3509114-1, MFR# 000510SK959, NM, 2000

15-day Rechallenge

A 67-year old male received Celebrex 200 mg daily for osteoarthritis for several months. His past medical history was significant for Grave’s disease and thyroid replacement therapy. He had no reported renal or adrenal disorders and he was on no other medications. While on Celebrex, he developed hyponatremia (serum sodium 123 mmol/L), fatigue and weakness. He discontinued Celebrex, restricted fluids and his serum sodium returned to normal (lab value was not reported). He resumed celecoxib and the sodium was gradually dropping. The reporter did not provide follow-up lab values.

DISCUSSION/CONCLUSION

The inhibition of COX enzymes decreases the production of prostaglandins in the kidneys, which affects the release of hormones involved in volume homeostasis by the kidney. The effects of renal prostaglandins on medullary blood flow, active chloride transport, and antidiuretic hormone are important for urine dilution.^{5,9,11} Therefore, it is biologically plausible that drugs that inhibit prostaglandin synthesis, such as COX-2 inhibitors, can cause hyponatremia by stimulating the release of ADH or sensitizing the kidney to ADH, or both.

We reviewed 37 U.S. and foreign cases of hyponatremia possibly associated with celecoxib (17) and rofecoxib (20) use. The mean age of patients was 80 years old or greater. Females made up slightly greater than 50% of the cases. Risk factors or precipitating factors such as the use of thiazide diuretics and other medications, recent stroke, lung cancer, and COPD were present in 13 of the 37 cases (35%) and might have contributed to the event.^{3,10} Older age and concomitant thiazide diuretic use were the most common risk factors. The hyponatremia did not appear to be dose related as the majority of the patients received the recommended daily dose.

Although not all cases provided adequate information to definitely support a diagnosis of isovolemic or euvolemic hyponatremia, none of the patients had signs or symptoms of volume depletion or overload and none had concurrent conditions such as renal failure, congestive heart failure, or gastrointestinal losses to account for the sodium imbalance. Our findings suggest that COX-2 inhibitors in elderly patients, particularly those exposed to thiazide diuretics, may be at risk for SIADH and hyponatremia. Although hyponatremia reports in AERS are not numerous, the actual number of severe hyponatremia cases may in fact be higher due to underreporting of adverse events in passive surveillance systems.

Current product labeling for both celecoxib and rofecoxib do not include hyponatremia. Because these cases were serious and potentially life threatening, we recommend including hyponatremia in the rofecoxib and celecoxib labeling.

REFERENCES

1. Vioxx® Product labeling. Merck & Co., Inc. 2000
2. Celebrex® Product labeling. G.D. Searle & Co, 2000
3. Carey, Lee, Woeltje. Manual of Medical Therapeutics. The Washington Manual. 29 th Edition. Lippincott, Williams& Wilkins.
4. The Merck Manual. Sixteenth Edition. 1992
5. Schultz N, Slaker R. De Piro et.al (editors).Pharmacotherapy. A Pathophysiologic Approach. ~~Electrolyte Homeostasis. Appleton & Lange. pg. 890- 917 , 1999~~
6. Troillet FX et.al. Severe hyponatremia induced by cyclooxygenase-2 inhibitors. Schweiz Med Wochenschr 130 (48, Suppl.124): 6S-6S, Dec 2, 2000 (FDA Attachment)
7. Petersson I et.al. Water intoxication associated with non-steroidal anti-inflammatory drug therapy. Acta Med Scand 1987; 221 (2): 221-3984
8. Dunn MJ. Nonsteroidal antiinflammatory drugs and renal function. Annu Rev Med. 1984; 35(9): 411-28
9. Rault RM. Case report: hyponatremia associated with nonsteroidal antiinflammatory drugs. Am J Med Sci 1993 May; 305 (5): 318-20
10. Mulloy A, Caruana R. Hyponatremic Emergencies. Med Clin N Amer 1995, 79 (1) 155-168
11. Zawada ET. Renal consequences of nonsteroidal antiinflammatory drugs. Postgrad Med 1982 May; 71(5): 223-30

**APPEARS THIS WAY
ON ORIGINAL**

Renan A. Bonnel, Pharm.D., M.P.H
Post-Marketing Safety Evaluator

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

/s/

Renan Bonnel
4/5/01 11:13:39 AM
PHARMACIST

Claudia Karwoski
4/5/01 11:30:20 AM
PHARMACIST

Julie Beitz
4/5/01 11:52:11 AM
DIRECTOR

**APPEARS THIS WAY
ON ORIGINAL**

**Department of Health and
Human Services
Food and Drug Administration
Center for Drug Evaluation and
Research**

Memo

To: NDA 20,998 Supplement 009

From: Lawrence Goldkind M.D.

Through: Jonca Bull M.D.

Date: 04/12/01

Re: Four-monthsafety update

The four-month safety update through September 2000 was submitted April 4, 2001. No additional adverse events or new safety signals were identified by the sponsor in the clinical trial setting during the period from the filing of the supplemental NDA in June 2000 and September 2000.

/s/

Lawrence Goldkind
4/11/01 04:54:09 PM
MEDICAL OFFICER

Jonca Bull
4/12/01 08:28:42 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

**NOT
NEEDED
SE-8**



DEPARTMENT OF HEALTH & HUMAN SERVICES

JAC
Public Health Service

Food and Drug Administration
Rockville MD 20857

Karen S. Kolba, M.D.
Pacific Arthritis Center
607 East Plaza Drive, Suite A
Santa Maria, California 93454

FEB 20 2001

Dear Dr. Kolba:

Between January 22 and 25, 2001, Mr. Ronald L. Koller, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of the clinical study (protocol #N49-98-02-035) of the investigational drug Celebrex (celecoxib), performed for G.D. Searle & Co. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Koller discussed with you and the study coordinator Ms. Duarte, observations made during the inspection. The discussion included the failure to perform the study according to the relevant protocol in that: a) subject 11012 did not return to the office for a final visit within 48 hours of the final dose; and b) subjects 209237, 20820, 20819, 20793, and 20411 were given Amoxicillin, and subject 11011 reported using an NSAID during the study. The protocol prohibits the use of Amoxicillin and NSAIDS. We acknowledge your explanations and trust that you will exercise more care to ensure that the findings discussed above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Koller during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

/s/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855



DEPARTMENT OF HEALTH & HUMAN SERVICES

JAC
Public Health Service

Food and Drug Administration
Rockville MD 20857

Ghodrat A. Siami, M.D., Ph.D.
Veterans Administration Medical Center
Room 4D109
1310 24th Avenue South
Nashville, Tennessee 37212

MAF 25

Dear Dr. Siami:

Between February 12 and 15, 2001, Mr. George J. Flynn, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of the clinical study (protocol #N49-98-02-102) of the investigational drug Celebrex (celecoxib), performed for G.D. Searle & Co. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to most pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. Although no Form FDA 483 was issued at the close of the inspection, Mr. Flynn discussed with you and your staff his inspectional observations. The discussion included your failure: 1) to report all concomitant medications for subject # 12816; and 2) to provide diary cards at baseline to most subjects in the trial. We acknowledge your explanations and trust that you will exercise more care to ensure that the findings discussed above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Flynn during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

AS
Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855



Food and Drug Administration
Rockville MD 20857

Walter F. Chase, M.D.
1301 West 38th Street, Suite 609
Austin, Texas 78705

MAR 28 2001

Dear Dr. Chase:

Between February 27 and March 2, 2001, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), met with you and your staff to review your conduct of a clinical study (protocol #N49-98-02-035) of the drug Celebrex (celecoxib), performed for G.D. Searle & Co. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to most pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Martinez discussed with you and your staff his inspectional observations. The discussion included your failure: 1) to report all concomitant medications for subject # 10078, #10668 and #10925; 2) to report past history of heparin use for subject # 10235; and 2) to provide subjects #11590, #11201 and #11202 with an updated version of the informed consent. We acknowledge your explanations and trust that you will exercise more care to ensure that the findings discussed above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

Sincerely yours,

/s/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855



CELEBREX (celecoxib) CAPSULES 100mg and 200mg

REC.
06/18/02
9:34 AM

NDA 20-998/S-009

**SE-8: Efficacy Supplement with Clinical Data to
Support a Labeling Claim**

Review Team:

James Witter, MD, PhD (Clinical Team Leader)

Lawrence Goldkind, MD (Deputy Director)

Sue-Chih Lee, PhD (Pharmacokinetics Reviewer)

Dennis Bashaw, PharmD (Pharmacokinetics Team Leader)

Laura Lu, PhD (Statistics Reviewer)

Stan Lin, PhD (Statistics Team Leader)

Josie Yang, PhD (Pharmacology/Toxicology Reviewer)

**Bob Osterberg, RPh, PhD (Acting Pharmacology/Toxicology
Team Leader)**

Barbara Gould (Project Manager)

Carmen DeBellas (Chief Project Manager)

Jane A. Dean (Project Manager)

Applicant: G. D. Searle

Contact: Eva Essig, PhD, Associate Director, Regulatory Affairs

847-982-8155 (Office)

847-982-8090 (Fax)



NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20998	Efficacy Supplement Type SE -8	Supplement Number 009
Drug: Celebrex™ (celecoxib capsules) Capsules 100 mg , 200 mg		Applicant: G.D. Searle L.L.C.
RPM: Barbara J. Gould		HFD-550 Phone #: 301 827-2090
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		June 21, 2002 June 12, 2001 April 12, 2001
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	(X)
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE, 12 April 2001 AE, 12 June 2001
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release (X) Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	06 June 02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	October 26, 1999
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

❖ Advisory Committee Meeting	
• Date of Meeting	7 Feb 2001
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	27 Dec 2000
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	NA
❖ Clinical review(s) (indicate date for each review)	September 20, 2000 February 07, 2000 GI January 05, 2001 CR June 06, 2002 Labeling
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	12 April 2001
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) (indicate date for each review)	February 16, 2001
❖ Biopharmaceutical review(s) (indicate date for each review)	December 18, 2000
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	February 20, 2001
• Bioequivalence studies	
❖ CMC review(s) (indicate date for each review)	NA
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	April 12, 2001
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>20-998</u> / SE <u>8</u> - <u>009</u>	
Drug <u>Celebrex (celecoxib) Capsules, 100 mg and 200 mg</u> Applicant _____	
RPM <u>Yoon Kong, Pharm.D.</u>	Phone <u>(301) 827-2504</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P
Pivotal IND(s) _____	
Application classifications: Chem Class <u>COX-2</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>April 13, 2001</u> Secondary <u>June 14, 2001</u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 - User Fee Waiver (attach waiver notification letter)
 - User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels
 - FDA revised labeling and reviews..... _____
 - Original proposed labeling (package insert, patient package insert) unannotated
 - Other labeling in class (most recent 3) or class labeling..... VIOXX
 - Has DDMAC reviewed the labeling? labeling not final, no review Yes (include review) No
 - Immediate container and carton labels N/A
 - Nomenclature review N/A

- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.
 - Exception for review (Center Director's memo)..... N/A
 - OC Clearance for approval..... N/A

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) Materials requested in AP letter
- ◆ Post-marketing Commitments X (part of orig. AP letter- 12/31/98)- see Post-Marketing tab
- Agency request for Phase 4 Commitments..... X
- Copy of Applicant's commitments X (see Post-Marketing tab)
- ◆ Was Press Office notified of action (for approval action only)?..... Yes No
- Copy of Press Release or Talk Paper..... N/A
-
- ◆ Patent
- Information [505(b)(1)] X
- Patent Certification [505(b)(2)]..... X
- Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... X
- ◆ Exclusivity Summary N/A (Approvable)
- ◆ Debarment Statement X
- ◆ Financial Disclosure
- No disclosable information X (See MO Review-page 84)
- Disclosable information – indicate where review is located _____
- ◆ Correspondence/Memoranda/Faxes X
- ◆ Minutes of Meetings X
- Date of EOP2 Meeting TCON mins. Regarding CLASS studies
_____; 4-3-98,9-22-98 (two),10-2-98, 1-25-01
 (Pre-Advisory Committee Meeting: 2/7/01)
- Date of pre NDA Meeting 9-13-00
- Date of pre-AP Safety Conference N/A
- ◆ Advisory Committee Meeting X
- Date of Meeting 2-7-01
- Questions considered by the committee X
- Minutes or 48-hour alert or pertinent section of transcript X
- ◆ Federal Register Notices, DESI documents X (Arthritis Advisory Meeting of 2-7-01)
-

CLINICAL INFORMATION:

**Indicate N/A (not applicable),
X (completed), or add a
comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) N/A
- ◆ Clinical review(s) and memoranda X *Larry's review pending*
- ◆ Safety Update review(s) See GI review (Larry's review)
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred
- Pediatric Page Not needed b/c SE-8
- Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda..... X (with a consult review from Biometrics)
- ◆ Abuse Liability review(s) N/A
- Recommendation for scheduling N/A
- ◆ Microbiology (efficacy) review(s) and memoranda N/A
- ◆ DSI Audits X (4 sites audited, 3 reviews received)
- Clinical studies bioequivalence studies

CMC INFORMATION:

**Indicate N/A (not applicable),
X (completed), or add a
comment.**

- ◆ CMC review(s) and memoranda N/A
 - ◆ Statistics review(s) and memoranda regarding dissolution and/or stability N/A
 - ◆ DMF review(s) N/A
 - ◆ Environmental Assessment review/FONSI/Categorical exemption N/A
 - ◆ Micro (validation of sterilization) review(s) and memoranda N/A
 - ◆ Facilities Inspection (include EES report)
 Date completed _____ Acceptable Not Acceptable
-

◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

**Indicate N/A (not applicable),
X (completed), or add a
comment.**

- ◆ Pharm/Tox review(s) and memoranda X (review of labeling only)
- ◆ Memo from DSI regarding GLP inspection (if any) N/A
- ◆ Statistical review(s) of carcinogenicity studies N/A
- ◆ CAC/ECAC report N/A

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Winifred M. Begley Senior Director, Worldwide Regulatory Affairs Searle 4901 Searle Parkway Skokie, Illinois 60077		3. PRODUCT NAME Celebrex (celecoxib)	
2. TELEPHONE NUMBER (Include Area Code) (847) 982-8155		4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).	
5. USER FEE I.D. NUMBER 4066		6. LICENSE NUMBER / NDA NUMBER NDA 20-998	

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 <i>(Self Explanatory)</i>	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <i>(See item 7, reverse side before checking box.)</i>
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i>	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act <i>(See item 7, reverse side before checking box.)</i>
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY <i>(Self Explanatory)</i>	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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DHHS, Reports Clearance Officer
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Hubert H. Humphrey Building, Room 531-H
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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Senior Director, Worldwide Regulatory Affairs	DATE 8 Dec 2000
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Number of Pages
Redacted 29



Draft Labeling
(not releasable)

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: Eva Essig

From: Yoon Kong, Pharm. D.

Fax: (847) 982-8090

Fax: 301-827-2531

Phone: (847) 982-8980

Phone: 301-827-2090

Pages: 25 (including cover page)

Date: April 12, 2001

Re: NDA 20-998/S-009 Action letter

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

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● **Comments:**

Dear Eva,

Please find attached a copy of the action letter for your supplemental NDA.

Please give me a call if you have any questions or need clarification.

Thank you.

/s/
Yoon Kong, Pharm.D.

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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: Eva Essig	From: Yoon Kong, Pharm. D.
Fax: (847) 982-8090	Fax: 301-827-2531
Phone: (847) 982-8980	Phone: 301-827-2090
Pages: 25 (Including cover page)	Date: April 12, 2001
Re: NDA 20-898/S-008 Action letter	
<input type="checkbox"/> Urgent <input type="checkbox"/> For Review <input type="checkbox"/> Please Comment <input type="checkbox"/> Please Reply <input type="checkbox"/> Please Recycle	

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● Comments:

Dear Eva,

Please find attached a copy of the action letter for your supplemental NDA.

Please give me a call if you have any questions or need clarification.

Thank you

YK
 Yoon Kong, Pharm.D.

Labeling review
NDA 20,998 S/009
Lawrence Goldkind MD.
HFD 550

Relevant reviews:

Medical Officers Reviews

James Witter MD., PhD. 4/3/01, 9/7/00 Medical Officer's Review
Lawrence Goldkind MD. 4/12/01 Gastrointestinal Consult Review
Douglas Throckmorton MD. 1/5/01 Cardiorenal Consult Review

Statistical Review:

Lu Hong PhD. 2/15/01

Introduction:

NDA 20,998 S/009 was submitted June 12, 2000. An advisory committee meeting was held February 7, 2001. Meeting transcripts and presentations are available for review in CDER electronic archives.

On June 12, 2001 an approvable letter was sent to the sponsor. Subsequently, extensive labeling negotiations have taken place. The sponsor submitted a request for dispute resolution on August 3, 2001 and the response was sent by the Center on 12/7/01.

This review summarizes the final labeling changes and their bases that appear in the approval letter of 6/7/02.

Attachments 1 and 2 include submission of data analyses that were requested by the Division during review following the advisory committee meeting of 2/7/01. These submissions were critical in the supporting the final approved labeling change.

Clinical Studies Section

A section of the label displaying information from the CLASS trial was felt necessary given the wealth of information provided in this study, especially related to co-use of aspirin. The study results failed to demonstrate statistical superiority of Celebrex over the combined NSAID group (diclofenac and ibuprofen) in the primary endpoint of clinically significant UGI events (CSUGIE) or either NSAID separately over the entire study period. In addition the study failed to demonstrate superiority over the combined NSAID

group for patients not taking aspirin. The failure to demonstrate a meaningful trend over the diclofenac (either non-aspirin or aspirin) treated group at the primary endpoint, CSUGIE or the post hoc endpoint of symptomatic or complicated ulcer (S+CSUGIE) -is of note. The lack of consistent trends versus both NSAID comparators obscures the potential relevance of any findings in comparisons between Celebrex and ibuprofen. The reader is referred to the medical officer’s reviews and advisory committee presentations by the FDA as well as the response to formal request for dispute resolution for further details of analysis and basis for labeling recommendations. Thus, superiority claims for Celebrex over the comparator NSAIDs at clinically relevant upper gastrointestinal events were considered inadequately supported. However, the absolute rates of CSUGIEs and S+CSUGIE in such a large study followed for a median of 9 months was felt to represent important safety information on Celebrex. The observed rates in the CLASS study for both endpoints are relevant to place into context the generic NSAID “Warning” section that quotes rates of UGI events associated with NSAIDs as a class. Thus, the following section has been added to the previously approved label for Celebrex.

“Use with Aspirin: The Celecoxib Long-Term Arthritis Safety Study (CLASS) was a prospective long-term safety outcome study conducted postmarketing in approximately 5800 OA patients and 2200 RA patients. Patients received CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively and the approved dose for FAP), ibuprofen 800 mg TID or diclofenac 75 mg BID (common therapeutic doses). Median exposures for CELEBREX (n = 3987) and diclofenac (n = 1996) were 9 months while ibuprofen (n = 1985) was 6 months. The Kaplan-Meier cumulative rates at 9 months are provided for all analyses. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction).

Patients were allowed to take concomitant low-dose (325 mg/day) aspirin (ASA) for cardiovascular prophylaxis (ASA subgroups: Celebrex, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between CELEBREX and the combined group of ibuprofen and diclofenac were not statistically significant. Those patients on concomitant low-dose aspirin experienced 4-fold higher rates of complicated ulcers compared to those not on aspirin (see WARNINGS-Gastrointestinal [GI] Effects). The results for CELEBREX are displayed in Table 4. For complicated and symptomatic ulcer rates, see WARNINGS-Gastrointestinal [GI] Effects.

Table 4
Effects of Co-Administration of Low-Dose Aspirin on Complicated Ulcer Rates with CELEBREX 400 mg BID (Kaplan-Meier Rates at 9 months [%])

	<i>Non-Aspirin Users N=3105</i>	<i>Aspirin Users N= 882</i>
Complicated Ulcers	0.32	1.12

Warning Section

The current Warning section for all NSAIDs includes extensive information on the risks associated with their use. Currently, drugs that selectively inhibit cyclooxygenase-2 (COX-2) at therapeutic doses are considered part of the class of drugs known as nonsteroidal antiinflammatory drugs (NSAID). However as each of these drugs develop unique safety databases, such information, if robust, becomes more relevant to their safe use than older data based on meta-analyses of less selective agents extrapolated to COX-2 selective NSAIDs that have different pharmacodynamic properties based on different degrees of COX-1 and COX-2 inhibition at clinically relevant doses. When meaningful data become available on such agents they should be reflected in the label. Thus, the following information generated from the CLASS study should add to the prescribers understanding of the UGI safety of Celebrex. The endpoint in this section represents an approximation of the UGI referred to in the Gastrointestinal effects- Warning section of all NSAID labels and is different than the endpoint referred to in the Clinical studies section referenced above.

The information on high-risk populations reinforces these risk factors even in patients treated with COX-2 drugs.

“CLASS Study: The estimated cumulative rates at 9 months of complicated and symptomatic ulcers (an adverse event similar but not identical to the “upper GI ulcers, gross bleeding or perforation” described in the preceding paragraphs) for patients treated with CELEBREX 400 mg BID (see Special Studies- Use with Aspirin) are described in Table 5.

Table 5 also displays results for patients less than or greater than or equal to the age of 65 years. The differences in rates between the CELEBREX alone and CELEBREX with ASA groups are due to the higher risk for GI events in ASA users and not due to any additive effect with CELEBREX.

Table 5
Complicated and Symptomatic Ulcers in Patients Taking CELEBREX 400 mg BID
(Kaplan-Meier rates at 9 months [%]) Based on Risk Factors

Complicated and Symptomatic Ulcer Rates

All Patients

Celebrex alone (n=3105)	0.78
Celebrex with ASA (n=882)	2.19

Patients < 65 Years

<i>Celebrex alone (n=2025)</i>	<i>0.47</i>
<i>Celebrex with ASA (n=403)</i>	<i>1.26</i>

Patients ≥ 65 Years

<i>Celebrex alone (n=1080)</i>	<i>1.40</i>
<i>Celebrex with ASA (n=479)</i>	<i>3.06</i>

In a small number of patients with a history of ulcer disease the complicated and symptomatic ulcer rates in patients treated with Celebrex alone or Celebrex with aspirin were respectively 2.65% in the CELEBREX (n=243) alone group and 6.85% in the CELEBREX with ASA group (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease (see WARNINGS-Gastrointestinal (GI) Effects-Risk of GI Ulceration, Bleeding, and Perforation)."

Precautions Section

Fluid retention, Edema and Hypertension

The absence of even a trend towards higher rates of edema and hypertension despite the use of twice the highest chronic arthritis dose of Celebrex compared to ibuprofen or diclofenac is valuable safety information that is relevant to the safety characterization of this COX-2 selective agent. Thus it was considered appropriate for inclusion in the label. This information does not represent a comparative claim. It was specified as a primary endpoint and was collected as part of a standard element of a safety database.

"In the CLASS study (see Special Studies- Use with Aspirin), the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively and the approved dose for FAP), ibuprofen 800 mg TID and diclofenac 75 mg BID were: 4.5%, 6.9% and 4.7%, respectively. The rates of hypertension in the CELEBREX, ibuprofen and diclofenac treated patients were: 2.4%, 4.2% and 2.5%, respectively."

Adverse Reactions

A section entitled " Safety data from CLASS" has been included to further characterize the safety of Celebrex.

Long term data on significant changes in hematologic parameters such as hemoglobin and hematocrit in several thousands patients is significant. Although not a primary endpoint of the study, post hoc analyses of replicated drops in these parameters supported by sensitivity analyses as well as supportive data from other databases as presented in the submission of October 15, 2001 are informative for considered relevant to labeling of Celebrex.

Safety Data from CLASS Study:

Hematological Events:

During this study (see Special Studies-Use with Aspirin), the incidence of clinically significant decreases in hemoglobin (>2 g/dL) confirmed by repeat testing was lower in patients on CELEBREX 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively and the approved dose for FAP) compared to patients on either diclofenac 75 mg BID or ibuprofen 800 mg TID: 0.5%, 1.3% and 1.9%, respectively. The lower incidence of events with CELEBREX was maintained with or without ASA use (see CLINICAL STUDIES- Special studies- Platelets).

Withdrawals and serious adverse events represent clinically meaningful events with standardized definitions within clinical trials. Thus, the information generated in the CLASS trial at twice the highest chronic arthritis dose adds to the safety characterization of Celebrex. In view of questions raised in the medical literature recently regarding overall safety of COX-2 inhibitors and specifically cardiovascular safety, the information displayed below is relevant to the characterization of the safety of Celebrex in the context of NSAID use. The study duration, size and multiplicity of comparators supports the inclusion of such data in the label. These data do not represent a comparative claim.

“Withdrawals/Serious Adverse Events:

Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for celecoxib, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e. those causing hospitalization or felt to be life threatening or otherwise medically significant) regardless of causality were not different across treatment groups, respectively, 8%, 7%, and 8%.

Based on Kaplan-Meier cumulative rates for investigator-reported serious cardiovascular thromboembolic adverse events*, there were no differences between treatment groups, regardless of ASA use. The rates in all patients at 9 months for celecoxib, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The rates for non-ASA users in the three treatment groups were less than 1%. The rates for myocardial infarction in the non-ASA patient groups were less than 0.2%.

****includes myocardial infarction, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks or ischemic cerebrovascular accidents”***

The kaplan-meier analyses were reviewed for all endpoint data referenced in the labeling changes above and there were no trends for accelerating rates later in the study. Nine months was chosen as the optimal time for display of kaplan-meier rates of events as there were stable estimates at this point for the endpoints including subgroups at high risk for particular events such as age and aspirin use. No changes in trends were seen among comparators after this timepoint. Thus, nine months represented an appropriate timepoint in the CLASS database to use for the labeling of event rates.

**APPEARS THIS WAY
ON ORIGINAL**

Attachment 1
Data submitted for review March 12, 2002

!Celecoxib_CLASS_I_and_II
N49_035_102 11MAR02:11:53 Page 1 of 1

FINAL eelhgb.sas

Table 1
Summary for Clinically Significant Hemoglobin (Hgb) Decreases: All Treated Patients

----- p-value -----		Celecoxib	Diclofenac	Ibuprofen
Celecoxib	Celecoxib	400 mg BID	75 mg BID	800
mg TID	vs			
(%)	Diclofenac	Ibuprofen	N (%)	N (%)
Number of Patients		3987	1996	1985
Hgb decrease >2 g/dL at 1 or more visits <0.001***	<0.001***	86 (2.2)	81 (4.1)	101 (5.1)
Hgb decrease >2 g/dL at 2 consecutive visits 0.002**	<0.001***	19 (0.5)	25 (1.3)	38 (1.9)

Note: P-value from Fisher's exact test.

**APPEARS THIS WAY
ON ORIGINAL**

Table 2
 Summary for Clinically Significant Hemoglobin (Hgb) Decrease: All Treated Patients not
 Taking Aspirin

----- p-value -----		Celecoxib	Diclofenac	Ibuprofen
Celecoxib	Celecoxib	400 mg BID	75 mg BID	800
mg TID	vs			
(%)	Diclofenac	Ibuprofen	N (%)	N (%)
Number of Patients		3105	1551	1573
Hgb decrease >2 g/dL at 1 or more visits		52 (1.7)	52 (3.4)	72 (4.6)
<0.001***	<0.001***			
Hgb decrease >2 g/dL at 2 consecutive visits		12 (0.4)	16 (1.0)	28 (1.8)
0.014*	<0.001***			

Note: P-value from Fisher's exact test.

**APPEARS THIS WAY
 ON ORIGINAL**