

MEMORANDUM

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

RCM#: 2006-837

DATE: February 8, 2008

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FROM: Joann H. Lee, Pharm.D., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Ann W. McMahon, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Celecoxib (Celebrex[®])
Pediatric Exclusivity Approval Date: 8/23/2006

1. Executive Summary

The Adverse Event Reporting System (AERS) database was searched for reports of all adverse events (serious and non-serious) associated with the use of celecoxib in pediatric patients. From the date of FDA approval, December 31, 1998, to the “data lock” date of 9/23/2007, AERS contained 28,186 cases for celecoxib (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.3% of the total (94/28186).

DDRE was asked to focus¹ on the 1-year period following the approval of pediatric exclusivity, 8/23/2006 to 8/23/2007. We used an AERS data lock date of 9/23/2007, to allow time for reports received up to 8/23/2007, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 6,144 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.3% of the total number of cases (19/6144). The 13-month interval from 8/23/2006 to 9/23/2007 will be referenced as the pediatric exclusivity period in the remainder of this review.

¹ A separate AERS search was conducted for ages 17 to 18 years for reports received during the 1-year Post-Pediatric Exclusivity Postmarketing Period. Previous OSE Reviews for the Adult Population that included celecoxib are summarized under appendix II.

The AERS search retrieved 10 unduplicated pediatric adverse event reports (fatal-2; nonfatal-8) for celecoxib during the pediatric exclusivity period for ages 0 to 16 years. The two death cases were both from a pilot study of newly diagnosed patients with metastatic Ewing's sarcoma. The reported events in the first case were fever, fluid overload, neutropenia and GI bleed; in the second case, the reported events were pancytopenia, pericardial effusion, and pulmonary hypertension. In both cases, a clear association between the use of celecoxib and the adverse events could not be established since many chemotherapeutic agents and radiation were given at the same time as celecoxib. However, the contributory role of celecoxib could not be ruled out for events such as GI bleed and pancytopenia, which are labeled for celecoxib. The cause of death was not reported in either case.

Of the remaining eight nonfatal cases, one case reported a positive dechallenge (skin reaction) possibly associated with celecoxib use. In the remaining 7 cases, the reported events were dyspnea (2), heart palpitations (2), pulmonary embolism (2), pneumonia, intracranial haemorrhage, pancytopenia, GI bleed, chest pain, and blood clots. All of the reported adverse events in these cases are labeled for celecoxib. However, all cases reported confounders as well such as the concomitant use of chemotherapy/radiation (causing immunosuppression), use of other drugs labeled for the reported events (e.g. oral contraceptives), or underlying medical history (e.g. brain tumors, H. Pylori, diabetes etc.) that could have contributed to the events.

A separate search was conducted on 1/18/2008 for all serious and nonserious AERS reports limited to age 17 to 18 years² received during the pediatric exclusivity period. The search retrieved three unduplicated, nonfatal (US=2, Foreign=1) reports. One of the three cases reported hepatic cholestasis jaundice with supporting lab values³. Second case reported erythema and dyspnea with a positive dechallenge; this patient also had a history of sulfa allergy. Based on the temporal association without concomitant drug use, it is possible that celecoxib may be associated with the reported events in these two cases. The 3rd case was reported by an attorney. An 18-year old female developed ischemic stroke after using multiple COX-2 inhibitors including celecoxib. Given the lack of therapy duration and clinical details, the role of celecoxib could not be determined. All the reported events were labeled for celecoxib⁴.

An additional search of AERS was performed to identify all fatal pediatric cases associated with celecoxib use prior to the 1-year post pediatric exclusivity period. This search retrieved an additional three unduplicated pediatric death cases. In one case, an 8-year old with end stage renal cell carcinoma developed cardiomyopathy and congestive heart failure (CHF) while being treated with interferon-alpha, vinblastine and celecoxib. Both cardiomyopathy and CHF are labeled for interferon-alpha; celecoxib is labeled only for cardiomyopathy (vinblastine is not labeled for either event). According to the

² Original AERS database search was limited to age 0 to 16 years per BPCA Template guidelines.

³ Bilirubin increased to 3 times the upper limit of normal (ULN), ALT increased to 6 times the ULN, and AST increased to 3 times the ULN.

⁴ All drug labeling refers to the adult population unless otherwise specified.

reporter, all the reported events were attributed to the progression of the underlying disease. In the 2nd fatal case, the patient experienced intracranial hemorrhage during treatment with thalidomide and celecoxib for a brain tumor. Celecoxib is labeled for fatal intracranial hemorrhage whereas thalidomide is not labeled for this event. A clear association between intracranial hemorrhage and celecoxib could not be established given the patient's underlying medulloblastoma. The last case involved a suicide in an adolescent male six days after starting celecoxib with an unknown dose. Given that there were no reported underlying disease or other suspect drugs, the role of celecoxib in the suicide case could not be excluded based on the temporal association.

In conclusion, the cases in this review did not reveal any notable unexpected safety concerns associated with celecoxib use in pediatric patients from 0 to 18 years of age^{1,2}. Deaths in four of the five fatal cases (two during and two prior to the pediatric exclusivity period) occurred in oncology patients receiving multiple chemotherapeutic agents and/or radiation in addition to celecoxib. The fifth death case was a suicide. We have no labeling recommendations at this time. We will continue to monitor these postmarketing adverse events.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

2.1 Celecoxib Products

Celecoxib is marketed in the U.S. as:

50, 100, 200, and 400 mg white capsules with various colored bands on the body and caps with markings of 7767. Respective strengths are imprinted on the body of each capsule.

2.2 Celecoxib Approved Indications

Celecoxib is indicated:

- *For relief of the signs and symptoms of osteoarthritis.*
- *For relief of the signs and symptoms of rheumatoid arthritis in adults.*
- *For relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older.*
- *For relief of the signs and symptoms of ankylosing spondylitis.*
- *For the management of acute pain in adults.*
- *For the treatment of primary dysmenorrhea.*
- *To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of celecoxib treatment will persist after celecoxib is discontinued. The efficacy and safety of celecoxib treatment in patients with FAP beyond six months have not been studied.*

2.3 Celecoxib Pediatric Labeling

The labeling for pediatric use includes the following information:

Celecoxib is approved for relief of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older. Safety and efficacy have not been studied beyond six months in children. The long-term cardiovascular toxicity in children exposed to celecoxib has not been evaluated and it is unknown if long-term risks may be similar to that seen in adults exposed to celecoxib or other COX-2 selective and non-selective NSAIDs.

The use of celecoxib patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a 12-week open-label extension. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. Patients with systemic onset JRA (without active systemic features) appear to be at risk for the development of abnormal coagulation laboratory tests. NSAIDs including celecoxib should be used only with caution in patients with systemic onset JRA, due to risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests.

2.4 Celecoxib Pediatric Filing History

A Pediatric Written Request (PWR) was issued to Pfizer, Inc. on January 25, 2002. The sponsor responded to the PWR on June 20, 2006 with the submission of an efficacy supplement to NDA 20-988. The submission consisted of Phase 3 efficacy and safety study, and four pharmacokinetic studies. The Agency granted Pfizer six months of additional marketing exclusivity for celecoxib on August 23, 2006 based on the study of an oral suspension of celecoxib in patients with JRA.

2.5 Previous OSE Review of Pediatric Cases for Celecoxib⁵

In October 2006, OSE completed an AERS review of all pediatric adverse events associated with Celebrex (celecoxib), in preparation for the November 29, 2006 Advisory Committee meeting to discuss the efficacy and safety of celecoxib in the treatment of juvenile rheumatoid arthritis (JRA). The AERS database was searched for all serious and nonserious pediatric adverse events reported between 12/31/98 and 8/10/06 for celecoxib. Thirty-one cases were included in this case series.

The age of patients ranged from 4 to 17 years with the mean of 14 years. Of the 30 cases reporting gender, there were 18 females and 12 males. Celecoxib was most commonly used for pain, JRA, and tendonitis. Most of the adverse events were mentioned in only one report, except for rash (4), chest pain (3), hematochezia (2), and headache (2), all of which are labeled events. Notable unlabeled adverse events included pseudoporphyria, epidermolysis bullosa, pericarditis, supraventricular arrhythmia, hypotension, DIC, ARDS, convulsions, and tongue discoloration. Expected adverse events such as acute renal failure, liver failure, leucopenia, neutropenia, thrombopenia, and various skin and GI symptoms were also reported.

Serious outcomes included hospitalization (7), life-threatening (1), and death (1). In the fatal case, a 15 year old male committed suicide 2-3 weeks after taking celecoxib with an

⁵ DFS'ed October 12, 2006. OSE postmarketing safety review of celecoxib (PID# D060611).

unknown dose for pain S/P anterior cruciate ligament reconstruction of the left knee. Both depression and suicide are labeled events for celecoxib (adult population)⁴. Given the limited information in this case, the relationship between the reported event and celecoxib use was unclear; however, this case was included in the case series because the role of celecoxib could not be excluded.

Most of the adverse events from this case series were included in the labeling for celecoxib; the cases involving unlabeled events were single reports. An additional monitoring of adverse events was recommended to establish a clear relationship with celecoxib use in the pediatric population.

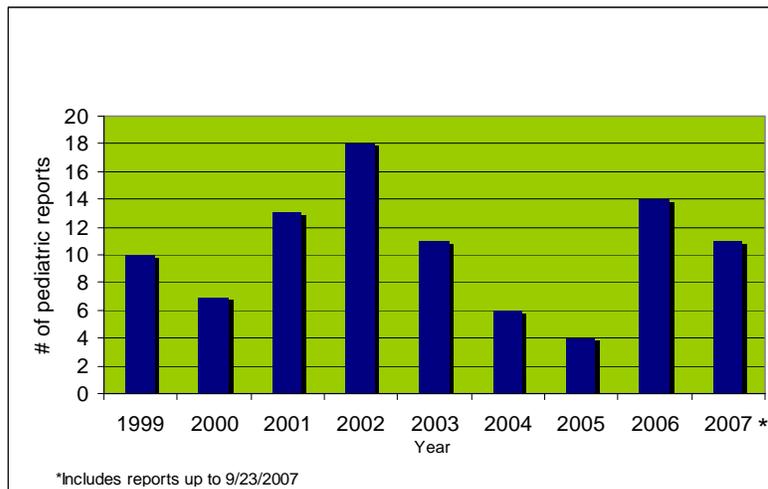
3. Summary of AERS Search Results for All Ages: Celecoxib (Celebrex®)

3.1 Count of Reports: AERS Search including all sources –U.S. and foreign from marketing approval date to 9/23/2007

| Table 1: Crude counts ¹ of AERS Reports for all sources from marketing approval date to 9/23/2007 | | | |
|--------------------------------------------------------------------------------------------------------------|------------------|---------------------------|-------------|
| (US counts in parentheses) | | | |
| | All reports (US) | Serious ² (US) | Death (US) |
| Adults (≥ 17 yrs.) | 18173 (15316) | 12309 (9509) | 1542 (1038) |
| Pediatrics (0-16 yrs.) | 94 (70) | 77 (53) | 13 (11) |
| Age unknown (Null Values) | 9919 (9376) | 6395 (5863) | 817 (742) |
| Total | 28186 (24762) | 18781 (15425) | 2372 (1791) |

¹May include duplicates
²Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

Figure 1. Reporting trend for pediatric reports from approval date (12/1998 to 9/23/2007)



3.2 Count of Reports: AERS search including all sources – U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

| Table 2: Crude counts ¹ of AERS Reports for all sources from date Pediatric Exclusivity was granted (US counts in parentheses) | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------|---------------------------|------------------|
| | All reports (US) | Serious ² (US) | Death (US) |
| Adults (≥ 17 yrs.) | 3211 (2990) | 3198 (2978) | 501 (479) |
| Pediatrics (0-16 yrs.) | 19 (13) | 19 (13) | 5 (5) |
| Age unknown (Null Values) | 2914 (2851) | 2910 (2847) | 409 (404) |
| Total | 6144 (5854) | 6127 (5838) | 915 (888) |

¹May include duplicates
²Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

4. Postmarketing Review of Pediatric (Age 0-16 years) Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

The crude AERS number of pediatric cases from age 0 to 16 years received during the 1-year post-pediatric exclusivity period was 19. Of the 19 cases, 10 unduplicated pediatric cases were included in this case series. The remaining nine cases were excluded for the following reasons.

| Table 4: Reasons for exclusion and number of excluded cases (n=9) | |
|-------------------------------------------------------------------|----------|
| Adult reports miscoded as pediatric | 1 |
| Drug overdose (associated with acetaminophen) | 2 |
| Adverse events unrelated to celecoxib* | 2 |
| Duplicate reports | 4 |
| Total | 9 |

*Follow-up clinical assessment of the reports stated that celecoxib was unlikely or not related to the reported events.

4.1 Case Characteristics of Pediatric (age 0-16 years) Reports Received During the Exclusivity Period :

Table 3 below describes the characteristics of the 10 pediatric cases reported during the pediatric exclusivity period.

| Table 3: Characteristics of pediatric cases reported during the pediatric exclusivity period n=10 | |
|---------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Gender [n=10] | Male: 1 Female: 9 |
| Age [n= 10] | < 1 month: 1 (exposure of drug via breast milk) 8 years: 2 12 years: 1 13 years: 2 14 years: 1 |

| | |
|--------------------------------------|------------------------------------------------------------------------------|
| | 16 years: 3 |
| Origin [10] | US: 7 Foreign: 3 |
| Event date [n=9]* | 1997 (1), 1998 (1), 2004 (1), 2006 (4), 2007(2) |
| FDA receipt date [n=10] | 2006 (5), 2007 (5) |
| Daily dose [n=7]* | Range (100 to 800 mg), Median (200 mg) |
| Estimated Duration of therapy [n=5]* | Range (1 day to 106 days) Average (44 days), Median (88 days) |
| Indications [n=3]* | Pain: 2, Glioblastoma: 1 |
| Outcomes [n=10]** | Death (2), Life-Threatening (2), Hospitalization (7), Disability (1), OT (3) |

*Not reported or unknown in the remaining cases; **A case could have more than one outcome

4.2 Summary of Cases (Age 0-16 years) received during the 1-year post-pediatric exclusivity period.

Ten unique pediatric cases are presented below, 2 of which are fatal cases. The unlabeled events for celecoxib are underlined.

Fatal Cases (N=2)

Two of the 10 fatal cases involved patients with metastatic Ewing's Sarcoma enrolled in a pilot study that required multi-chemotherapy agents. The reported events in the first death case were fever, fluid overload, neutropenia and GI bleed; in the second death case, the reported events were pancytopenia, pericardial effusion, and pulmonary hypertension. In both cases, a clear association between the use of celecoxib and the adverse events could not be established since many chemotherapeutic agents and radiation were given at the same time as celecoxib. However, the contributory role of celecoxib could not be ruled out for events such as GI bleed and pancytopenia (labeled for celecoxib) due to the temporal association. The cause of death was not reported in either case.

The narratives of the 2 death cases are as follows:

ISR# 5120107; Foreign; Fatal

A 12-year old female was enrolled in a pilot study of newly diagnosed metastatic Ewing's Sarcoma. The protocol required multi-agent chemotherapy including cyclophosphamide, doxorubicin, vincristine along with radiation and celecoxib (therapy dates not given). She was admitted to the hospital with a fever, neutropenia and fluid overload. The patient required aggressive mechanical ventilation and inotrope support. Her respiratory and cardiovascular conditions seemed to improve; however, a couple of days later, the patient deteriorated rapidly with an internal GI bleed (diffuse esophagitis, gastritis, and duodenitis) with increasing ventilatory requirements. She also developed hospital acquired gram positive streptococcus; renal and hepatic failures ensued and the patient died on September 5, 2006. Celecoxib was listed as the suspect drug only for the GI bleed. Chemotherapy and radiation were listed as suspect for the other reported events.

ISR# 5297836; Foreign; Fatal

A 16-year old patient was enrolled in a pilot study of newly diagnosed metastatic Ewing's Sarcoma. She completed a multi-agent chemotherapy on January 27, 2007 per protocol that included cyclophosphamide, doxorubicin along with radiation and celecoxib. She developed increased shortness of breath and pulmonary edema secondary to radiation pneumonitis in January 2007. Further complications included pancytopenia, pericardial effusion and pulmonary hypertension⁶. She was treated with furosemide, enalapril and bosentan. On March 7th, the patient had a cardiac arrest after undergoing pericardiocentesis. Two days later, she arrested again and died. The reporter attributed the adverse events in this case as probably related to doxorubicin and radiation.

Non-fatal Cases (N=8)

The remaining eight of 10 cases were non-fatal reports. The reported events were dyspnea (2), heart palpitations (2), pulmonary embolism (2), bullous eruptions, pneumonia, intracranial haemorrhage, pancytopenia, GI bleed, chest pain, and blood clots. All of the reported adverse events in the non-fatal cases are labeled for celecoxib. These events are discussed below in more detail.

Bullous Eruption

A 4-day-old infant was exposed to celecoxib through breast milk; the newborn developed bullous eruptions three days after the nursing mother started celecoxib. The reported event improved after celecoxib was discontinued. No further details were given. According to Pfizer's product labeling, celecoxib is excreted in human milk, and serious skin reactions are also labeled.

Comment: In this case, it is possible that the event was associated with celecoxib use based on the positive dechallenge and temporal association.

Pneumonia

An 8-year-old male experienced dyspnea, breathing difficulty, pneumonia and fever during treatment with cyclophosphamide (indication unknown). He was also being treated with etoposide, celecoxib, carbamazepine, and phenytoin (duration of use not given; indication unknown). In spite of the treatment with antibiotics, the patient had not recovered at the time of this report. It was reported that the suspect drugs were unlikely related to the events.

Comment: Since this patient was immunosuppressed from chemotherapy, it is possible that the reported events were most likely not related to celecoxib; however, the contributory role of celecoxib (which is labeled for pneumonia/infection) could not be ruled out.

⁶ Celecoxib is labeled for hypertension

Intracranial hemorrhage; subdural hematoma

An 8-year-old male patient with a medical history of medulloblastoma and relapse presented with an intracranial hypertension that revealed subdural hematoma and intracranial hemorrhage, requiring surgery. The patient was treated with celecoxib, cyclophosphamide, and etoposide for three months prior to these events. Other concomitant drugs included phenytoin, carbamazepine, clonazepam, omeprazole and prednisolone; however, cyclophosphamide and celecoxib were reported as the suspect drugs. He recovered at the time of this report. Fatal intracranial hemorrhage and hypertension are labeled events for celecoxib (both unlabeled for cyclophosphamide).

Comment: Medulloblastoma was probably the likely cause of the reported events, but the contributory role of celecoxib could not be excluded based on the temporal association and its labeling.

Pancytopenia, GI bleed

A 13-year old male patient who was enrolled in a “protocol”⁷ and taking celecoxib presented with a fever and pancytopenia. He was found to have a GI bleed and a positive H. Pylori stool culture. The patient was treated with antibiotics and given platelet transfusions. It was not clear how long the patient was taking celecoxib prior to this hospital admission and whether fluconazole⁸ was previously used concurrently with celecoxib. The patient was instructed to stop taking celecoxib on admission.

Comment: GI bleed was most likely related to H.Pylori, but it is possible that celecoxib could also have contributed to the event since there is a temporal association and it is labeled for GI bleed. Similarly, pancytopenia is a labeled event for celecoxib, but since we do not know what other medications were administered as part of this protocol and the lack of information regarding the patient’s underlying medical conditions, a clear drug-event relationship could not be established.

Heart Palpitations, Chest Pain (n=2)

The first case described a 13-year-old female who initiated ibuprofen to treat spinal and nerve pain sustained from an auto accident. Her mother reported that she was taken off Ibuprofen because of GI bleed and placed on celecoxib. The patient discontinued celecoxib after two months due to heart palpitations and chest pain. The patient’s neurosurgeon attributed the reported events to her central pain disorder. Further, the physician did not have any objective documentation of the heart palpitations associated with celecoxib.

Comment: Given the lack of objective clinical information, a causality assessment could not be made in this case.

The 2nd case was reported by an attorney describing a 14-year-old female who suffered heart palpitations and difficulty breathing in 2003 after taking valdecoxib for three years

⁷ Protocol details and its indication were not provided.

⁸ Fluconazole, which can significantly increase celecoxib levels (2 fold), was one of the drugs administered at this hospital admission and also during three other hospital admissions within the prior six months to treat a fungal infection. Therefore, the involvement of a drug interaction could not be determined.

(10/2000 to 11/2003; indication not given). Celecoxib was also taken from 2002 to 2004 in addition to rofecoxib in 2003 (indication not given). Celecoxib and rofecoxib were reported as other suspect drugs. No further details were given. This report was not confirmed by a healthcare professional.

Comment: Although it appears NSAIDS could have contributed to these labeled events based on the time line of drug use, we cannot determine if the events were specifically related to celecoxib given the concomitant use of all three COX-2 inhibitors.

Pulmonary Embolism (n=2)

A CT angiogram of the chest in a 16-year-old female with medulloblastoma revealed significant bilateral pulmonary emboli about 10 weeks after starting a five drug chemotherapy regimen. She also developed lower extremity blood clots. The chemotherapy regimen consisted of thalidomide, fenofibrate, celecoxib daily with alternating 3 week courses of oral etoposide and cyclophosphamide to treat glioblastoma. The patient was also treated for medulloblastoma 10 years prior. No other medical history was reported. The underlying medical condition and the concomitant chemotherapy most likely increased this patient's risk for blood clots.

Comment: Given the temporal association, it is also possible thalidomide and celecoxib (both are labeled) contributed to pulmonary embolism. In addition, these two drugs were reported as the suspect drugs.

In the 2nd case, a 16-year-old female with diabetes presented with pulmonary embolism (PE) approximately 2 weeks after initiating celecoxib for possible psoriatic arthritis. The patient was treated with tissue plasminogen activator and embolectomy for clots in the pulmonary artery. She also required a right lower leg fasciotomy. It was noted that the patient had significant pain of the right lower leg prior to the event. A strong family history of thrombosis and systemic lupus were also reported. Although celecoxib (labeled for PE) was the suspect drug listed, she was also taking oral contraceptives at the time of the event (duration of use not given).

Comment: Temporal relationship suggests celecoxib could have been associated with blood clots in this case; however, the concomitant use of oral contraceptives, a history of diabetes, and a strong family history of thrombosis could have increased the patient's risk of clotting. Therefore, a clear causality relationship to celecoxib could not be established.

5. AERS cases for age 17 to 18 years During Pediatric Exclusivity Period (n=3, nonfatal)^{1,2}

The AERS database was searched on 1/18/2008 for all serious and nonserious adverse event reports (U.S. and foreign) received during the pediatric exclusivity period limited to age 17 to 18 years. The search retrieved three unduplicated, nonfatal reports and they are described below.

Hepatic Cholestasis Jaundice (US, n=1)

A 17-year old female developed hepatic cholestasis jaundice with supporting labs³ after receiving 2 doses (100 mg twice daily) of celecoxib for arthritis during a recent hospital stay. The patient's medical history included enterocutaneous fistula with partial cecectomy for ruptured appendix, rheumatoid arthritis, reflux, prolapsed rectum, short bowel syndrome, ileal resection at 1 week old. At the time of the jaundice report, the patient was post-op ileal colonic resection with perforated diverticulitis and fistula. Celecoxib is labeled for jaundice. No concomitant medications were reported.

Comment: Temporal association between cholestasis jaundice and celecoxib use in absence of concomitant drug use suggests that celecoxib could have contributed to this event.

Erythema and Dyspnea (Foreign, n=1)

An 18-year-old female with a history of sulfa allergy experienced erythema and mild shortness of breath after three doses of celecoxib 200 mg twice daily taken for abdominal pain. The patient was switched from naproxen to celecoxib. Celecoxib was discontinued and the event resolved per reporter. No concomitant medications were reported. Both erythema and dyspnea are labeled events.

Comment: Based on the patient's history of sulfa allergy, temporal association between celecoxib use and the events, and a positive dechallenge, celecoxib could be associated with erythema and dyspnea. Furthermore, the reporter also could not exclude the role of celecoxib.

Ischemic Stroke (US, n=1)

An attorney reported that an 18-year-old female took celecoxib 200 mg twice daily starting on 9/19/2001 and/or valdecoxib on an unknown date. Duration of use for either celecoxib or valdecoxib were not reported. She also used rofecoxib for about one year. Approximately one month after discontinuing rofecoxib and one month after starting celecoxib, she suffered an ischemic stroke on 10/31/2001 requiring hospitalization. Primary suspect drug was listed as celecoxib and rofecoxib was listed as the co-suspect drug. The patient did not claim any injuries or damages due to valdecoxib. No further details were given.

Comment: According to the report, rofecoxib was used for a longer duration than celecoxib prior to the onset of the event. Based on the lack of clinical details and duration of celecoxib use, the role of celecoxib could not be determined.

6. Review of Fatal Pediatric (Age 0-16 years) Celecoxib Cases before the 1-year Post-Pediatric Exclusivity Period

An additional AERS search was performed on 10/24/2007 to identify all fatal pediatric cases associated with celecoxib before the pediatric exclusivity period. The search retrieved 8 death reports associated with celecoxib use. Of the eight reports, five reports

were excluded for the following reasons: non-pediatric reports (2); events unrelated to celecoxib (3).

In the remaining 3 cases, the reported events were cardiomyopathy/congestive heart failure (CHF), intracranial hemorrhage, and suicide, respectively. The reporter for the first case attributed cardiomyopathy and CHF to the patient's renal cell carcinoma. The other two events (intracranial hemorrhage and suicide) are both labeled for celecoxib and it is possible that celecoxib could have contributed to the event. It is noteworthy, however, that the patient in the second case had medulloblastoma, which could have caused the intracranial hemorrhage. See below for more details of each case.

ISR# 4493033; Foreign; Fatal

An eight-year old male diagnosed with renal cell carcinoma of the left kidney (end stage) was being treated with vinblastine and celecoxib. Due to disease progression, this therapy was discontinued for a month and re-started. Three month later, the patient was passing blood in his stools with dizzy spells that brought him to the emergency room. He was tachycardic and anemic. The patient was treated in the intensive care unit for about two weeks then transferred to the oncology ward. He continued to cough and complained of chest pain and fatigue with head and neck pain. The patient continued to deteriorate and died 17 days after presenting to the emergency room. No etiology could be determined for the cardiomyopathy and congestive heart failure based on the autopsy. According to the reporter, the events were attributed to the progression of the underlying chronic illness. Celecoxib is labeled for CHF (unlabeled for cardiomyopathy).

ISR# 4304400; US; Fatal

A 9-year-old male patient with medulloblastoma experienced intracranial hemorrhage during treatment with thalidomide and celecoxib. The duration of therapy for thalidomide was from 4/11/03 to 11/5/03 (dates of use for celecoxib not given). The rate of disease progression slowed during drug therapy and the patient tolerated both drugs very well. However, the patient died on 11/5/03. The prescriber assessed the death as unrelated to thalidomide. Celecoxib is labeled for fatal intracranial hemorrhage.

Comment: In this case, it is likely that the patient's medulloblastoma was associated with the reported event; however, the contributory role of celecoxib could not be ruled out given the lack of clinical details.

ISR# 3645457; US; Fatal

A 15-year old male committed suicide six days after starting celecoxib (dose not specified) for knee pain. Concomitant medication was reported as an "unknown patch." No further details were given. Suicide is a labeled event for celecoxib.

Comment: The role of celecoxib could not be excluded based on the temporal association.

7. Summary/Recommendations

The AERS database was searched for all adverse events (serious and nonserious) associated with celecoxib use in pediatric patients from age 0 to 16 years during the pediatric exclusivity period. The search retrieved 10 unduplicated reports (fatal-2; nonfatal-8). The two death cases were both from a pilot study of newly diagnosed patients with metastatic Ewing's sarcoma. The reported events in the first case were fever, fluid overload, neutropenia and GI bleed; in the second case, the reported events were pancytopenia, pericardial effusion, and pulmonary hypertension. In both cases, a clear association between the use of celecoxib and the adverse events could not be established since many chemotherapeutic agents and radiation were given at the same time as celecoxib. However, the contributory role of celecoxib could not be ruled out for events such as GI bleed and pancytopenia, which are labeled for celecoxib. The cause of death was not reported in either case.

Of the remaining eight nonfatal cases, one case reported a positive dechallenge (skin reaction) possibly associated with celecoxib use. In the remaining 7 cases, the reported events were dyspnea (2), heart palpitations (2), pulmonary embolism (2), pneumonia, intracranial haemorrhage, pancytopenia, GI bleed, chest pain, and blood clots. All of the reported adverse events in these cases are labeled for celecoxib. However, all cases reported confounders as well such as the concomitant use of chemotherapy/radiation (causing immunosuppression), use of other drugs labeled for the reported events (e.g. oral contraceptives), or underlying medical history (e.g. brain tumors, H. Pylori, diabetes etc.) that could have contributed to the events.

A separate search of the AERS database was performed on 1/18/2008 for all adverse events limited to age 17 to 18 years during the pediatric exclusivity period². Additional three nonfatal, unduplicated (US=2; Foreign=1) cases were retrieved on 1/18/2008 and they are included in this review; there were no death reports in this search. The reported events were hepatic cholestasis jaundice, erythema, dyspnea, and ischemic stroke which are all labeled events for celecoxib. The reported events in the two of the three cases could be associated to celecoxib use based on the temporal relationship. In the 3rd case (ischemic stroke), the role of celecoxib could not be assessed given the lack of clinical details and duration of therapy. In this case, multiple COX-2 inhibitors including celecoxib were used further confounding the report.

An additional search of AERS was performed to identify all fatal pediatric (age 0-16 years) cases associated with celecoxib use prior to the 1-year post pediatric exclusivity period. This search retrieved an additional three unduplicated pediatric death cases. In one case, an 8-year old with end stage renal cell carcinoma developed cardiomyopathy and congestive heart failure (CHF) while being treated with interferon-alpha, vinblastine and celecoxib. Both cardiomyopathy and CHF are labeled for interferon-alpha; celecoxib is labeled only for cardiomyopathy (vinblastine is not labeled for either event). According to the reporter, the events were attributed to the progression of the underlying disease. In the 2nd fatal case, the patient experienced intracranial hemorrhage during treatment with thalidomide and celecoxib for a brain tumor. Celecoxib is labeled for fatal intracranial hemorrhage (unlabeled for thalidomide); however, a clear association

between intracranial hemorrhage and celecoxib use could not be established given the patient's underlying medulloblastoma. The last case involved a suicide (labeled for celecoxib) in an adolescent male six days after starting celecoxib with an unknown dose. Given that there were no reported underlying disease or other suspect drugs, the role of celecoxib could not be excluded based on the temporal association.

In conclusion, the cases in this review did not reveal any notable unexpected safety concerns associated with celecoxib use in pediatric patients from age 0 through 18 years. Deaths in four of the five fatal cases (two during and two prior to the pediatric exclusivity period) occurred in oncology patients receiving multiple chemotherapeutic agents and/or radiation in addition to celecoxib. The fifth death case was a suicide. We have no labeling recommendations at this time. We will continue to monitor these postmarketing adverse events.

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Appendix I. Line Listing of AERS Cases During Pediatric Exclusivity Period

| Table 5: Cases Reported for Age 0-16 Years During the Pediatric Exclusivity Period (n=10) | | | | | |
|-------------------------------------------------------------------------------------------|---------------------|-----------------------|----------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ISR# Source | Age (yrs) Gender | Total daily dose (mg) | Outcome [†] | Adverse Event (AE) Estimated time to onset (from day 1 of treatment) | Comments |
| 5120107 Canada | 12 F | Not reported | DE, HO | Neutropenia, GI bleed Not reported | Pilot Study of Ewing's Sarcoma Patients: concurrent treatment with chemotherapy, radiation and celecoxib |
| 5297836 Canada | 16 F | Not reported | DE, HO | Pancytopenia, pericardial effusion, pulmonary hypertension | Pilot Study of Ewing's Sarcoma Patients: concurrent treatment with chemotherapy, radiation and celecoxib |
| 5202706 Brazil | 4 day-old F | 200 | OT | Bullous eruptions 3 days | Celecoxib exposure from breast milk (positive dechallenge) |
| 5097040 France | 8 M | 100 | HO | Dyspnea, pneumonia Not reported | Per reporting physician, doubtful that event is related to suspect drugs. |
| 5143141 France | 8 M | 100 | LT, HO | Intracranial haemorrhage 106 days | Concurrent disease: medulloblastoma |
| 5390143 U.S. | 13 M | 800 | HO, DI | Pancytopenia, GI bleed 1 day | Drug interaction: fluconazole significantly (two fold) increases celecoxib levels ³ |
| 5308891 U.S. | 13 F | 200 | OT | Heart palpitations, irregular heart beat 70 days | Switched from ibuprofen to celecoxib d/t GI bleed. |
| 5419734 U.S. | 14 F | Not reported | OT | Heart palpitations, dyspnea, chest pain Not reported | Reported by an attorney: concomitant drugs included rofecoxib and valdecoxib (removed from market). |
| 5146191 U.S. | 16 F | 800 | HO | Pulmonary emboli, lower extremity clots 70 days | AE developed 10 weeks post chemotherapy: thalidomide, fenofibrate, celecoxib daily with alternating 3 week courses of oral etoposide and cyclophosphamide |
| 5168188 U.S. | 16 F | 400 | LT, HO | Pulmonary embolism 14 days | Confounded by a strong family hx of thrombosis, oral contraceptive use and underlying diabetes. Per reporter, AE was most likely related to an underlying condition but role of celecoxib cannot be ruled out. |

†DE=death, HO=hospitalization, LT=life threatening, OT=other, DI=disability
(a case may have more than one outcome)

| Table 6: Cases Reported for Age 17-18 years During the Pediatric Exclusivity Period (n=3)[‡] | | | | | |
|--------------------------------------------------------------------------------------------------------------|------------------|------------------------------|----------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ISR# | Age (yrs) | Total daily dose (mg) | Outcome[†] | Adverse Event (AE) | Comments |
| Source | Gender | | | Estimated time to onset (from day 1 of treatment) | |
| 5211684 U.S. | 17 F | 200 | HO | Jaundice Cholestatic 1 day | Developed jaundice after 2 doses (100 mg bid) of celecoxib. Supported by Lab values. |
| 5212389 Netherlands | 18 F | 400 | OT | Dyspnea, erythema 2 days | Pt w/ a history of sulfa allergy developed erythema and mild shortness of breath after 3 doses of celecoxib. |
| 5288918 U.S. | 18 F | 400 | HO, OT | Ischemic Stroke Not reported | Used multiple COX-2 inhibitors (valdecoxib, rofecoxib) along w/ celecoxib. Celecoxib listed as the primary suspect drug (role of celecoxib could not be determined). |

[†]DE=death, HO=hospitalization, LT=life threatening, OT=other, DI=disability
(a case may have more than one outcome)

[‡]No death was reported for age 17 to 18 years during the pediatric exclusivity period

Appendix II. SUMMARY OF DDRE AERS REVIEWS WITH CELECOXIB USE IN ADULTS*

| Date | Reviewer(s) | Drug(s) | Event(s) | OSE Findings (Cases Reviewed) | OSE Recommendation/Conclusion |
|----------|--------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7/1/99 | Susan Lu, Katherine Bennett | Celecoxib | Hepatotoxicity, drug interaction with warfarin, GI bleeding and deaths | <ul style="list-style-type: none"> • 8 Hepatotoxicity cases possibly associated w/ celecoxib use: liver failure (3), hepatitis (2), and jaundice (3) • 5 cases of possible drug interaction with celecoxib and warfarin resulting in increased INR or bleeding • 30 cases of GI bleeding possibly associated w/ celecoxib • 19 death cases reported in association w/ celecoxib use | <p>Current Celecoxib (10/2007) Labeling</p> <p>Hepatotoxicity, including potentially fatal liver failure, and the warfarin drug interaction should be added to the labeling</p> <p><u>Current Labeling</u> Precautions and Adverse Reactions (post-marketing experience): <i>Hepatotoxicity including liver failure</i></p> <p>Precaution (drug interactions): <i>Drug interaction w/ warfarin (bleeding)</i></p> |
| 12/29/00 | Joyce Weaver | Celecoxib, Etodolac, Rofecoxib | US deaths related to Gastrointestinal (GI) bleeding, obstruction, perforation, or stenosis | <ul style="list-style-type: none"> • 82 US deaths related to GI bleeding, obstruction, perforation, or stenosis in AERS database • All cases temporally related to therapy: etodolac (9), celecoxib (36), or rofecoxib (37) • 12 fatal cases for all drugs: the patients bled and died despite taking a gastro-protective drug concomitantly w/ NSAIDS that include celecoxib | <ul style="list-style-type: none"> • Add the information to the labeling regarding the occurrence of fatal GI bleeding despite attempts to protect the GI tract • Also, add to the celecoxib and rofecoxib labeling: the fatalities w/ concomitant use of aspirin or warfarin <p><u>Current Labeling</u> NSAID Class Black Box Warning and Warnings Section: <i>Gastrointestinal Effects-Risk of GI Ulceration, Bleeding, and Perforation</i></p> |
| 2/6/2001 | Renan Bonnel, Claudia Karwoski, Allen Brinker | Celecoxib, Rofecoxib, Etodolac | Thrombotic Vascular Events | <ul style="list-style-type: none"> • 223 US cases of thrombotic or embolic events possibly associated with rofecoxib (99), celecoxib (102), and etodolac (22) • Events included myocardial infarction, cerebrovascular events, pulmonary embolism, deep venous thrombosis, and misc thrombotic events | <ul style="list-style-type: none"> • Many patients were older and/or had possible predisposing factors or underlying disease, therefore, unable to determine the role of each agent in causing the event • Continued thrombotic events are an important finding since the actual number of thrombotic cases may in fact be higher due to underreporting of adverse events in passive surveillance systems <p><u>Current Labeling</u> NSAID Class Black Box Warning and Warning-CV Effects: <i>Cardiovascular (CV) Thrombotic Events--Chronic use of celecoxib</i></p> |

| | | | | | |
|-----------|--------------|-------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | | | | | <i>may cause an increased risk of serious adverse CV thrombotic events, myocardial infarction, and stroke, which can be fatal</i> |
| 6/13/2001 | Renan Bonnel | Celecoxib | Hearing Loss | <ul style="list-style-type: none"> • 31 cases involved hearing loss with celecoxib listed as a suspect drug • Majority of patients had other risk factors that might have contributed to hearing loss | <p>This review supports (already labeled) a possible association of hearing loss in post-marketing phase with celecoxib in high risk patients</p> <p><u>Current Labeling</u> Adverse Reactions (Hearing and vestibular): <i>Deafness, ear abnormality, earache, tinnitus</i></p> |
| 3/11/02 | Renan Bonnel | Celecoxib, Rofecoxib, Naproxen, Diclofenac, Ibuprofen | Thrombotic Vascular Events Between 12/1/200 to 2/1/2003 | <ul style="list-style-type: none"> • Thrombotic events reported in AERS between 12/1/00 to 2/1/02: celecoxib (176), rofecoxib (375), diclofenac (49), naproxen (18), ibuprofen (52) • Recent publicity related to a potential increase in the rate of heart attack, stroke, and other CV events with use of rofecoxib and celecoxib may have stimulated reporting in these two agents | <ul style="list-style-type: none"> • FDA continues to receive post-marketing serious, life-threatening CV thrombotic event swith COX-2 inhibitor agents • Actual number of thrombotic adverse events may in fact be higher due to underreporting of adverse events in passive surveillance systems <p><u>Current Labeling</u> NSAID Class Black Box Warning and Warning-CV Effects: <i>Cardiovascular (CV) Thrombotic Events--Chronic use of celecoxib may cause an increased risk of serious adverse CV thrombotic events, myocardial infarction, and stroke, which can be fatal</i></p> |
| 12/13/02 | Renan Bonnel | Celecoxib, Rofecoxib | Aseptic Meningitis | <ul style="list-style-type: none"> • 10 cases of aseptic meningitis temporally associated with celecoxib use (subset of these cases provided sufficient clinical data to support a possible association) • All patients had a serious outcome and required hospitalization • One patient had a positive dechallenge after stopping celecoxib | <p>This review is in agreement with the inclusion of aseptic meningitis as is currently labeled</p> <p><u>Current Labeling</u> Adverse Reactions (Nervous System): <i>aseptic meningitis</i></p> |
| 6/26/2002 | Renan Bonnel | Celecoxib Rofecoxib, | Myopathy/Rhabdomyolysis | <ul style="list-style-type: none"> • 51 cases reviewed: rofecoxib (27), celecoxib (24) • 24 cases were temporally associated with celecoxib use (9=rhabdomyolysis) • 12 patients developed acute renal failure (celecoxib-3, rofecoxib-9) | <p>“significant serum CPK elevation, myopathy including rare cases of rhabdomyolysis” be added to the adverse reactions or post-marketing section of both labels</p> <p><u>Current Labeling</u> Adverse Reactions (metabolic and nutritional): <i>CPK increased</i></p> |

| | | | | | |
|---------|--------------|----------------------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6/11/03 | Renan Bonnel | Celecoxib, Rofecoxib | Ischemic Colitis (IC) | <ul style="list-style-type: none"> • 22 cases in AERS database of IC temporally related: celecoxib (5), rofecoxib (14), and valdecoxib (3) • One of more predisposing conditions were noted in 12 patients and included: diabetes mellitus (3), estrogen therapy (3), atherosclerosis/underlying vascular disorder (1), recent or concomitant NSAID use (3), intestinal vascular insufficiency (2), coagulopathy of the colon (1) | <ul style="list-style-type: none"> • Based on this review, OSE continues to receive a small number of well-documented cases of IC for rofecoxib and celecoxib • Significance of these cases is unclear • Inclusion of this post-marketing safety information could be considered in the celecoxib and rofecoxib labeling <p><u>Current Labeling</u> Adverse Reactions-Gastrointestinal : <i>colitis w/ bleeding</i></p> |
| 2/2/05 | Mark Avigan | Celecoxib, Rofecoxib, Valdecoxib, Non-selective NSAIDS (including aspirin) | Thrombotic Cardiovascular and GI Events | <ul style="list-style-type: none"> • Adverse events of interest are thrombotic cardiovascular (CV) events (including MI, stroke, thrombosis) and GI events (including GI hemorrhage, stenosis, obstruction and perforation) • CV thrombotic and GI adverse events have been reported in premarketing clinical trials as well as from postmarketing studies for celecoxib and rofecoxib • Due to the limitations of spontaneous data, it is difficult to determine the contribution of drug exposure alone in each reported case in postmarketing AERS reports. • Both thrombotic CV and GI events have high background incidence rates in the general population, also multiple medical and lifestyle risk factors are associated with these conditions | <ul style="list-style-type: none"> • Assessing the degree to which a drug is responsible for these adverse events is often extremely difficult • In these situations, AERS data alone cannot meaningfully isolate and quantify the drug-related risk for these events • An evaluation of risk associated with drug exposure and adverse events under these conditions must depend on studies in defined populations, such as clinical trials and epidemiological studies <p><u>Current Labeling</u> NSAID Class Black Box Warnings for CV and GI Events and also in Warnings</p> |
| 6/8/06 | Joyce Weaver | Celecoxib | Metabolic acidosis, nephrolithiasis, bony fractures | <p><u>Nephrolithiasis</u></p> <ul style="list-style-type: none"> • 7 cases reporting kidney stone w/ celecoxib use (Serious outcomes: 4-hospitalized; 0-death, 0-life-threatening) <p><u>Metabolic acidosis</u></p> <ul style="list-style-type: none"> • 14 cases of acidosis w/ celecoxib use (Serious outcomes: 7-hospitalized, 2-life threatening, 7-death) <p><u>Bony fractures</u></p> <p>13 cases of bony fractures associated w/ celecoxib (Serious outcomes: 7-hospitalized, 1-death)</p> | <p>Inconclusive Data (will continue to monitor)</p> <p><u>Current Labeling</u> Adverse Reactions (Musculoskeletal): <i>Fracture accidental</i></p> |

*This summary chart may exclude crude counts or some OSE reviews with inconclusive data (e.g. no labeling recommendations)

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/s/

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