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Memorandum

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SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event
Review (PID # D040141)
Rofecoxib (Vioxx®), NDA 021647, 021042, 021052
Pediatric Exclusivity Approval Date: February 18, 2004

Executive Summary

As requested by the Office of Counter-Terrorism and Pediatrics, this consult reviews the pediatric adverse events associated with rofecoxib (Vioxx) during a 12-month period starting from February 18, 2004.

Vioxx is a prescription COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) that was approved by the FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, the management of acute pain in adults, and the treatment of menstrual symptoms. Subsequently, it was approved for relief of the signs and symptoms of rheumatoid arthritis in adults and for the acute treatment of migraine attacks with or without aura in adults. On August 19, 2004, it was approved for the relief of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients 2 years and older who weigh 10 kg (22 lb) or more.

On September 30, 2004, Merck & Co., Inc. announced a voluntary withdrawal of Vioxx (rofecoxib) from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients treated with Vioxx.

We reviewed 16 pediatric adverse event cases reported to the FDA during the Pediatric Exclusivity period. The range of types of adverse events in children are overlapping with those reported in adults. Most events are either labeled or associated with labeled events.

The most frequently reported adverse events included renal and cardiac systems. The adverse events were renal insufficiency, acute renal failure, proteinuria, nephrolithiasis/interstitial cystitis, dyspnea, palpitations, and chest discomfort. The next most frequently reported groupings of events were CNS and gastrointestinal adverse events including dizziness, syncope, esophagitis, gastritis, and exacerbation of colitis.

Three of 16 cases reported use of higher than the recommended dose of rofecoxib (prescribed overdose), possibly contributing to the reported adverse events, including erosive esophagitis/ non-erosive gastritis, exacerbation of colitis, and nephrolithiasis/interstitial cystitis. Six of 16 cases reported the use of rofecoxib for unapproved indications including fever/arthritis, ankylosing spondylitis, renal wasting disorder, and Gitelman's syndrome.

Six of 16 cases suggested a possible association between the use of rofecoxib and the reported adverse events, including acute renal failure (2), renal insufficiency (1), proteinuria (1), exacerbation of colitis (1), and erosive esophagitis/ gastritis (1). These events were temporally related to rofecoxib use, and four patients recovered after discontinuation of the drug. The remaining 10 cases did not provide sufficient data to assess the exact role of rofecoxib in the adverse events.

There was one case of congenital anomaly which described sacro-coccygeal dimple and pes valgus in a baby born to a woman who received rofecoxib during the second trimester of pregnancy. The causal role of rofecoxib in this case is unknown.

There were three foreign death reports. A child with a history of hereditary renal electrolyte wasting disorder died after receiving treatment with rofecoxib for 18 months for this unapproved indication. The cause of death (post-mortem) was aspiration, pulmonary emphysema, bleeding underneath the pulmonary pleura, and significant enlargement of the right heart. There was no histological evidence of myocardial infarction. The role of rofecoxib was unknown, and infection and myocarditis could not be ruled out. The second case involved a child who was receiving rofecoxib 25 mg, methotrexate, Chinese traditional medicine, and spiruline for the treatment of rheumatoid arthritis and died after chest tightness. The causal role of rofecoxib remains unknown in this case. The third case was actually a fetal death after an elective abortion involving a 14-year old female who used rofecoxib for an unspecified indication.

Overall, the pediatric profile of adverse events was overlapping with the profile observed in adult patients. The prescribed overdoses and the use of rofecoxib for unapproved indications in pediatric patients were notable findings.

AERS Search Results: Rofecoxib

To analyze the adverse events, two AERS searches were conducted in both the adult and pediatric age groups: (1) May 20, 1999 (approval date) to March 18, 2005, and (2) February 18, 2004 (pediatric exclusivity date) to March 18, 2005, which was selected as the termination date to allow for a one-month lag time for report entry into AERS. The search included U.S and foreign sources.

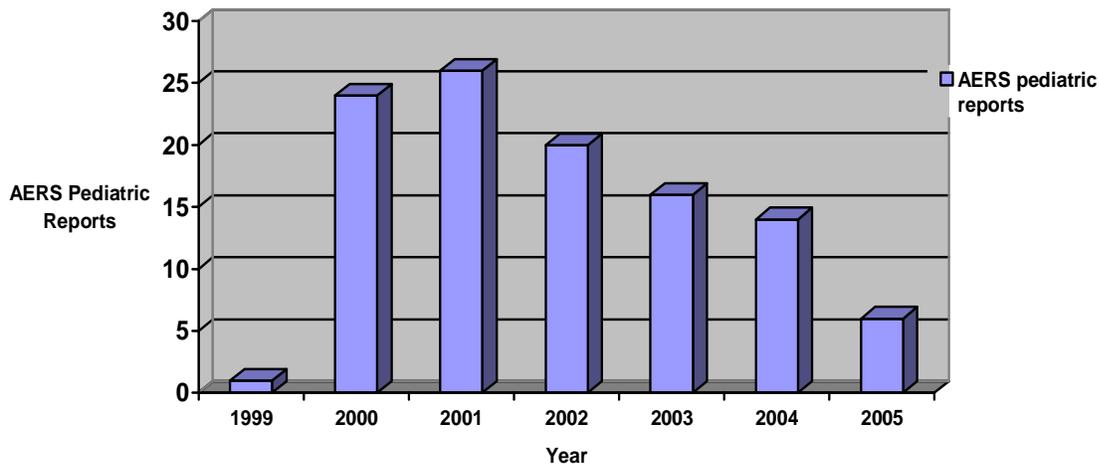
A. Adverse events from marketing approval date, May 20, 1999, to March 18, 2005:

1. Raw counts of reports: see Table 1

Table 1: Raw counts of all serious and non-serious reports from US approval date through AERS data cut-off date			
	All reports (US)	Serious (US)	Deaths (US)
All ages	35,002* (28,835)	19,508 (12,993)	2,088 (1,289)
Adults (≥ 17 yrs)	24,305 (18,688)	14,302 (8,725)	1463 (792)
Peds (0-16 yrs)	107 (70)	71(36)	8 (1)

- includes 10,590 null age values

Fig.1- Reporting trend for AERS pediatrics reports from approval date (May 20, 1999 until March 18, 2005



2. Counts of top 20 reported adverse event PTs and labeling status of these events (underline denotes unlabeled events):

All ages:

Myocardial infarction (3346), cerebrovascular accident (2505), drug ineffective (2393), edema peripheral (2165), dyspnea (1641), blood

pressure increased (1557), hypertension (1427), chest pain (1396), nausea (1335), diarrhea (1301), dizziness (1302), gastrointestinal hemorrhage (1238), headache (1180), asthenia (1121), abdominal pain (1119), cardiac failure congestive (1026), fatigue (1026), dyspepsia (880), weight increased (862), pruritus (819), pain (795)

Adults:

Myocardial infarction (1841), drug ineffective (1728), edema peripheral (1709), dyspnea (1416), cerebrovascular accident (1400), chest pain (1217), hypertension (1181), nausea (1160), dizziness (1119), blood pressure increased (1100), diarrhea (1089), headache (1013), asthenia (881), gastrointestinal hemorrhage (926), abdominal pain (912), fatigue (1026), cardiac failure congestive (835), dyspepsia (690), weight increased (683), pruritus (651)

Pediatrics:

Headache (9), prescribed overdose (9), dizziness (8), vomiting (8), asthenia (6), dyspepsia (6), acute renal failure (6), abdominal pain (5), alopecia (95), gastritis (5), gastrointestinal disorder (5), hypoaesthesia (5), intentional overdose (5), confusional state (4), diarrhea (4), aseptic meningitis (4), suicide attempt (4), syncope (4), upper abdominal pain (3), CSF lymphocyte count increased (3)

B. From pediatric exclusivity approval date (February 18, 2004) through AERS data cut-off date of March 18, 2005:

1. Raw counts of reports; see Table 2

Table 2: Raw Counts of reports from February 18, 2004 (pediatric exclusivity approval date) to March 18, 2005			
	All reports (US)	Serious (US)	Deaths (US)
All ages	9626* (7212)	9530 (7135)	1049 (775)
Adults (≥ 17 yrs)	6215 (4296)	6133 (4232)	655 (437)
Peds (0-16 yrs)	19 (5)	18 (5)	3 (0)

* includes 3392 null age values

2. Counts of top 20 reported adverse event PTs and labeling status of these events (underline denotes unlabeled events):

All ages:

Myocardial infarction (2826), cerebrovascular accident (2148), chest pain (831), hypertension (746), cardiac disorder (588), dyspnea (566), adverse event (551), coronary artery disease (451), dizziness (447), headache

(412), injury (411), congestive heart failure (395), depression (386), peripheral edema (366), blood pressure increased (355), transient ischemic attack (334), angina pectoris (332), anxiety (327), fatigue (327), nausea (325)

Adults:

Myocardial infarction (1454), cerebrovascular accident (1148), chest pain (743), hypertension (680), dyspnea (519), coronary artery disease (417), dizziness (412), headache (391), depression (375), cardiac disorder (364), peripheral edema (343), congestive heart failure (340), anxiety (315), blood pressure increased (315), nausea (314), fatigue (309), angina pectoris (298), adverse event (292), asthenia (278), transient ischemic attack (276)

Pediatrics:

Prescribed overdose (7), dizziness (3), gastritis (3), drug exposure during pregnancy (2), myocardial infarction (2), palpitations (2), proteinuria (2), acute renal failure (2), syncope (2), vomiting (2), abdominal discomfort (1), abdominal pain (1), abortion induced (1), aspiration (1), asthenia (1), asthma (1), blood alkaline phosphatase increased (1), blood calcium decreased (1), blood pressure increased (1), cerebrovascular accident (1)

Postmarketing hands-on review of all peds adverse event reports from all sources received during the one-year after the pediatric market exclusivity approval (February 18 ,2004 to March 18, 2005)

A total of 19 pediatric adverse event reports were identified in this period. Three of 19 cases were excluded from further analysis due to the following reasons: adult patients (2); duplicate report (1)

A. Description of demographics and other case characteristics of the remaining 16 pediatric reports regarding gender, age, indications, dose, and outcomes.

Table 3: Characteristics of pediatric cases (reported during the 1-year period after receiving pediatric market exclusivity)	
Gender	Female-10 Male- 6
Age (Standard AERS age breakdown)	0-<1 months - 1 1 mon- <2 yrs -1 2 yrs-5yrs - 0 6 yrs-11 yrs - 5 12yrs-16 yrs - 9

Indications or clinical conditions for which the drug was used:	Migraine-1 Back pain- 1 Ankle pain-1 Fever/ Arthralgia-1 Ankylosing spondylitis-2 Juvenile rheumatoid arthritis-4 Gitelman's syndrome-2 Renal tubular disorder with sodium wasting-1 Unknown- 3
Dosage range*	0.5mg/kg/day- 2 0.7mg/kg/day-1 2mg/kg/day-1 5mg/day-1 25mg/day- 8 50mg/day-1 Unknown-2
Serious outcomes	deaths- 3 hospitalizations- 6 life-threatening- 2 disability- 4 congenital anomaly- 1

*

The recommended dose, based on reviews of two NDA pediatric supplements, is **0.6 mg/kg/day up to a maximum dose of 25 mg per day** in JRA patients ≥ 2 years and ≤ 17 years of age. The bolded numbers in Table 3 indicate prescribed overdoses.

B. Comments regarding pediatric studies, labeling status of the top 20 adverse events and similarities to adult adverse event profile.

On May 7, 2001, DAAODP (HFD-550) issued a pediatric Written Request (WR) to Merck Research Laboratories (MRL) to obtain needed pediatric information about rofecoxib (Vioxx) tablets and suspension to investigate the use of rofecoxib for the treatment of JRA. On December 5, 2003, the sponsor submitted six studies, including four pharmacokinetic studies, one Phase 3 clinical efficacy and safety study, and one open-label extension study in JRA patients. FDA granted MRL six months of marketing exclusivity for Vioxx on February 18, 2004 based on the submitted pediatric supplements cited above.

Carolyn L. Yancey, M.D., (CDER, DAAODP) reviewed the pediatric efficacy and safety of 12 week double-blind (310 JRA patients) and 52-week open-label extension safety studies (227 JRA patients). There were no deaths, malignancies, significant overdoses or pregnancies. Cardiovascular outcome measures including blood pressure

and edema were ascertained in clinical studies. The most commonly reported adverse events included abdominal pain, upper abdominal pain, diarrhea, nausea, upper respiratory tract infection, headache, pyrexia, and elevated hepatic enzymes. The importance of safety monitoring for the risk of hepatotoxicity with concomitant medications, particularly with DMARD therapy was emphasized in the medical officer's review. Based on the reviews of two NDA pediatric supplement data, the recommended rofecoxib dose was 0.6 mg/kg/day up to a maximum dose of 25 mg per day in JRA patients ≥ 2 years and ≤ 17 years of age.

In August 2004, rofecoxib was approved for relief of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis in patients 2 years and older who weigh 10 kg (22 lbs) or more.

In the AERS database, the following unlabeled events were reported most frequently in the pediatric cases during the one-year pediatric exclusivity period (see top 20 PTs): prescribed overdose (7), abortion induced (1), aspiration (1), blood alkaline phosphatase increased (1), blood calcium decreased (1)

The following events (see top 20 PTs) regardless of labeling status were reported for children, but not for adults in the pediatric exclusivity period: prescribed overdose (7), gastritis (3), drug exposure during pregnancy (2), palpitations (2), proteinuria (2), acute renal failure (2), syncope (2), vomiting (2), abdominal discomfort (1), abdominal pain (1), abortion induced (1), aspiration (1), asthma (1), blood alkaline phosphatase increased (1), blood calcium decreased (1)

The prescribed overdose, induced-abortion, aspiration, blood alkaline phosphatase increased, syncope, and blood calcium decreased were unlabeled events reported in children.

C. Comments and analysis of events uniquely reported in pediatric patients (not reported in adult patients)

There were 2 cases associated with events uniquely reported in pediatric patients but not in adults.

One case reported congenital anomaly involving sacro-coccygeal dimple and pes valgus in a baby born to a woman who used rofecoxib during the second trimester.

The second case reported an induced-abortion involving a 14-year-old female (10th week of gestation) who had used rofecoxib 25mg (duration and indication were unknown). The pregnancy was electively terminated.

D. Comments of increased frequency reporting of any expected events.

Not observed in the selected dataset.

E. Summary of all reports of death and comments on whether deaths were related to drug use

There were three foreign death reports.

A 12-year-old female received rofecoxib 25 mg /day for the treatment of rheumatoid arthritis. Concomitant therapy included methotrexate, Chinese traditional medicine and spiruline. Five months later, she experienced chest tightness and died. The role of rofecoxib was unknown.

The second case involved a 14-year-old female with Gitelman's syndrome, hypokalemia, hypomagnesemia, QT prolongation and a history of convulsions who received rofecoxib 25mg (0.5 mg/kg/d). Concomitant medications were potassium and magnesium. During the 18 months of rofecoxib therapy, the patient had multiple episodes of electrolyte imbalance, supraventricular arrhythmias, hypokalemia, hypomagnesemia that were attributed to the patient's underlying renal disorder. She required repeated hospitalizations during this time period for treatment. Approximately 18 months after starting rofecoxib, she was found unresponsive, had breathing difficulty and muscular hypotonia following a cold episode. An infection or myocarditis could not be ruled out. The patient subsequently expired and an autopsy was performed. The cause of death was aspiration, pulmonary emphysema, bleeding underneath the pulmonary pleura, and significant enlargement of the right heart. There was no histological evidence of myocardial infarction. The role of rofecoxib was unknown.

The third case involved a 14-year old pregnant girl who received rofecoxib and had an elective abortion. The narrative of the case implied fetal death due to abortion.

F. Summary of the pediatric adverse event profile during the 1-year period.

We received 16 pediatric adverse event cases during the pediatric exclusivity period. The following events were reported:

- Renal events (proteinuria, renal insufficiency, acute renal failure (2), and nephrolithiasis/interstitial cystitis)- **5**
- Cardiovascular events (dyspnea, palpitations, and chest discomfort) -**3**
- Gastrointestinal events (exacerbation of colitis, and esophagitis/gastritis) -**2**
- CNS events (dizziness, syncope,) - **2**
- Drug exposure during pregnancy and/or congenital anomaly -**2**
- Asthma/hypersensitivity-**1**
- Other- **1** (a case reporting multiple adverse events involving gastrointestinal, CNS, and cardiac systems)

The most frequently reported events were renal (5 cases) and cardiovascular adverse events (3 cases).

Five **renal adverse events** were reported and included acute renal failure (2 cases), renal insufficiency, proteinuria, and nephrolithiasis/interstitial cystitis.

The first case (FDA # 4496938, Literature)¹ involved a 14-year old male with a history of rheumatic fever (non-compliant to aspirin) who received ibuprofen 200 mg six times a day for two days for ongoing fever and arthralgia. This was changed to rofecoxib 25 mg daily (weight unknown) for three days prior to presentation. He presented with persistent fever, lethargy, arthralgia and abdominal pain. Urinalysis showed hematuria and mild proteinuria. Blood tests were consistent with acute renal failure (urea 15.2 mmol/L and creatinine 240 umol/L). Renal ultrasound and DMSA scan were consistent with nephritis with the suggestion of a renal infarct. Rofecoxib was discontinued and he received steroids. His renal function returned to normal within 9 days and had remained normal in follow-up.

The second case (FDA# 4363369, Literature)¹ involved an 18-month old female with Gitelman's syndrome who was changed to 5 mg rofecoxib (weight unknown) from indomethacin (3 mg daily) due to worsening gastritis two days prior to presentation. She presented with a 2 day history of watery diarrhea, vomiting and irritability. Admission labs revealed hyperkalemia (K 10.3 mmol/L), hypernatremia (Na 165 mmol/L), severe metabolic acidosis (pH 6.9, HCO₃ 3mmol/L) and acute renal failure (urea 27.9 mmol/L and creatinine 164 umol/L). Following correction of acidosis her renal function returned to normal in six days and has remained normal in follow-up despite restarting therapy with indomethacin and lisinopril.

The third case (FDA# 4363369) was a 15-year old female who received rofecoxib 25 mg daily (0.5 mg/kg/day- indication was unknown) and developed gastritis and renal insufficiency; she required hospitalization. The serum creatinine was 118-259 umol/L and urine protein was 0.65 g/L. Rofecoxib therapy was discontinued. The patient recovered from gastritis and renal insufficiency. The reporting physician felt that the events were related to rofecoxib.

The fourth case involved a 14-year old female who developed proteinuria (1gram/24 hours) and required hospitalization after receiving rofecoxib 25 mg daily (weight unknown) for the treatment of juvenile idiopathic arthritis. Concomitant medication included sulfasalazine. She had no other clinical symptoms. The patient recovered after discontinuation of rofecoxib. The reporting physician felt that proteinuria was related to rofecoxib.

The fifth child developed nephrolithiasis, interstitial cystitis, and an ovarian cyst after receiving rofecoxib 50 mg daily (prescribed overdose) for one year for migraine. The patient required hospitalization and underwent a procedure to remove the kidney stones. She also received pentosan polysulfate sodium (Elmiron) for interstitial cystitis.

Three **cardiovascular events** were reported and included chest tightness, palpitations/dyspnea, and QT prolongation/arrhythmias. One case involved a 12-year-old female who received rofecoxib 25 mg /day (weight unknown) for the treatment of rheumatoid arthritis. Concomitant therapy included methotrexate, Chinese traditional medicine and spiruline. Five months later, she experienced chest tightness and died. The role of rofecoxib was unknown.

The second case involved a 14-year-old female with Gitelman's syndrome, hypokalemia, hypomagnesemia, QT prolongation and a history of convulsions who received rofecoxib 25mg (0.5 mg/kg/d). Concomitant medications were potassium and magnesium. During 18 months of rofecoxib therapy, the patient had multiple episodes of electrolyte imbalance, supraventricular arrhythmias, hypokalemia, hypomagnesemia that were attributed to the patient's underlying renal disorder. She required repeated hospitalizations during this period for treatment. Approximately 18 months after starting rofecoxib, she was found unresponsive, had breathing difficulty and muscular hypotonia following a cold episode. She subsequently expired and an autopsy was performed. The cause of death was aspiration, pulmonary emphysema, bleeding underneath the pulmonary pleura, and significant enlargement of the right heart. There was no histological evidence of myocardial infarction. The role of rofecoxib was unknown.

The third patient was a 15-year old girl who developed dyspnea, palpitations, and a benign neck nodule after receiving 25 mg rofecoxib (a total of three tablets, unknown interval) for the treatment of back pain. The role of rofecoxib was unknown.

Two **gastrointestinal adverse events** were reported and included an exacerbation of colitis and erosive esophagitis/gastritis. The first patient was a 14-year old male who developed stomach pain, diarrhea, weakness, loss of appetite and weight loss after using rofecoxib 50 mg daily (prescribed overdose) for 6 weeks for an ankle sprain. An endoscopy showed erosive esophagitis and non-erosive gastritis. A colonoscopy was performed and the results were unknown; however, the patient was prescribed metronidazole therapy for an unspecified indication. A gallbladder scan was normal. At the time of the report, the patient did not recover.

A second patient was a 7-year old male who was a premature baby in the 27th week of gestation with hypertension. The patient had a history of unspecified colitis while on prior therapy with indomethacin. He received rofecoxib 0.7mg/kg/day for the treatment of renal tubular disorder with sodium wasting (unapproved indication). Concomitant medications included potassium, sulfasalazine, and amlodipine. He developed an exacerbation of colitis with rofecoxib and the drug was discontinued for 2 months. Two months later, rofecoxib was restarted at 0.2 mg/kg/day. Diarrhea did not recur, but he developed hypertension (150/90 mmHg). The patient's increased blood pressure persisted. The physician felt that both events were probably related to rofecoxib and the exacerbation of colitis was most likely related to the high dose rofecoxib.

Two **central nervous system** adverse events were reported and included two cases of dizziness and syncope after receiving rofecoxib. The dose was 25 mg in one case and it was unknown in the second case. Rofecoxib was used for the treatment of JRA or ankylosing spondylitis. The role of rofecoxib was unknown in both cases. No further information was provided.

There were two cases of **drug exposure during pregnancy**. One case reported congenital anomaly involving sacro-coccygeal dimple and pes valgus in an infant born to a woman who used rofecoxib during the second trimester.

The second case reported an induced-abortion in a 14-year-old female (10th week of gestation) who had used rofecoxib 25mg (duration and indication were unknown). The pregnancy was electively terminated.

One case reported **hypersensitivity/asthma**. A 12-year old girl with a history of asthma and allergy to indomethacin developed an asthma attack while receiving rofecoxib 25 mg daily for the treatment of ankylosing spondylitis. She continued rofecoxib for one year and the therapy was discontinued for an unknown reason. There were no concomitant medications. Hypersensitivity and asthma are labeled events for rofecoxib.

One case reported **multiple adverse events** involving gastrointestinal, CNS, and cardiac systems. This case involved an 11-year old female with juvenile rheumatoid arthritis, growth hormone abnormality, a history of hypersensitivity, and gastroesophageal reflux disease who received rofecoxib 25 mg daily over 2 years for JRA. Concomitant medications included acetaminophen, somatropin, calcium carbonate, cetirizine, etanercept, methotrexate, omeprazole and folic acid. Two and a half years after starting rofecoxib therapy, she developed circumular pallor, sweating, rigidity, palpitations, headache, dizziness and abdominal pain. The attack resembled pheochromocytoma, but blood and urine lab results did not confirm the diagnosis. She required hospitalization. Blood chemistry, hematology, liver, thyroid and inflammatory function tests, and ANA results were normal. The blood pressure measurement was 105/62 mmHg. Etanercept was discontinued, rofecoxib dose was increased (unspecified dose), and her symptoms worsened. Subsequently, rofecoxib was discontinued, etanercept therapy was resumed, and celecoxib 200 mg twice daily was prescribed. The patient improved. The reporter felt that all adverse events were probably related to therapy with rofecoxib.

Overall, 6 of 16 cases suggested a possible association between the use of rofecoxib and the reported adverse events, including acute renal failure (2), renal insufficiency (1), proteinuria (1), exacerbation of colitis (1), and erosive esophagitis/ gastritis (1). These events were temporally related to rofecoxib use, and four patients recovered after the discontinuation of the drug. The remaining 10 cases did not provide sufficient information to assess the exact role of rofecoxib in the adverse events.

Summary

The AERS database was searched for reports of adverse events occurring with the use of rofecoxib in pediatric patients. We focused on the 1-year period (2/18/2004 to 3/18/2005) following the pediatric exclusivity approval. Rofecoxib was withdrawn from worldwide marketing on September 30, 2004.

We reviewed 16 pediatric cases. The most frequently reported events were renal (proteinuria, renal insufficiency, acute renal failure, and nephrolithiasis/interstitial cystitis) and cardiovascular adverse events (dyspnea, palpitations, chest discomfort, and cardiac arrhythmias). Renal and cardiovascular side effects are known to occur in adults with rofecoxib and are included in the labeling.

Six of 16 cases suggested a possible association between the use of rofecoxib and the reported adverse events, including acute renal failure (2), renal insufficiency (1), proteinuria (1), exacerbation of colitis (1), and erosive esophagitis/ gastritis (1). These events were temporally related to rofecoxib use, and four patients recovered after the discontinuation of the drug. The remaining 10 cases did not provide sufficient data to assess the exact role of rofecoxib in the adverse events.

There was one case of congenital anomaly which described sacro-coccygeal dimple and pes valgus in a baby born to a woman who received rofecoxib during the second trimester of pregnancy. The role of rofecoxib in this case was unknown.

There were three deaths; all were foreign cases. A child with Gitelman's syndrome died after receiving rofecoxib for 18 months for an unapproved indication. The cause of death (post-mortem) was aspiration, pulmonary emphysema, bleeding underneath the pulmonary pleura, and significant enlargement of the right heart. There was no histological evidence of myocardial infarction. The role of rofecoxib was unknown. The second case involved a child who was receiving rofecoxib 25 mg, methotrexate, Chinese traditional medicine, and spiruline for the treatment of rheumatoid arthritis and died after chest tightness. The causal role of rofecoxib was unknown in this case. The third case described a fetal death after an elective abortion and involved a 14-year old female who used rofecoxib when pregnant.

Overall, the pediatric profile of adverse events was similar to the profile in adult patients. The adverse events linked to prescribed overdoses and the use of rofecoxib for unapproved indications were notable findings.

REFERENCES:

1. JT Fletcher, N Graf, SI Alexander. Acute renal failure with COX-2 inhibitors in three children. *Pediatric Nephrology* 2004; 19 (9): C199)(P431)

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