One Year Post Exclusivity Adverse Event Review: Celebrex® (celecoxib)

Pediatric Advisory Committee Meeting
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Outline

- **Background Drug Information**
- **Drug Use Trends**
- **Pediatric Exclusivity Studies**
- **Pediatric Exclusivity Labeling Changes**
- **Additional Relevant Safety Labeling**
- **Adverse Events**
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  - One-year post exclusivity
- **Summary**

Background Drug Information

- **Drug:** Celebrex® (celecoxib)
- **Therapeutic Category:** Non-Steroidal Anti-inflammatory Drug (NSAID)
- **Sponsor:** G.D. Searle
- **Original Market Approval:** December 31, 1998
- **Pediatric Exclusivity Granted:** August 23, 2006
- JRA Approval: December 15, 2006

Background Drug Information

Adults only:

- Relief of the signs and symptoms of:
  - Osteoarthritis
  - Rheumatoid arthritis
  - Ankylosing Spondylitis
- Management of acute pain
- Treatment of primary dysmenorrhea
- Adjunctive treatment in Familial Adenomatous Polyposis (FAP)

Pediatric patients:

- Relief of the signs and symptoms of juvenile rheumatoid arthritis (JRA) 2 years and older

Background Drug Information

Dosage:

- **Adult patients:**
  - OA 200 mg/day as one dose or 100 mg BID
  - RA: 100 to 200 mg BID
  - Ankylosing Spondylitis: up to 400 mg per day
  - Acute Pain or Primary dysmenorrhea: 400 mg initially, then 200 mg BID prn
  - FAP: 400 mg BID with food
- **Pediatric patients:**
  - 10 to 25 kg: 50 mg BID
  - >25 kg: 100 mg BID

Drug Use Trends: celecoxib

Drugs Selected for Review:

leflunomide + **NSAID's**

celecoxib
diclofenac
etodolac
fenoprofen
flurbiprofen
ibuprofen
indomethacin
ketoprofen
meclofenamate
mefenamic acid
meloxicam
naproxen
nabumetone
oxaprozin
piroxicam
rofecoxib
sulindac
tolmetin
valdecoxib

Drug Use Trends: celecoxib

Primary Use: Outpatient setting (91%)[1]

- Retail sales channels (65%)
- Mail order (26%)
- Non-retail channels (9%)

Majority of use in adults (>99%)[2]

- 3rd in terms of prescription volume for selected products

Trends in prescription volume (adults)[2]

From baseline (Sept 2004 to Aug 2005) to post exclusivity period (Sept 2006 to Aug 2007) decreased by 20%

Slight increase pre- (Sept 2005 to Aug 2006) and post-exclusivity period (Sept 2006 to Aug 2007) 2%

[1]IMS Health, IMS Nationals Sales Perspectives™ , Sept 2006 to August 2007, Data extracted Jan 2008
[2]Verispan, LLC, Vector One® National (VONA), Data extracted Jan 2008

Drug Use Trends: celecoxib

Celecoxib 8th in terms of prescription volume for selected products in pediatric patients

Trends in prescription volume (pediatric)[2]

- Baseline (Sept 2004 to Aug 2005) to post exclusivity period (Sept 2006 to Aug 2007): 28% decrease
- Pre- (Sept 2005 to Aug 2006) and post-exclusivity period (Sept 2005 to Aug 2006): 3% increase

Prescriber Specialty[2]

General practice (33 to 35%)

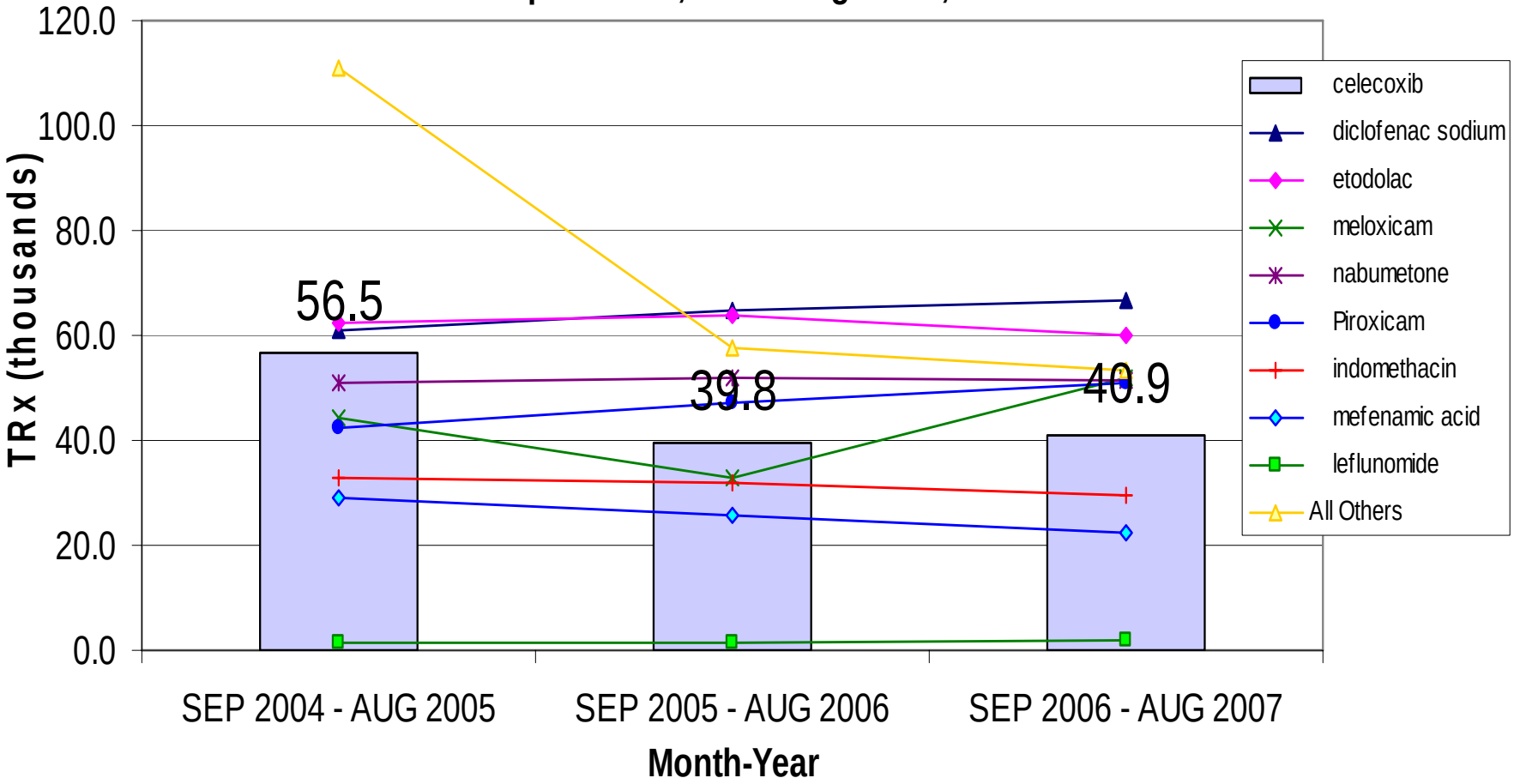
Internal Medicine (25 to 26%)

Pediatrics (<1%)

[2]Verispan, LLC, Vector One® National (VONA), Data extracted Jan 2008

Drug Use Trends: celecoxib

Figure 3: Total number of dispensed prescriptions for selected anti-rheumatic drug market* (minus ibuprofen, naproxen) in the pediatric population (ages 0-18), September 1, 2004 - August 31, 2007



Drug Use Trends: celecoxib

Pediatric Indications for Use[3]

- sprains and strains (33%)
- osteochondropathy (16%)
- related to rheumatoid arthritis/other polyarthropathy (4%)

Duration of Use (pediatric patients)[3]

- Baseline (Sept 2004 to Aug 2005): 8 to 15 days (28%) and >91 days (17%)
- Pre-exclusivity (Sept 2005 to Aug 2006): 16 to 30 days (36%)
- Post-exclusivity (Sept 2006 to Aug 2007): 16 to 30 days (67%)

[3]Verispan LLC, Verispan Physician Drug and Diagnosis Audit, extracted Jan 2008

http://www.fda.gov/cder/pediatric/Summaryreview.htm

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Summaries of Medical and Clinical Pharmacology Reviews
of Pediatric Studies
as of January 15, 2008

Total Number of Drugs with Summaries Posted: 88

Summaries of Medical and Clinical Pharmacology Reviews

Drug	Sponsor	Review Summary	
Carvedilol - Coreg	GlaxoSmithKline	Medical	Clinical Pharmacology
Celecoxib - Celebrex	G.D. Searle	Medical	Clinical Pharmacology
Ciprofloxacin - Ciloxan	Alcon	Medical	None*
Ciprofloxacin - Cipro	Bayer	Medical	Clinical Pharmacology

Pediatric Exclusivity Studies: celecoxib

- Relative bioavailability study: capsule and suspension (adults, n=195)
  - C_{max} 50% higher (capsule vs. suspension)
  - AUC 15% higher (capsule vs. suspension)
- Relative bioavailability study: intact capsule and capsule sprinkled on applesauce (adults)
  - Similar C_{max} and AUC
- Clinical efficacy study of celecoxib suspension (100 mg/5 mL)

Pediatric Exclusivity Study: celecoxib

- Mean clearance lower in children 2 to 5 years (32% lower) and >5 to 11 years (26%) compared with adults
- Mean clearance in adolescents (>11 to <17 years) similar to adults
- 3-fold increase in body weight yielded a 50% increase in clearance
- Additional considerations in dose selection:
  - Exposure-response analysis suggests greater percentage of early responders achievable with higher dose
  - matching exposures to the minimum doses (6 mg/kg) found to be non-inferior to naproxen (efficacy boundary)
  - Achieving exposures less than those found from doses up to 12 mg/kg of the suspension during JRA trial (safety boundary)

Pediatric Exclusivity Studies: Labeling changes

Pharmacokinetics: Special Populations- Pediatrics

- pK findings in 152 JRA patients ≥10kg
- Oral clearance increases less than proportionally with increasing body weight
- Compared with 70 kg adult:
  - 10 kg patient have 40% lower clearance
  - 25 kg patient have 24% lower clearance
- Similar plasma concentrations should be achieved by:
  - 50 mg BID for ≥10 to ≤ 25kg
  - 100 mg BID for >25 kg

Dosage and Administration: JRA 2 years and older

Pediatric Exclusivity Studies: Efficacy celecoxib

- Randomized, double-blind, active control study of celecoxib 6 or 12 mg/kg/day with naproxen 15 mg/kg/day
- Primary outcome: percent patients achieving a JRA definition of improvement 30 (DOI-30)
- Improvements seen in all components of JRA DOI-30
- Established non-inferiority of both doses to naproxen

Labeling Changes: Efficacy of celecoxib

Clinical Studies (JRA)

- 12 week, non-inferiority trial (n= 242)
- Response rates (JRA DOI 30) at week 12
  - Celecoxib 6 mg/kg divided BID: 69%
  - Celecoxib 12 mg/kg divided BID 80%
  - Naproxen 15 mg/kg divided BID: 67%
- Safety and efficacy not studied beyond 6 months
- Cardiovascular toxicity not evaluated

Indications and Usage: relief of signs and symptoms of JRA 2 years and older

Precautions: Pediatric Use:

- Reiterates approval and describes pediatric trial and limitations
- Patients with systemic onset JRA appear to be at risk of abnormal coagulation tests

Pediatric Exclusivity Study: Safety celecoxib

No deaths in either 12 wk PCT (n =242) or OL extension

Data available for 6 months of treatment (n= 202)

Most common AEs: GI, infections and infestations, and nervous system disorder

Serious AEs:

- in low-dose, more frequent than naproxen arm, but no dose-response seen
- did not differ from AE profile of NSAIDs

Pediatric Exclusivity Study: Safety Labeling Changes celecoxib

Adverse events from JRA study

- Most common (>5%): headache, fever, upper abdominal pain, cough, nasopharyngitis, lower abdominal pain, nausea, arthralgia, diarrhea and vomiting
- No observable deleterious effect on growth compared with naproxen
- No exacerbations of uveitis or systemic JRA
- Includes table of AE

Postmarketing Commitments: celecoxib

- Short-term study of gastrointestinal toxicity and hypertension risk (6-week, randomized, open-label trial in 200 patients celecoxib vs. naproxen)
- Enhanced pharmacovigilance:
  - Active surveillance of pediatric networks
  - Prospective observational registry (400 patients)
  - Creation of Independent Pediatric expert panel

Additional Relevant Safety Labeling: celecoxib

Boxed Warning (class):

- Increase risk of serious, potentially fatal cardiovascular thrombotic events (MI, stroke)
- Increased risk of serious gastrointestinal AEs, including bleeding, ulceration and perforation

Contraindication:

- Allergy-type reaction to sulfonamide
- Asthma, urticaria or allergic-reaction after NSAID or aspirin

Additional Relevant Safety Labeling: celecoxib

Warnings:

- Cardiovascular thrombotic events with chronic use
- Hypertension (class)
- Congestive heart failure and edema
- Renal effects (class)- renal papillary necrosis and other renal injury
- Advanced renal disease- not recommended, monitor
- Anaphylactoid reactions (class)
- Skin reactions such as SJS, TENS, exfoliative : related to sulfonamide
- Avoid in late pregnancy (premature closure of ductus)
- Bolded: treatment in FAP not shown to reduce risk of GI cancer, prophylactic colectomy or other FAP-related surgery

Additional Relevant Safety Labeling: celecoxib

Precautions:

- General: Not a substitute for corticosteroids; avoid with non-aspirin NSAID, may diminish ability to detect fever or inflammation
- Hepatic: borderline elevations 15%, serious 1%
- Hematological: anemia
- Systemic JRA- use with caution, including DIC
- Asthma- severe bronchospasm in aspirin-sensitive asthma
- Laboratory tests: Monitor for signs and symptoms GI bleeding, periodic CBC and chemistry profile

Note: warnings and precautions reiterated in information for patients, MedGuide

Additional Relevant Safety Labeling: celecoxib

Pregnancy Category C: increased risk of VSD, bony abnormality (rabbits)

Nursing: excreted in animals, limited data indicates also in humans

Overdosage: up to 2400 mg, no serious toxicity

Symptoms usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain

GI bleeding

Rare: hypertension, acute renal failure, respiratory depression, and coma

Anaphylaxis

Previous OSE Reviews: Celecoxib

- Hepatotoxicty, GI bleeding and death (7/1999)
- Fatal GI bleeding, obstruction, perforation or stenosis (12/2000)
- Thrombotic Vascular events (2/2001, 12/2002, 2/2005)
- Hearing loss (6/2001)
- Aseptic Meningitis (12/2002)
- Myopathy/Rhabdomylosis (6/2002)
- Ischemic colitis (6/2003)
- Metabolic acidosis, nephrolithiasis, bony fractures (6/2006)

Adverse Event Reports since Approval (Dec 1998 to Sept 23, 2007): celecoxib

Raw counts*	All reports (US)	Serious (US)	Death (US)
All ages	28186 (24762)	18781 (15425)	2372 (1791)
Adults (≥ 17)	18173 (15316)	12309 (9509)	1542 (1038)
Pediatrics (0-16)	94 (70)	77 (53)	13 (11)
Unknown Age	9919 (9376)	6395 (5863)	817 (742)

*includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

Fatal Adverse Events since Approval: celecoxib

*Raw counts: 13

Since approval (Dec 1998) to one-year exclusivity period (Aug 2006): 8*

hands on review: 3 pediatric cases

One-year post exclusivity period (Aug 2006 to Sept 2007): 5*

hands on review: 2 pediatric cases

*includes duplicates, events in adults or events unrelated to celecoxib

Fatal Adverse Events (Dec 1998 to August 2006): celecoxib

8 y/o female with endstage renal carcinoma, congestive heart failure and cardiomyopathy (multiple medications including inteferon-alpha, vinblastine, celecoxib)

9 y/o male with medulloblastoma and intracranial hemorrhage (multiple medications including celecoxib, thalidomide)

Adolescent male with completed suicide 6 days after starting celecoxib (concomitant medications: salmeterol, fluticasone and“unknown patch.”)

Labeling: CHF (warnings), intracranial hemorrhage (boxed warning), suicide (adverse events)

Adverse Event Reports during One-Year Post Exclusivity Period (8/23/2006 to 9/23/2007): celecoxib

Raw counts*	All reports (US)	Serious (US)	Death (US)
All ages	6144 (5854)	6127 (5838)	915 (888)
Adults (≥ 17)	3211 (2990)	2910 (2847)	501 (479)
Pediatrics (0-16)	19 (13)	19 (13)	5 (5)
Unknown Age	2914 (2851)	2910 (2847)	409 (404)

*includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

Adverse Events during Pediatric Exclusivity Period

10 unduplicated cases:

- Fatalities (n=2) during pilot study of newly diagnosed Ewing's sarcoma
- nonfatal AEs (n=8)
  - Dyspnea (2)
  - Palpitations (2)
  - Pulmonary embolism (2)
  - Single reports of bullous eruptions, intracranial hemorrhage, pancytopenia, GI bleed, chest pain, blood clots

Fatal Adverse Events during Pediatric Exclusivity Period (n=2)

12 y/o female with newly diagnosed metastatic Ewing's Sarcoma admitted for fever, neutropenia, fluid overload; required aggressive mechanical ventilation and inotrope therapy, ultimately developed GI bleed, sepsis, renal and hepatic failure and died

16 y/o female with newly diagnosed metastatic Ewing's Sarcoma, developed radiation pneumonitis, pancytopenia, pericardial effusion and pulmonary hypertension, s/p pericardiocentesis, recurrent cardiac arrest and died

Possible confounders: chemotherapy, radiation therapy, underlying disease. Note off-label indications

Summary: celecoxib

- Labeling updated with new pediatric indication (JRA), dose, and limitations of study
- AEs incorporated: increased risk of DIC, common AEs (GI, infectious symptoms, arthralgia)
- No new unexpected pediatric AEs were identified for celecoxib from the postmarketing reports reviewed for this report.
- Data from studies focusing on safety assessments during the Postmarket period are still pending and the proposed studies will be presented by the Sponsor today.

A follow up report will be presented to the AC after the Post Marketing Commitment studies have been completed. Does the Advisory Committee concur with this plan?

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