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

Pediatric Advisory Committee Meeting
March 25, 2008

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Office of New Drugs
Food and Drug Administration
Outline

• Background Drug Information
• Drug Use Trends
• Pediatric Exclusivity Studies
• Pediatric Exclusivity Labeling Changes
• Additional Relevant Safety Labeling
• Adverse Events
  – Since approval
  – 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

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>celecoxib</td>
<td>diclofenac</td>
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<tr>
<td>etodolac</td>
<td>fenoprofen</td>
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<tr>
<td>flurbiprofen</td>
<td>ibuprofen</td>
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<td>rofecoxib</td>
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<tr>
<td>sulindac</td>
<td>tolmetin</td>
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<tr>
<td>valdecoxb</td>
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</table>
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%)\(^2\)
- 3\(^{rd}\) 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\(^{TM}\), 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 Specialty²

- General practice (33 to 35%)
- Internal Medicine (25 to 26%)
- Pediatrics (<1%)

²Verispan, 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

<table>
<thead>
<tr>
<th>Month-Year</th>
<th>TRx (thousands)</th>
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<tbody>
<tr>
<td>SEP 2004 - AUG 2005</td>
<td>56.5</td>
</tr>
<tr>
<td>SEP 2005 - AUG 2006</td>
<td>39.8</td>
</tr>
<tr>
<td>SEP 2006 - AUG 2007</td>
<td>40.9</td>
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</table>

* Anti-rheumatic market - selected NSAID's and leuflunomide, an immunomudulatory agent.
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
Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies as of January 15, 2008

Total Number of Drugs with Summaries Posted: 88

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor</th>
<th>Review Summary</th>
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<tbody>
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<td>Carvedilol - Coreg</td>
<td>GlaxoSmithKline</td>
<td>Medical</td>
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<td></td>
<td></td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Celecoxib - Celebrex</td>
<td>G.D. Searle</td>
<td>Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical Pharmacology</td>
</tr>
<tr>
<td>Ciprofloxacin - Ciloxan</td>
<td>Alcon</td>
<td>Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Ciprofloxacin - Cipro</td>
<td>Bayer</td>
<td>Medical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical Pharmacology</td>
</tr>
</tbody>
</table>
Pediatric Exclusivity Studies: celecoxib

- Relative bioavailability study: capsule and suspension (adults, n=195)
  - $C_{\text{max}}$ 50% higher (capsule vs. suspension)
  - AUC 15% higher (capsule vs. suspension)

- Relative bioavailability study: intact capsule and capsule sprinkled on applesauce (adults)
  - Similar $C_{\text{max}}$ 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 to ≥12 to ≤25kg
  – 100 mg BID >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

- Hepatotoxicity, GI bleeding and death (7/1999)
- Fatal GI bleeding, obstruction, perforation or stenosis (12/2000)
- Hearing loss (6/2001)
- Aseptic Meningitis (12/2002)
- Myopathy/Rhabdomyolysis (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

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

*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 interferon-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)

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<tbody>
<tr>
<td>All ages</td>
<td>6144 (5854)</td>
<td>6127 (5838)</td>
<td>915 (888)</td>
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<tr>
<td>Adults (≥ 17)</td>
<td>3211 (2990)</td>
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<td>Pediatrics (0-16)</td>
<td>19 (13)</td>
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<td>5 (5)</td>
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<tr>
<td>Unknown Age</td>
<td>2914 (2851)</td>
<td>2910 (2847)</td>
<td>409 (404)</td>
</tr>
</tbody>
</table>

*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, 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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