

# Celecoxib for JRA: Assessing Risks & Benefits

Jeffrey Siegel, M.D.  
FDA/CDER/ODE2/DAARP  
Arthritis Advisory Committee  
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# Approval of Celebrex for JRA

- Celebrex approved for use in children with JRA in December 2006
- Efficacy based on randomized trial assessing non-inferiority to naproxyn
- Major issue at advisory committee was potential safety concerns based on GI and cardiovascular signals observed in adults



Safety

# Exposure in Study 195

- 242 children enrolled in randomized portion of study receiving celecoxib 6 or 12mg/kg/d or naproxen 15 mg/kg/d for 3 months
- 202 enrolled in subsequent 3-month open-label phase receiving celecoxib 12 mg/kg/d for 3 months

# Safety in Study 195

- At 6 mg/kg/d dose most common adverse events were GI, infections and infestations, and nervous system disorders
- Overall, common adverse events similar in type and frequency to those seen with naproxen

# Serious Adverse Events in Study 195

- In Study 195, SAEs seen more frequently with celecoxib include GI disorders (upper abdominal pain), pyrexia and musculoskeletal, connective tissue and bone disorders
- Overall serious adverse events and severe adverse events seen in children receiving celecoxib represented events seen in this patient population and events known to be associated with other NSAIDs

# Post-Marketing Reports at Time of Initial Approval for Children

- Review of post-marketing database gave no new safety signals reported for children receiving celecoxib off-label

# Risks Associated with celecoxib, NSAID Class

- Known risks
  - Adverse events associated with NSAID class include cardiovascular toxicity, GI toxicity, fluid retention, edema, renal toxicity, hepatic enzyme elevation and bronchospasm in patients with aspirin-sensitive asthma
  - Serious skin reactions have been seen with celecoxib, including Stevens Johnson syndrome
- Pediatric experience in Study 195
  - One case of liver enzyme elevations and one case of severe asthma seen in Study 195
  - Overall these adverse events not seen at a rate clearly higher than naproxen

# Risk of GI Bleeding

- COX-2 selective class of NSAIDs originally developed to reduce life-threatening GI bleeds
- While celecoxib shown to reduce GI ulcers endoscopically incidence of clinical GI bleeds not shown to be reduced
- In children, GI bleeding an uncommon adverse event with NSAIDs
- No GI bleeds seen in pediatric Study 195

# Cardiovascular Risks

- Data indicate an increased risk of cardiovascular thromboembolic events, in particular myocardial infarction, in adults treated long-term with COX-2 selective NSAIDs, including celecoxib
- Risk of cardiovascular events with non-selective NSAIDs not clearly less than COX-2 selective NSAIDs

# Cardiovascular Risks in Children

- Given that it is primarily adults who are at risk for cardiovascular thromboembolic events such events were not expected in the celecoxib trial and none were observed
- However, long-term risk for children treated with celecoxib is unknown
- Cardiovascular risk a potential concern in children with JRA in view of:
  - Risk of accelerated atherosclerosis associated with inflammatory rheumatic disease in adults (e.g., SLE, RA)
  - Recognition that increasing numbers of children have risk factors for cardiovascular disease, e.g., obesity, hypertension, hyperlipidemia, type II DM.

# Safety: Summary

- Overall, risk of adverse events was similar in children receiving celecoxib as those receiving naproxen
- Overall safety profile in study 195 similar to that known for NSAID class

# Considerations in Assessing Risk/Benefit Relationship

- In assessing the risk/benefit relationship for celecoxib in JRA it is important to consider:
  - the observed safety profile of celecoxib in JRA
  - the known risks of NSAIDs in this patient population
  - potential long-term risks based on knowledge gained from studies in adults

# Post-Marketing Commitments

- Blood pressure/safety study in children with JRA
  - Includes assessment of GI events
- Prospective observational registry
- Pharmacovigilance activities