

FDA Pediatric Advisory Committee

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**Celebrex Juvenile Rheumatoid Arthritis:
Review of Post-Approval Commitments**

Pfizer Delegation

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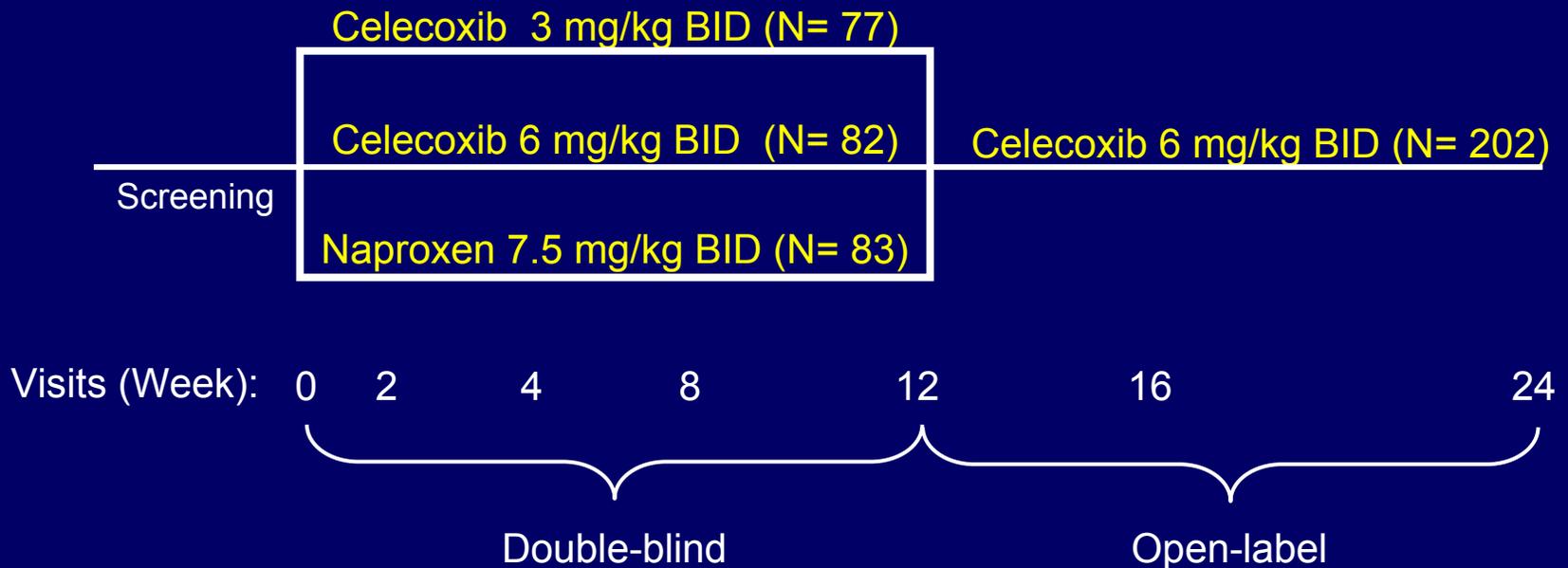
Regulatory Affairs

Agenda

- Review JRA approval and labeling
- Describe Post-Approval commitments:
 - Results for commitments in progress
 - Finalizing details on remaining commitments

Basis of JRA Approval

- Pivotal Study 195 in JRA Patients (2-16 years)
 - Efficacy: %Responders on the Pediatric ACR30



Celebrex JRA Indication

CELEBREX is indicated:

- 1) For relief of the signs and symptoms of osteoarthritis.
- 2) For relief of the signs and symptoms of rheumatoid arthritis in adults.
- 3) For relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older (see CLINICAL STUDIES and ADVERSE REACTIONS - *Adverse Events from JRA Study*).
- 4) For the relief of signs and symptoms of ankylosing spondylitis.
- 5) For the management of acute pain in adults (see CLINICAL STUDIES).
- 6) For the treatment of primary dysmenorrhea.
- 7) To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery) . .

Juvenile Rheumatoid Arthritis:

Pediatric Patients (2 years and older)	Dose
≥10 kg to ≤25 kg	50 mg capsule twice daily
>25 kg	100 mg capsule twice daily

Method of Administration

For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2-8° C/ 35-45° F).

- 50mg capsule was introduced to the US market in January 2007

Post-Approval Commitments for JRA

- In addition to the ongoing Pharmacovigilance program, and in accord with FDA conditions for approval, Pfizer has committed to the following programs specific to the JRA indication:
 1. Independent Pediatric Expert Panel
 2. Active Surveillance
 3. Prospective Observational Registry
 4. Clinical Blood Pressure/Safety Study

Independent Pediatric Expert Panel

- **Objective:** Ongoing evaluation of cumulative safety data, with attention to Celebrex safety in children with JRA
 - Pharmacovigilance, Active Surveillance, JRA Registry, JRA-BP Study
- **Multidisciplinary panel:**
 - 5 panelists total: General pediatric, and pediatric specialists in rheumatology, nephrology, gastroenterology, hematology
- **Activities and conclusions to date:**
 - June 22, 2007: review of data through May 2007
 - December 3, 2007: review of data through October 2007
 - Conclusion at both reviews: no change in risk profile
 - Next meeting is scheduled for June 2008

Active Surveillance Program

- **Objective and Method:**
 - Survey of pediatric rheumatologists to identify Serious Adverse Events that occur in JRA patients receiving NSAIDs, including Celebrex, during normal practice
 - Monthly surveys for new Serious Adverse Events
 - Surveys twice annually for numbers of JRA patients treated
- **Conducted by:**
 - Childhood Arthritis Rheumatology Research Alliance (CARRA), a non-profit consortium of North American pediatric rheumatologists
- **Activities to date:**
 - 149 pediatric rheumatologists have been invited (total in US is 237):
 - 105 participants at 39 sites; additional recruitment is ongoing
 - First survey cycle requests data from June 30 to December 31, 2007:
 - Soon to begin, pending remaining IRB approvals

Prospective Observational Registry

- **Objective:**
 - To gather increased experience and monitor long-term safety in actual clinical practice for JRA patients treated with Celebrex
- **Protocol:**
 - Non-randomized, non-interventional; US pediatric rheumatology centers
 - 400 JRA patients
 - 200 celecoxib users and 200 users of other NSAIDs
 - Duration of follow-up: minimum 2 years
 - Four clinic visits in first year, twice yearly thereafter
 - All serious adverse events collected
 - Particular attention to CV, GI, hypertension
- **Timeline:**
 - Initial protocol submission to FDA: May 22, 2007
 - FDA comments on draft protocol: December 7, 2007
 - Final agreement with FDA on protocol details: March 12, 2008
 - Expected study start: Beginning of 2009, with completion 5 years later

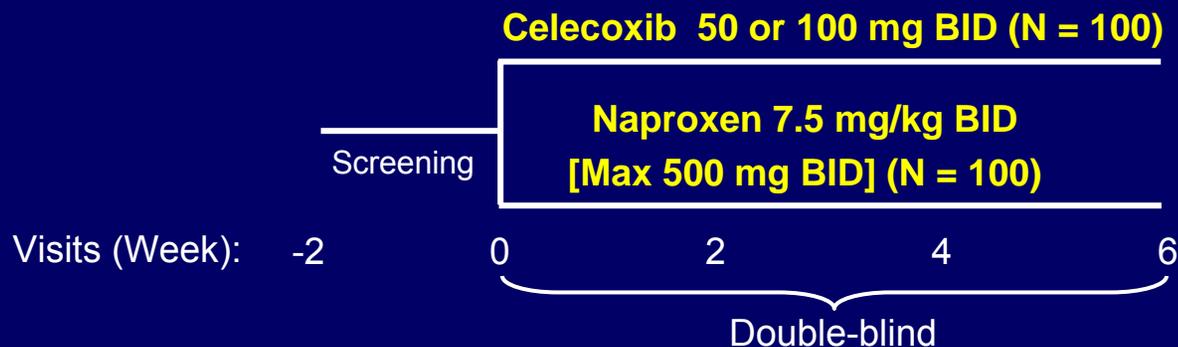
Blood Pressure/Safety Study

- **Objective:**

- To evaluate the effect of treatment with celecoxib on systolic blood pressure compared to treatment with naproxen in JRA patients

- **Protocol:**

- JRA patients ≥ 2 and < 18 years of age
- Primary Evaluation: Change from baseline in Systolic Blood Pressure
 - Traditional cuff measure of blood pressure
 - Substudy (2 sites) with ABPM measure of blood pressure



- **Timeline:**

- Initial protocol submission to FDA: April 30, 2007
- FDA comments on draft protocol: November 19, 2007
- Agreement on main protocol design with FDA: March 12, 2008
- Expected study start: Mid-year 2009, with completion 2-3 years later

Conclusions

- **To support JRA approval, Pfizer agreed to implement a robust post-approval safety program**
- **Pfizer pharmacovigilance to date reveals no new safety concerns for children with JRA**
- **Two post-approval commitments have been implemented:**
 - Independent Pediatric Expert Panel
 - Active Surveillance Program
- **Two post-approval commitments in progress, with patient enrollment anticipated to begin in 2009:**
 - Prospective Observational Registry
 - Blood Pressure/Safety Study