# ERRATA FOR BRIEFING DOCUMENT

# ADVISORY COMMITTEE MEETING

# CELECOXIB FOR JUVENILE RHEUMATOID ARTHRITIS (NDA 20-998/S-021)

November 29, 2006

**AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION**

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## 1. BACKGROUND

On 30 October 2006, Pfizer submitted to the Food and Drug Administration (FDA) a briefing document for the scheduled meeting of the Arthritis Advisory Committee (to be held on 29 November 2006) to discuss the New Drug Application (NDA) 20-998/S021 for CELEBREX® (celecoxib capsules) for the proposed indication of the relief of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients 2 years and older. Subsequently, Pfizer has identified some minor inconsistencies in the document, in which certain information was misquoted or presented unclearly. These errata do not involve the clinical data on celecoxib that are the main focus of the document, nor are they consequential to the document's overall conclusions. Nevertheless, corrections are presented herein in an effort to improve the clarity and effectiveness of the specific sections of the document that are affected.

## 2. ERRATA AND CORRECTIONS

Errata are presented below for affected text in the briefing document, identified by section number in parallel with the original briefing document. They are further identified by page number and paragraph or partial paragraph in which they appear. The revised or added text is designated by bold italics.



### Section 3 (Characteristics, Epidemiology, and Treatment of JRA)

### Partial Paragraph Concluding Page 9

The partial paragraph concluding Page 9 should be revised as follows to correct a factual error:

> Much of JRA pain is mild to moderate in intensity; however, ***slightly over 10%*** of children report pain of "high intensity."[14] Higher levels of pain in children with chronic arthritis have been…

### Section 4.1 (Gastrointestinal Effects)

### Last Paragraph, Page 11

The last paragraph on Page 11 should be revised as follows for clarification and for correction of factual errors:

> Many of these clinical trials were of short duration, with the longest exposure being 1 year, thus providing limited information on long-term use. A number of trials and observational studies have been conducted to determine the prevalence of GI complications of NSAID therapies over time and in a real-world clinical setting. Estimates of NSAID-associated gastropathy in patients with JRA range from 0.7% to 75%, depending on differences in study design.[26,39,40,41,42,43]
>
> - ***One of the most comprehensive studies retrospectively assessed 570 children seen in a pediatric rheumatology clinic over a 3-year period, 303 of whom (53%)***

***had JRA (the remainder had seronegative enthesopathy/arthropathy, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease, or overlap syndromes); of these 570 children, a total of 344 were taking NSAIDs.[42] The incidence of abdominal pain in children taking NSAIDs was 27.9% over the 3-year observation period, compared to 14.6% in the 226 children not taking NSAIDs. There were 47 children treated with NSAIDs and 14 children not treated with NSAIDs who underwent GI evaluation due to their abdominal pain, with the result that gastroduodenal injury (ulcer or gastritis/duodenitis) was observed in 16 NSAID users (34% of those with evaluations and 4.7% of all NSAID users; mean duration of exposure to NSAIDs in patients with gastroduodenal injury = 22.1 months) compared to 1 non-NSAID user (7% of those with evaluations and 0.4% of all NSAID non-users). The relative risk for gastroduodenal injury was 4.8 (P = 0.09) in pediatric rheumatology patients taking NSAIDs compared to those not taking NSAIDs.***

- Recently, a tool (the Gastrointestinal Symptom Scale for Kids [GISSK]) has been developed and validated, which assesses dyspepsia symptoms in children with JRA.[44] A total of ***81% of the 77 patients in the validation study were taking NSAIDs, including 10% who were taking COX-2 selective inhibitors***. Despite the fact that ***32% of these 77 patients*** were taking concomitant GI-protective medications (primarily proton-pump inhibitors or histamine-2 receptor antagonists [$H_2$RA]), 58% reported GI symptoms, and high scores on this GI symptom scale correlated with lower quality-of-life assessment scores, regardless of JRA disease activity. This is complicated by the fact that 84% of patients took methotrexate, 55% took anti-TNF-$\alpha$ biologics, and ***13% took oral corticosteroids***. Methotrexate and corticosteroids may especially also cause GI symptoms. Nevertheless, dyspepsia is a common symptom in children with JRA, and concomitant NSAID therapy is a likely contributor.



**Section 4.2 (Cardiovascular and Renal Effects)**

**Third Paragraph, Page 12**

The third paragraph on Page 12 should be revised as follows for clarification:

A review of the published literature suggests that renal-related adverse events are rarely reported during clinical trials. In one recent trial (rofecoxib versus naproxen, 12-week double-blind phase with 52-week open-label phase)[24] in 310 JRA patients, 1 patient receiving naproxen experienced an elevation of creatinine and ***2 patients experienced edema (1 patient each taking naproxen or rofecoxib)*** during the double-blind phase of the study. During the open-label phase of the study, 3 patients receiving rofecoxib developed edema. In a trial of flurbiprofen, 9% of patients developed hematuria.[34] No other trials report overt renal adverse events. Sporadic reports of renal events in children with JRA receiving NSAIDs exist in the literature. The most common of such events appears to be acute, idiosyncratic renal failure, which generally occurs early in therapy and is reversible on cessation of the offending therapy.[9] This is also known to occur in otherwise healthy children who take brief courses of NSAID treatment for other

indications, such as fever associated with infections. Other reported renal complications include renal papillary necrosis, nephrotic syndrome, and interstitial nephritis. The precise incidence of such events cannot be determined, but they seem rare. This is corroborated by a 4-year prospective study of 226 JRA patients taking NSAIDs for a median of 1.3 years of previous use (range 0.5-8 years).[46] ***Although 22 children (10%) had abnormal findings on one or more urinalysis, only 1 of these abnormalities was clearly attributed to therapy with NSAIDs.*** No patient developed hypertension or elevated serum creatinine, and no other renal adverse events were reported.

**Section 9.2 (Postmarketing Data from Sponsor's Safety Database)**

**First Paragraph, Page 48**

The first paragraph on Page 48 should be revised as follows for completeness and clarification:

***The 203 reported pediatric cases included 21 expedited cases. Review of these*** identified 7 cases of unlabeled, serious events for which no alternate etiologies or contributory factors were reported: 1) upper intestinal occlusion (in an infant breast-fed while the mother was taking celecoxib; patient recovered); 2) suicide; 3) seizure or syncopal episode (patient recovered); 4) low calcium reading (after ingesting 25 to 30 celecoxib capsules; no outcome information provided); 5) pulmonary infiltrates (no outcome information provided); 6) breathlessness and trembling (events abated at an unknown time); 7) dehydration, fever, lethargy, loss of appetite, herpes zoster, and a "mild heart murmur" (outcome unknown at the time of the report).

**Fourth Paragraph, Page 48**

The fourth paragraph on Page 48 should be revised as follows for completeness and clarification:

***Six fatal cases*** have been reported: 1 report contained insufficient information for a proper assessment, ***1 case was a completed suicide***, and alternate causes of death were reported in the other 4 cases (1 case of aneurysm rupture and 3 cases of cancer progression).

**Section 14 (References)**

**Reference 29, Page 61**

A typographical error in the citation for Reference 29 should be corrected as follows:

Giannini EH, Brewer EJ, Miller ML, Gibbas D, Passo MH, Hoyeraal HM, Bernstein B, Person DA, Fink CW, Sawyer LA, Scheinbaum ML. Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. J Pediatr ***1990***:117:645-652.