



of this information. In total, the relevant risk information is summarized below, with the proposed new information highlighted in italics:

- **Valdecoxib contains a sulfonamide moiety; patients with a known history of a sulfonamide allergy may be at a greater risk of skin reactions. *Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.***
- **Serious skin reactions, including fatalities, have been reported through postmarketing surveillance in patients receiving Bextra® (valdecoxib).**
- ***Patients appear to be at highest risk for these events early in the course of therapy; the onset of the event occurring in the majority of cases within the first 2 weeks of treatment.***
- **Bextra should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.**
- ***Serious skin reactions have been reported with other COX-2 inhibitors during postmarketing experience. The reported rate of these serious skin events appears to be greater for Bextra as compared to other COX-2 agents.***

This additional information should now be considered by physicians when evaluating Bextra for their patients. Pfizer will continue to work with the FDA to further evaluate this risk.

#### Cardiovascular Safety

In addition, we want to summarize for you available clinical information concerning the cardiovascular safety of Bextra in view of the cardiovascular concerns raised in connection with the Vioxx withdrawal. Available clinical trial data in patients treated with Bextra for OA and RA do not suggest an increased risk of cardiovascular thromboembolic events.

##### 1. Cardiovascular Events in Osteoarthritis (OA) and Rheumatoid Arthritis (RA)

A pooled analysis of valdecoxib clinical trials in OA and RA was recently published.<sup>i</sup> The analysis included 10 randomized OA and RA trials. The duration of treatment were 6 weeks (2 studies), 12 weeks (5 studies), 26 weeks (2 studies) and 52 weeks (1 study); including 7,934 subjects treated with valdecoxib (10–80 mg daily, n=4,531), non-specific NSAID (diclofenac 75 mg BID, ibuprofen 800 mg TID, or naproxen 500 mg BID, n=2,261) or placebo (n=1,142). Serious CV events were prospectively defined as acute myocardial infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, or peripheral arterial thrombosis. *There were no significant differences in the exposure adjusted event rates for serious CV events between valdecoxib, placebo and NSAIDs. Similarly for the individual events of MI and stroke, and for all measures in aspirin-users, non-aspirin users, or all subjects, no significant differences were observed.* Two additional analyses of this database have also been conducted and reached similar conclusions.<sup>ii</sup>

##### 2. Cardiovascular Safety in the Surgical Setting (Investigational Use)

Three separate clinical studies (two coronary artery bypass graft (CABG) surgery studies and a single general surgery study) evaluated the safety, in particular the cardiovascular safety, of the investigational agent parecoxib (the parenteral pro-drug of valdecoxib) followed by valdecoxib and of valdecoxib alone. The general surgery study, which included primary cancer resection, abdominal, gynecological and non-cardiac thoracic surgery, evaluated the safety of parecoxib/valdecoxib 40 mg initially followed by 20 mg BID given for up to 10 days in 1050 patients (525 on parecoxib/valdecoxib and 525 on placebo/placebo). The first CABG study, which was published in 2003 in the Journal of Thoracic and Cardiovascular Surgery,<sup>iii</sup> evaluated the safety of parecoxib/valdecoxib 40 mg BID given for up to 14 days in 462 patients (311 on parecoxib/valdecoxib and 151 on placebo). The second CABG study, completed this year, evaluated the safety of parecoxib/valdecoxib 40 mg initially followed by 20 mg BID or valdecoxib alone 20 mg BID given for up to 10 days in 1671 patients (544 receiving parecoxib/valdecoxib, 544 placebo/valdecoxib, and 548 placebo/placebo).

In the general surgery study, the incidence of cardiovascular thromboembolic events was similar in both treatment arms of the study, parecoxib/valdecoxib and placebo/placebo.

Results of the two CABG studies were consistent. *In these studies a higher rate of serious cardiovascular thromboembolic events (e.g., myocardial infarction, cerebrovascular accident) was observed in the parecoxib/valdecoxib and valdecoxib alone treatment arms compared to the group of patients receiving placebo.*

In conclusion, increased cardiovascular thromboembolic events have been seen with high-dose valdecoxib in the high-risk cardiovascular surgery setting of CABG but not in the general surgery setting. However, the post-surgical use of Bextra® (valdecoxib) in these settings is not approved in the United States. Available clinical trial data in patients treated with Bextra for OA and RA do not suggest an increased risk of cardiovascular thromboembolic events.

#### Summary

We believe physicians should consider all the Bextra information provided in this letter when making treatment decisions. Available clinical trial data in patients treated with Bextra for OA and RA do not suggest an increased risk of cardiovascular thromboembolic events.

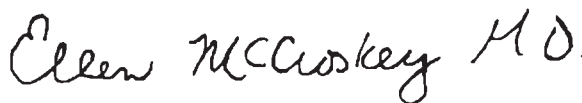
Pfizer is committed to further understanding the efficacy and safety profile of Bextra. We are planning further studies to assess the long-term CV safety of Bextra in patients who require chronic treatment for arthritis with a COX-2 specific inhibitor.

As always, Pfizer continues to monitor and assess Bextra's safety. We actively collaborate with the FDA to take appropriate steps to update product labeling and inform physicians and patients when necessary.

Sincerely,



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Pfizer Inc.



Ellen McCroskey, MD  
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A copy of the current Package Insert for Celebrex® (celecoxib) capsules is available on [www.Celebrex.com](http://www.Celebrex.com).

A copy of the current Package Insert for Bextra tablets is available on [www.Bextra.com](http://www.Bextra.com). Any revisions to the labeling will be included on this site once finalized with the FDA. Further information regarding Bextra can be obtained at this site or by contacting Pfizer Medical Information at 1-800-438-1985.

<sup>i</sup> White WB, Strand V, Roberts R, Whelton A. "Effects of the cyclooxygenase-2 specific inhibitor valdecoxib versus nonsteroidal anti-inflammatory agents and placebo on cardiovascular thrombotic events in patients with arthritis." *Am J Ther.* 2004 Jul-Aug;11(4):244-50.

<sup>ii</sup> Whelton A, Kent J, Recker D, et al. No difference in thrombotic events in rheumatoid arthritis patients: valdecoxib vs naproxen and placebo. *Arthritis Rheumatism.* 2002; 46(suppl 9): S153 and Edwards J, McQuay H, Moore R. Efficacy and safety of valdecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomized controlled trials. *Pain*, Volume 111, Issue 3, October 2004, Pages 286-296.

<sup>iii</sup> Ott E, Nussmeier N, Duke P, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg.* 2003 Jun;125(6):1481-92.