

April 7, 2005
INFORMATION FOR VA CLINICIANS:
FDA Requests Voluntarily Withdrawal of Valdecoxib (Bextra®) from US Markets
Guidance For Switching Current Users in the VA
Pharmacy Benefits Management-Strategic Healthcare Group (PBM) and the Medical Advisory
Panel (MAP)

April 7, 2005, the Food and Drug Administration (FDA) requested that Pfizer voluntarily remove valdecoxib from U. S. markets. Pfizer has agreed to stop the sales and marketing of their product “pending further discussions” with the FDA. The FDA requested withdrawal of valdecoxib after careful review of the available data concluding that the risks of valdecoxib may outweigh the benefits. The FDA cited several reasons to support their request for withdrawal including a lack of adequate long-term cardiovascular safety data for valdecoxib; an increased risk of cardiovascular events observed during short-term use in patients after coronary artery bypass surgery (CABG); serious and unpredictable life-threatening skin reactions; and finally a lack of evidence to support an advantage of valdecoxib compared with other nonselective NSAIDs.¹

In addition to valdecoxib, recommendations were also made concerning celecoxib. At this time, the FDA has concluded that Pfizer may continue the marketing of celecoxib with certain revisions to the product labeling. These revisions include a boxed warning of risk for cardiovascular and gastrointestinal (GI) events. In addition, all nonselective NSAIDs available by prescription will receive this warning in their labeling. Refer to the FDA website for additional details regarding these important changes.¹

In October 2004, the PBM-MAP distributed an electronic bulletin recommending that valdecoxib be avoided until more conclusive data were obtained with regard to risk of cardiovascular events. In January 2005, the PBM-MAP created additional guidance regarding the COX-2 inhibitors and nonselective NSAIDs. In that document, recommendations were made to switch all valdecoxib users to alternative treatments and that no new patients receive valdecoxib.² In response to the patient safety concerns raised by the FDA, the VA PBM has stopped availability of valdecoxib. Please see recommendations for switching current users of valdecoxib to alternative treatments. (For more information on COX-2 guidance, refer to the PBM website).

As of April 11th, 2005, all VA facilities must discontinue prescribing and dispensing of valdecoxib.

Current users of valdecoxib who are considered to be at high risk for nonsteroidal anti-inflammatory drug (NSAID) induced upper gastrointestinal (UGI) events should be managed by alternative modalities if possible. However, if alternative modalities are not a reasonable option and anti-inflammatory analgesia is required, patients should be switched to salsalate or etodolac. If a patient has previously experienced either a lack of effectiveness or adverse events with salsalate or etodolac, consideration can be given to switching to an alternative nonselective NSAID (e.g. naproxen, diclofenac) with a PPI or lastly, meloxicam (nonformulary nationally).

If the patient is currently receiving aspirin for cardiovascular or cerebrovascular protection, consider a nonselective NSAID (e.g. naproxen, diclofenac) plus a proton-pump inhibitor (PPI). If they are already receiving a PPI, switch to a nonselective NSAID in combination with the PPI.

Although much of the available data do not support a cardiovascular safety concern with celecoxib, data from a recent long-term prospective trial supports a cardiovascular safety risk with celecoxib³ similar to that reported with rofecoxib in the APPROVe trial.⁴ Therefore, celecoxib should be initiated ONLY in those patients with no significant risk for cardiovascular or cerebrovascular disease and at high risk for UGI complications with NSAIDs and an inadequate response or adverse effects to etodolac and/or salsalate. The decision should involve a discussion between the clinician and the patient.

Patients with prior history of NSAID related GI bleeding: These patients are at high risk for repeated adverse events regardless of whether they are given a COX-2 inhibitor or a NSAID plus PPI. Therefore, it

is recommended that these patients be managed with alternative modalities if at all possible. However, if a patient with a history of prior GI bleeding and is considered to require NSAID therapy, consider etodolac, salsalate or lastly, meloxicam (nonformulary nationally) combined with a PPI. In those patients without a history of or sufficient risk for cardiovascular or cerebrovascular disease and a lack of response or intolerance to etodolac, salsalate or meloxicam combined with a PPI, celecoxib with a PPI can be considered. To restate, although there is no evidence that combining a COX-2 selective agent with a PPI provides additional GI safety over the combination of a nonselective NSAID plus a PPI, prudence is required in treating these patients with NSAID or COX- inhibitors. If the decision has been made to initiate celecoxib with the PPI, consideration of the patient's cardiovascular and cerebrovascular history and risk are recommended.

*In light of the controversy surrounding the cardiovascular risk of the COX-2 inhibitor class, the question arises of whether there may be some risk with the preferentially selective COX-2 NSAIDs. Although NSAIDs have enjoyed widespread use for many years, there have been no prospective trials evaluating the cardiovascular safety or the cardiovascular benefit of preferentially COX-2 selective NSAIDs or nonselective NSAIDs. The PBM Outcomes Research Department has examined the cardiovascular events in users of NSAIDs or COX-2s. To date, this analysis has confirmed a potential risk with rofecoxib and celecoxib but has not demonstrated an excess cardiovascular risk with etodolac or naproxen.

To assist you in communicating with your patients, the PBM will be issuing a template letter that individual medical centers can use to provide information to patients requiring the switch from valdecoxib or who otherwise have questions about the suspension of sales.

1. <http://www.fda.gov/cder/drug/advisory/COX2.htm>
2. http://vaww.pbm.med.va.gov/clinicians/COX-2_guidance.pdf
3. Solomon SD, McMurray JMV, Pfeffer MA, et al. Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention. NEJM 2005;352:downloaded Feb 15, 2005.
4. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial. NEJM 2005;352: downloaded February 15, 2005.