FDA Alert for Practitioners
Celebrex (celecoxib)

FDA ALERT 12/17/04: Based on emerging information, including preliminary reports from one of several long term National Institutes of Health (NIH) prevention studies, the risk of cardiovascular events (composite endpoint including MI, CVA and death) may be increased in patients receiving Celebrex. FDA will be analyzing all available information from these studies to determine whether additional regulatory action is needed.

Prescribing Considerations

Physicians with patients taking celecoxib, or who are considering prescribing the drug, should consider the following:

- Information about the CV risk of celecoxib is evolving and patients should be informed accordingly.
- Alternatives to celecoxib should be considered, based on individual patient needs and risk factors.
- If alternatives to celecoxib are not acceptable, the lowest effective dose of the drug should be used.
- The currently approved dosing regimens are:
  For osteoarthritis: 200 mg once a day or 100 mg twice per day
  For rheumatoid arthritis: 100 to 200 mg twice per day
  For pain: 400 mg to start, then 200 mg twice a day, if needed
  For colon polyps: 400 mg twice a day with food
- FDA is aware of no long term safety studies of older, COX-2 nonselective inhibitor NSAIDS that address CV risk.

Data Summary

In light of the recent information about cardiovascular (CV) risks associated with COX-2 selective inhibitors, the NIH, in the past week, evaluated three large prevention studies to assess CV risks associated with celecoxib use in several long term prevention studies.

Based on this evaluation, the National Cancer Institute (NCI) today stopped drug administration in a three year celecoxib (Celebrex) study [*Adenoma Prevention with Celecoxib (APC)*] because an interim analysis by the study's Data Monitoring Committee showed a statistically significant increase in the risk of CV events (composite endpoint of cardiovacular death, acute myocardial infarction and stroke) in patients randomized to celecoxib. The study, a three-year evaluation of celecoxib compared to placebo for reducing the risk of colon polyps in approximately 2000 patients (average duration of treatment 33 months), was expected to be complete in the spring of 2005. The interim analysis revealed:

- placebo - 6 CV events

- celecoxib 200 mg bid - 15 CV events (2.5 fold increase over placebo)
- celecoxib 400 mg bid - 20 CV events (3.4 fold increase over placebo)

Two other studies of celecoxib (*Prevention of Spontaneous Adenomatous Polyps Trials* and *Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)*), similar in size and duration to *APC*, have been evaluated by data monitoring committees and are continuing because increased risk of CV events was not observed.

Prior to today's announcement, the only available long term information about celecoxib was from the *Celecoxib Long-Term Arthritis Safety Study (CLASS)*, in which about 8000 patients were randomized in a comparison of celecoxib 400 mg bid to ibuprofen or diclofenac for the treatment of osteoarthritis and rheumatoid arthritis. Patients were followed for approximately one year, and the study did not reveal a difference in cardiovascular risk.

The findings from the *APC* study are similar to recent results from a study of rofecoxib (Vioxx), another COX-2 selective inhibitor. Vioxx was removed from the market voluntarily by Merck Laboratories in September, 2004, upon learning of the CV findings. Another drug in this class, valdecoxib (Bextra) has recently been shown to have an increased risk of CV events in the setting of pain management immediately following coronary artery bypass grafting (CABG).

FDA will continue to evaluate all available data regarding CV and other risks of celecoxib in order to determine whether additional regulatory action is needed. This information page will be updated accordingly.

To report any unexpected adverse or serious events associated with the use of Celebrex, please contact the FDA MedWatch program at 1-800-FDA-1088 or http://www.fda.gov/medwatch/report/hcp.htm

We encourage you to provide a copy of FDA's Patient Information Sheet [link] to your patient.

Approved Product Labeling

http://www.fda.gov/cder/foi/label/2004/20998slr016_celebrex_lbl.pdf