



Minnesota Department of **Human Services**

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1. **Consideration of PA criteria for celecoxib (Celebrex®), valdecoxib (Bextra®)**
2. **Consideration of placing meloxicam (Mobic®) under PA restrictions.**

**Current Status**

Celecoxib and valdecoxib are currently under prior authorization coverage restrictions. See Addendum A for current PA algorithm.

There are currently no coverage restrictions for meloxicam.

**Summary Points**

1. Re-analysis of data from the CLASS trial data indicate that
  - The gastro-protective effect of celecoxib is questionable
  - Cardiovascular safety or risk with celecoxib is unclear
2. Emerging data on valdecoxib question its cardiovascular safety. These data are not yet published. However, it appears prudent to protect Medicaid recipients until the FDA reviews the cardiovascular safety of these drugs in early 2005.
3. Mobic shares increased significantly after Vioxx was withdrawn from the market. This drug represents an expensive NSAID alternative where less expensive drugs are effective and readily available.

**Staff Recommendation**

The Department recommends the following PA criteria for celecoxib, valdecoxib, and meloxicam:

- Greater than 65 years of age will have to meet all of the PA criteria;
- Must not have hypertension, a previous MI, a risk factor for stroke, or risk factors for other CV complications
- Must not be taking a proton pump inhibitor, aspirin, or corticosteroid
- Must not have a documented allergic reaction to sulfonamides
- Must fail on at least 3 different generic NSAIDs. One of these trials must be diclofenac.

Additionally

- not approved for short-term use;
- will not be approved solely on the basis of a history of GI complications

It is further recommended that the department develop a one page provider education sheet that will be faxed from the medical review agent at the time a claim is denied when fax numbers are available.

**Table 1. Indications and dosing<sup>1-3</sup>**

Indication	Dosage
<b>Celebrex</b>	
Relief of the signs and symptoms of osteoarthritis	200 mg/ day as a QD or BID dose
Relief of the signs and symptoms of rheumatoid arthritis	100 mg to 200 mg BID
Management of acute pain in adults	400 mg initially followed by 200 mg prn the first day and 200 mg BID on subsequent days
Primary dysmenorrhea	400 mg initially followed by 200 mg prn the first day and 200 mg BID on subsequent days
Familial adenomatous polyposis (FAP)	400 mg BID
<b>Bextra</b>	
Osteoarthritis and Adult Rheumatoid Arthritis	10 mg once daily.
Primary dysmenorrhea	20 mg twice daily, as needed.
<b>Mobic</b>	
Relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis	7.5 to 15 mg once daily

**Summary Points**

1. No trial has ever definitively shown that a COX-2 NSAID is superior in efficacy compared to a traditional NSAID.
2. NSAIDs are similar with respect to therapeutic efficacy; however, responsiveness to a particular agent varies with individual patients.<sup>4</sup> Lack of response to one NSAID, does not preclude response to another NSAID.
3. There is no robust evidence that gastrointestinal adverse events are a risk factor for ulcer related complications.
4. The complete dataset from the Celecoxib Long Term Arthritis Safety Study (CLASS) did not demonstrate a statistically significant advantage in terms of the primary endpoint (complicated event or PUB\*) at any time for celecoxib compared to NSAIDs (pooled or individual).<sup>5</sup>
5. In the CLASS trial, patients who were concomitantly using aspirin and celecoxib had no difference in symptomatic ulcers or upper GI complications compared to patients who were concomitantly using aspirin and a traditional NSAID.<sup>6</sup> In fact, in patients taking aspirin, there was a combined rate of complicated and symptomatic ulcers 4 times that of patients not taking aspirin.
6. Corticosteroid use was not significantly associated with the incidence of upper GI complications in either the celecoxib or traditional NSAID groups.<sup>6</sup>
7. It has been shown that there is no difference in prevention of recurrent bleeding in patients with a recent history of ulcer bleeding between patients taking celecoxib and patients taking diclofenac plus a proton pump inhibitor.<sup>7</sup> The high rates of recurrent bleeding in both the celecoxib-treated patients and in the diclofenac plus omeprazole group - over 10 times as high as the rate in the CLASS trial - suggest that NSAIDs and COX-2 NSAIDs should be used with caution, if at all, in patients who have a recent history of a bleeding ulcer.<sup>8</sup>
8. It has also been shown that celecoxib does not provide superior prevention against the development of recurrent ulcers as compared to diclofenac plus omeprazole.<sup>9</sup>
9. In the Adenomatous Polyp Prevention on Vioxx (aPPROVe) study, the incidence of myocardial infarction and thrombotic stroke in the Vioxx and placebo groups began to diverge progressively after a year or more of treatment.<sup>10</sup>

\* PUB defined as perforation, symptomatic ulcer or bleeding

10. In Vioxx Gastrointestinal Outcomes Research (VIGOR), at 8 months there was no significant difference between rofecoxib and naproxen in the cumulative incidence of thrombotic events. From 8 to 12 months, the incidence of events in the rofecoxib group rose sharply, while that of naproxen did not.<sup>8</sup>
11. In both the VIGOR and CLASS studies during the first 30-90 days, there was no separation between the time-to-event curves. There does not appear to be a clinically meaningful advantage of COX-2 NSAIDs when used short-term.
12. There is no long term safety data with valdecoxib.

### **Discussion**

COX-2 NSAIDs have never been shown to be more effective than traditional NSAIDs in reducing the symptoms of arthritis or acute pain. A potential advantage may be that they have been shown, in short term trials, to cause less endoscopically visualized ulcers (defined as a mucosal break  $\geq 3$  mm in diameter with unequivocal depth). However, most ulcers identified by endoscopy do not cause clinical problems, and it is not known whether such small endoscopically defined ulcers are an accurate predictor of ulcer complications, the most common being gastrointestinal bleeding.

### **Analysis of the CLASS trial**

The main publication of the CLASS trial was reported as a six month, randomized, three arm trial comparing celecoxib 800 mg/day with ibuprofen 2400 mg/day and diclofenac 150 mg/day in osteoarthritis or rheumatoid arthritis, and the data were reported as annualized incidence.<sup>6</sup> However, the original designs were 2 separate trials. One trial compared celecoxib to ibuprofen (originally planned for 15 months, mean duration of exposure 7 months). One trial compared celecoxib to diclofenac (originally planned for 12 months, mean duration of exposure 6.5 months). The two trials had separate patient recruitment and randomization procedures. There were highly significant differences at baseline between trials in patients' age, disease severity, ethnic group, histories of intolerance to non-steroidal anti-inflammatory drugs and use of alcohol.

A prespecified primary outcome in the CLASS trial was ulcer related complications (bleeding, perforation or obstruction) with a 12 to 15 month follow-up, not a combined definition of ulcer related complications and symptomatic ulcers during the first six months of treatment – as described in the publication. The published trial concluded that, compared with the traditional NSAIDs, celecoxib “was associated with a lower incidence of symptomatic ulcers and ulcer complications combined.”<sup>6</sup> The full data set showed clearly that celecoxib did not differ from the traditional NSAIDs in its effect on the predefined primary outcome.<sup>5</sup>

Analysis according to a pre-specified protocol showed similar numbers of ulcer related complications in the comparison groups. Almost all the ulcer complications that had occurred during the second half of the trials were in users of celecoxib.<sup>11</sup> These results contradict the published conclusions of the CLASS trial.<sup>11</sup>

The absolute number of dropouts and withdrawals, both overall and due to GI adverse events, increased gradually without sudden increase after Month 6 in any of the treatment groups.<sup>11</sup> The numerical order of the drop out rates stayed the same across the entire study period in the different groups. Therefore, there is no reason to include information only in the first six months.

The published CLASS trial combined both diclofenac and ibuprofen data as the “NSAID group”. The only statistically significant published finding was that in patients not using aspirin, the annualized incidence of upper GI ulcer complication was significantly lower with celecoxib vs. NSAIDs (0.44% vs. 1.27% p=0.04).<sup>6</sup> However, these p-values can not be interpreted by their face

value since: 1) at least 34 subgroup analyses had been conducted to reach this finding, 2) subgroup analyses based on aspirin use was not even mentioned in the protocol, and 3) the pre-specified primary endpoint (upper GI ulcer complication) did not show statistical significance.<sup>5</sup>

Despite the large size of the CLASS trial, there was no decrease in the incidence of death due to gastrointestinal complications (no deaths due to GI complications in CLASS). In fact, the incidence of total mortality was higher with COX-2 NSAIDs than with traditional NSAIDs.<sup>12</sup> The incidence of serious adverse events, including death, admission to hospitals, and any life-threatening event or event leading to severe disability, was significantly higher with the COX-2 NSAID than with traditional NSAIDs.<sup>12</sup>

A careful analysis of the FDA data suggests an increase in serious cardiac events with celecoxib. The incidence of cardiac serious adverse events (myocardial infarction, combined anginal events and atrial arrhythmias) was 0.6% higher with celecoxib than with the comparator NSAIDs (RR 1.55 95% CI 1.04-2.30).<sup>12</sup> Cardiovascular events were the main cause of death in the CLASS trial, (69% of 36 deaths) [and as a comparison 46% of 37 deaths in VIGOR trial].<sup>12</sup>

In summary, evidence suggests that celecoxib offers no better efficacy than traditional NSAIDs, it offers no advantage over traditional NSAIDs for serious GI adverse events, and it may cause more morbidity when cardiovascular data is taken into consideration.

### **Valdecoxib**

There is no long term available evidence for valdecoxib. There is one study in patients undergoing CABG, where the treatment with the valdecoxib prodrug, parecoxib, was associated with a cluster of cardiovascular events.<sup>11</sup> The cardiovascular effects of valdecoxib was studied and presented at the November 2004 American Heart Association by Dr. Garret Fitzgerald, but are not published, therefore not discussed here. A short article in BMJ notes that the manufacturer was not forthcoming in presenting cardiac safety data in 2 trials of valdecoxib in patients undergoing CABG.<sup>13</sup>

It is recommended that Bextra be subject to the same restrictive PA criteria.

### **Other information**

Based on the safety concerns reported in the rofecoxib trials, and the possibility that these extend to other COX-2 NSAIDs, the National Cancer Institute is rapidly reviewing data about these drugs.<sup>14</sup>

## References

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**ADDENDUM A**

**MINNESOTA DEPARTMENT OF HUMAN SERVICES  
COX-2 inhibitor prior authorization criteria algorithm established 12-17-01**

