Summary of the Criteria for the Non-formulary Use of Cyclooxygenase 2 (COX-2) Inhibitors in High-Risk Veteran Patients

(The compete criteria are available at **www.vapbm.org**)

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Certain individuals are at higher risk for upper GI events associated with NSAIDs and may be candidates for acetaminophen (for patients with osteoarthritis-OA), salsalate, nonselective NSAIDs in combination with appropriate gastric cytoprotection (e.g. proton-pump inhibitor-PPI or misoprostol), preferential COX-2 inhibitors (e.g. etodolac or diclofenac) or a COX-2 inhibitor (e.g. celecoxib or rofecoxib). **Limited data exists in high-risk individuals receiving celecoxib or rofecoxib so caution must be used, as with other NSAIDs, in these patients. It is imperative to determine whether patients truly need treatment with a NSAID or COX-2 inhibitor prior to their initiation.**

A. Individuals with a higher risk for NSAID-induced GI injury: (High risk patients with OA must receive a therapeutic trial of acetaminophen 4000 mg qd prior to a COX-2 inhibitor).

1. Prior history of a hospital admission for a **serious** gastrointestinal event (gastroduodenal perforation, ulcer or bleed).
2. Concurrent use of warfarin (reinforce to patients to report any signs and symptoms of bleeding. In addition, patients and their INRs should be monitored more closely when any new drug is initiated). Both celecoxib and rofecoxib may increase INR and may increase the risk for bleeding.

B. Other individuals: Patients **not** having a history of hospital admission for a significant gastrointestinal event or those **not** receiving warfarin must have a **GI Score** (see appendix 1 in the criteria at www.vapbm.org) calculated in order to identify their risk level prior to receiving a COX-2 inhibitor. Once the GI Score has been calculated, refer to table below for appropriate treatment:

Recommendations for The Use of NSAIDs or COX-2 Inhibitors in Veteran Patients:

Risk Level	First Line Agent	Alternative(s)	Comments
1-No Risk (GI Score 0-10)	Formulary non-selective NSAID (ibuprofen, naproxen, etc)		
2-Moderate Risk (GI Score 11-15)	Formulary non-selective NSAID (ibuprofen, naproxen, etc)		
3-Significant Risk (GI Score 16-20) [Greater than 30 days use]	Salsalate, etodolac* or diclofenac†	If no response or intolerant, then non-selective NSAID (ibuprofen, naproxen, etc) plus PPI or misoprostol or a COX-2 inhibitor	**In patients receiving low dose aspirin for cardiovascular prophylaxis, a non-selective NSAID plus a PPI or misoprostol is preferred since the GI safety of the COX-2 inhibitors is reduced or lost ‡.**
4-Substantial Risk (GI Score >20)	Salsalate, non-selective NSAID (ibuprofen, naproxen, etc) plus PPI or misoprostol, or a COX-2 inhibitor.		**In patients receiving low dose aspirin for cardiovascular prophylaxis, a non-selective NSAID plus a PPI or misoprostol is preferred since the GI safety of the COX-2 inhibitors is reduced or lost ‡.**
Until more conclusive evidence, regarding the use of the COX-2 inhibitors in patients with cardiovascular disease becomes available, the COX-2 selective agents should <u>not</u> be routinely chosen over the nonselective NSAIDs in this group of individuals ∂.			

If patient is already on a PPI for another indication, requires NSAIDs and is considered to be at risk for a GI event, adding a non-selective NSAID would be indicated over choosing a COX-2 inhibitor in all high-risk patients except those receiving warfarin.
*Although limited, data does exist supporting etodolac to be a safer alternative to traditional NSAIDs.
†Unpublished data from the CLASS trial and Merck's Phase 2b/3 osteoarthritis trials did not show a difference in GI event rates between diclofenac and either celecoxib or rofecoxib [1,2].

Patients with an allergy to sulfonamides should **not** receive celecoxib.
Dyspepsia is **not** a reason to use a COX-2 inhibitor since COX-2 inhibitors may also lead to dyspeptic symptoms.
Lack of response to NSAIDs is **not** a reason to use a COX-2 inhibitor. COX-2 inhibitors are not more effective than other NSAIDs
‡The use of low dose aspirin (325 mg qd or less) may reduce or eliminate any GI protective benefit of the COX-2 inhibitors, but did not appear to significantly increase the GI toxicity of NSAIDs (ibuprofen or diclofenac) in the CLASS trial [1].
∂ In a recent meta-analysis, the annualized rate of MI was calculated using data from the COX-2 groups of the CLASS (celecoxib) and VIGOR (rofecoxib) trials and was compared to the annualized rate of MI in the placebo arm of 4 ASA primary prevention trials. Rates of MI were statistically greater in the COX-2 groups of the CLASS and VIGOR trials compared to rate of MI in the placebo groups of these primary prevention trials. Authors concluded that their analysis has significant limitations. However, should raise caution for the potential increase in the risk of cardiovascular events and urge caution when prescribing these agents to patients with known cardiovascular disease until more conclusive evidence is available (see full criteria for prescribing COX-2 inhibitors at www.vapbm.org to obtain references and more detailed discussion of results) [3].

1. Silverstein FE, Faich G, Goldstein, et al. Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis: The CLASS Study: a randomized controlled trial. JAMA 2000;284:1247-1255.
2. Langman MJ, Jensen D, Watson D, et al. Adverse Upper Gastrointestinal Effects of Rofecoxib Compared With NSAIDs. JAMA 1999;282:1929-1933.
3. Mukherjee D, Nissen SE, Topol EJ. Risk of Cardiovascular Events Associated with Selective COX-2 Inhibitors. JAMA 2001;286:954-959.