# Texas Vendor Drug Program

## Drug Use Criteria: Cyclooxygenase-2 Inhibitors

### Publication History

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Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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# 1 Dosage

Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor nonsteroidal anti-inflammatory drug (NSAID), demonstrates anti-inflammatory, analgesic and antipyretic effects through inhibiting prostaglandin synthesis, predominantly by inhibiting COX-2**.** Like nonselective NSAIDs, celecoxib is associated with an increased risk of potentially fatal thrombotic cardiovascular events, including myocardial infarction and stroke. Therefore, celecoxib should be used cautiously in patients with cardiovascular disease or with risk factors for cardiovascular disease. To minimize the risk of celecoxib-associated cardiovascular events, the lowest celecoxib dose for the shortest treatment duration should be utilized. Celecoxib is FDA-approved to manage ankylosing spondylitis, juvenile rheumatoid arthritis, osteoarthritis, acute pain, primary dysmenorrhea, and rheumatoid arthritis.[1-6] A new therapy combining celecoxib with amlodipine (Consensi™) has been approved for use to manage hypertension in patients with osteoarthritis. This medication is slated to be available in the second half of 2019.[7, 8]

## 1.1 Adults

Maximum recommended celecoxib doses are listed in Table 1. Dosages exceeding these recommendations will be reviewed. Maximum recommended dosages for amlodipine/celecoxib combination therapy are summarized in Table 2.

**Table 1: Adult Recommended COX-2 Inhibitor Daily Dosages: Monotherapy**[1-4]

| Treatment Indication | Drug Name | Dosage Form / Strength | Maximum Recommended Dosage |
|---|---|---|---|
| acute pain (including primary dysmenorrhea) | celecoxib (Celebrex®) | 50 mg, 100 mg, 200 mg, 400 mg capsules | 400 mg/day* |
| ankylosing spondylitis | | | 400 mg/day |
| osteoarthritis | | | 200 mg/day |
| rheumatoid arthritis | | | 400 mg/day |

- *an additional 200 mg dose may be given on the first day only to manage acute pain

**Table 2: Adult Recommended Maximum Daily Dosages for COX-2 Inhibitors: Combination Therapy**[1-3, 7, 8]

| Treatment Indication | Drug Name | Dosage Form / Strength | Maximum Recommended Dosage |
|---|---|---|---|
| hypertension in patients with osteoarthritis | amlodipine/celecoxib (Consensi™)* | 2.5 mg/ 200 mg, 5 mg/ 200 mg, 10 mg/ 200 mg tablets | 10 mg/ 200 mg/day |

- * product anticipated availability in second half of 2019

## 1.2 Pediatrics

Celecoxib is FDA-approved for use in pediatric patients 2 years of age and older with a diagnosis of juvenile rheumatoid arthritis (JRA), now also known as juvenile arthritis (JA) or juvenile idiopathic arthritis (JIA).[9, 10] However, celecoxib long-term cardiovascular toxicity as well as extended treatment for greater than six months have not been evaluated in pediatric patients. Therefore, the lowest celecoxib dose for the shortest treatment duration should be employed. Celecoxib safety and efficacy have not been determined in pediatric patients younger than 2 years of age.[1-4] Additionally, celecoxib/amlodipine (Consensi™) combination therapy is not approved for use in pediatric patients as safety and efficacy have not been established in this patient population. Recommended celecoxib pediatric dosages are summarized in Table 3.

**Table 3: Recommended COX-2 Inhibitor Pediatric Daily Dosages**[1-4]

| Treatment Indication | Drug Name | Dosage Form / Strength | Maximum Recommended Dosage |
|---|---|---|---|
| • Juvenile rheumatoid arthritis (JRA)<br>• Juvenile arthritis (JA)<br>• Juvenile idiopathic arthritis (JIA) | celecoxib (Celebrex ®) | 50 mg, 100 mg capsules | Greater than 2 years of age:<br>• 10 kg to less than or equal to 25 kg:<br>  ‣ 50 mg twice daily<br>• Greater than 25 kg:<br>  ‣ 100 mg twice daily |

## 1.3 Hepatic Impairment[1-4]

In patients with moderate hepatic impairment (Child-Pugh Class B), the celecoxib dose should be reduced by 50%. Celecoxib is not recommended for use in patients with severe hepatic impairment.

# 2 Duration of Therapy

Due to the potential for increased cardiovascular and gastrointestinal adverse events, celecoxib and amlodipine/celecoxib should be prescribed as the lowest effective dose for the shortest treatment duration that satisfies patient treatment goals.

## 2.1 Therapy Limits[1-6]

1. Celecoxib is prescribed on an as needed basis in the management of acute pain or dysmenorrhea. However, treatment regimens extending beyond a two-week time period will be evaluated.
2. Celecoxib dosages used in osteoarthritis, rheumatoid arthritis, familial adenomatous polyposis, and ankylosing spondylitis may be chronically administered based on patient need.
3. Celecoxib safety and efficacy in pediatric patients 2 years of age and older with JRA for greater than a six-month treatment duration have not been established. Patient profiles containing prescriptions for JRA for greater than 6 months will be reviewed.

## 2.2 COX-2 Inhibitor Use in Elderly Patients[9-11]

Elderly patients are frequently prescribed a COX-2 specific NSAID like celecoxib to manage acute and chronic pain. Several issues surface with COX-2 inhibitor use in elderly patients, including potential adverse effects and drug interactions. NSAID-induced gastrointestinal toxicity is prevalent in the elderly; therefore, COX-2 inhibitors like celecoxib or nonselective NSAIDs plus proton pump inhibitors may offer safer alternatives to these patients. Renal toxicity as well as adverse central nervous system effects are more prevalent in elderly patients due to changes in metabolism, underlying disease states, and concurrent drug therapy and should be considered prior to prescribing celecoxib, especially in higher doses. The potential for increased cardiovascular risk with COX-2 inhibitor use is also a factor when

evaluating NSAID therapy in elderly patients. Elderly patients prescribed celecoxib, especially those at higher risk, should be evaluated for appropriateness of therapy as well as potential for drug-drug interactions. Appropriate therapy duration and dosages should also be assessed. Preventive measures such as gastric antisecretory agents administered should be considered in some individuals to reduce GI complications. Medication profiles of elderly patients greater than 60 years of age prescribed celecoxib in high doses or in patients with increased risk factors for adverse events or drug-drug interactions will be reviewed.

## 2.3 Selective NSAID Use and Cardiovascular Risk[12-20]

Some clinical trials have shown that patients prescribed selective and nonselective NSAIDs may be at increased risk for serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, all of which can be fatal. Patients at greater risk are those with known CV disease or risk factors for CV disease. Due to the lack of long-term clinical trial data, CV risks associated with NSAID use remains controversial, especially in high-risk patients. Risk also varies between nonselective NSAIDs and cyclooxygenase-2 (COX-2) inhibitors, as well as between individual NSAIDs. The Center for Drug Evaluation and Research has determined that the increased risk of CV events associated with NSAID use should be considered a class effect for both selective and nonselective NSAIDs until more results are available. Patients should be prescribed the lowest effective NSAID dose for the shortest possible treatment duration to minimize the potential for cardiovascular adverse events.

NSAIDs may induce new onset hypertension or worsen pre-existing hypertension in some patients, which may contribute to the development of cardiovascular adverse events. Blood pressure should be routinely monitored in patients prescribed NSAIDs.

NSAIDs may cause fluid retention or edema in some patients, and should be used cautiously in patients with a history of fluid retention or heart failure.

## 2.4 Selective NSAID use and Gastrointestinal Risk

Like nonselective NSAIDs, celecoxib use may be associated with an increased risk of serious gastrointestinal (GI) adverse events, including potentially fatal GI bleeding, ulceration, or gastric/intestinal perforation. The risk of NSAID-associated severe GI adverse events increases in patients with a history of peptic ulcer disease, GI bleeding, smoking, alcohol use, concurrent use of anticoagulants or oral

corticosteroids, advanced age, poor health and prolonged NSAID use. However, celecoxib may be associated with fewer GI adverse events due to selective COX-2 inhibition.[1, 21] Short-term trials (3 to 6 months) have shown celecoxib to be associated with significantly fewer GI complications compared to a nonselective NSAID plus a proton pump inhibitor (PPI) (e.g., diclofenac plus omeprazole) and a Cochrane review found significantly fewer ulcer complications with COX-2 inhibitors compared to nonselective NSAIDs.[22-24] Chan and cohorts[25], in a randomized, double-blind trial, found that celecoxib administered concurrently with the PPI, esomeprazole, was significantly better in preventing ulcer bleeding in high risk patients compared to celecoxib monotherapy. In a case-control study, Patterson et al[26] observed that outpatients in the United States using commonly prescribed nonselective NSAIDs and COX-2 inhibitors from 1999 to 2003 were two times more likely to be hospitalized for peptic ulcer bleeding and perforation following nonselective NSAID use compared to those receiving celecoxib. Additionally, a recent small study suggests that lower GI bleeding may occur less frequently following COX-2 inhibitor use compared to that seen with nonselective NSAIDs. [23] This study was criticized, though, as investigators used hemoglobin decrease rather than documented lower GI bleeds to assess outcomes.[27] Further long-term studies are necessary to substantiate the perceived lower GI risk associated with COX-2 inhibitors.[28]

# 3 Duplicative Therapy

The combined use of specific COX-2 inhibitors and nonspecific COX-1, COX-2 inhibitors does not provide additional therapeutic benefit and may result in additive adverse effects, including gastrointestinal toxicity. However, because celecoxib lacks antiplatelet effects, celecoxib may be used concurrently with low-dose aspirin prescribed for cardiovascular prophylaxis. While an increased incidence of gastrointestinal adverse effects has been observed with combined celecoxib-aspirin therapy, the combination is cautiously warranted due to the potential cardiovascular benefits. Concurrent therapy with celecoxib and nonspecific COX-1, COX-2 inhibitors other than low-dose aspirin is not recommended and will be reviewed.

# 4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically significant for celecoxib are summarized in Table 4[2, 3, 29]. Only those drug-drug interactions classified as clinical significance level 1/contraindicated or those considered life-threatening which have not yet been classified will be reviewed.

**Table 4: COX-2 Inhibitor Drug-Drug Interactions[2, 3, 29]**

| Target Drug | Interacting Drug | Interaction | Recommendation | Clinical Significance Level# |
|---|---|---|---|---|
| amlodipine/ celecoxib | clopidogrel | combined administration may reduce clopidogrel antiplatelet activity and increase risk of thrombotic events as both medications are metabolized by the CYP3A4 enzyme (CYP3A4 converts clopidogrel to active metabolite) | administer cautiously together and observe patients for changes in clopidogrel efficacy | major (DrugReax) 3-moderate (CP) |
| amlodipine/ celecoxib | CYP3A4 inducers (e.g., rifampin) | adjunctive administration may result in reduced amlodipine serum levels and therapeutic efficacy due to induction of amlodipine metabolism by CYP system | observe patients for sustained therapeutic effects and adjust amlodipine dosages, if needed; may consider alternate therapy that does not induce CYP3A4 | major (DrugReax) 3 – moderate (CP) |

| Target Drug | Interacting Drug | Interaction | Recommendation | Clinical Significance Level# |
|---|---|---|---|---|
| amlodipine/ celecoxib | CYP3A4 inhibitors (e.g., clarithromycin) | co-administration may result in enhanced amlodipine pharmacologic and adverse effects, including hypotension and acute kidney injury, as amlodipine is metabolized by CYP3A4 | use cautiously together, if at all; observe patients for amplified pharmacologic/ adverse effects; adjust dosages as necessary | major (DrugReax) 2-major (CP) |
| amlodipine/ celecoxib | simvastatin | due to an unknown mechanism, combined use may cause enhanced simvastatin availability (increased area under curve, maximum concentration) and increased pharmacologic / adverse effects including myopathy and rhabdomyolysis | avoid combined use, if possible; if combined administration necessary, simvastatin dose should not exceed 20 mg/day; patients maintained on high-dose simvastatin who require amlodipine therapy should be converted to another statin with fewer interactions | major (DrugReax) 2-major (CP) |
| amlodipine/ celecoxib | tacrolimus | increased tacrolimus serum levels with possible enhanced pharmacologic / adverse effects may result with combined use; tacrolimus is a CYP3A4 substrate with a narrow therapeutic index and amlodipine is weak CYP3A4 inhibitor | use cautiously together; monitor patients for tacrolimus adverse effects (e.g., renal dysfunction, cholestasis, paresthesias) | major (DrugReax) 3-moderate (CP) |

| Target Drug | Interacting Drug | Interaction | Recommendation | Clinical Significance Level# |
|---|---|---|---|---|
| celecoxib | ACE inhibitors, angiotensin receptor blockers | potential for decreased antihypertensive effects, increased renal impairment risk with combined therapy; NSAIDs may block production of vasodilator and natriuretic prostaglandins | monitor blood pressure and renal function, modify therapy as needed; use combination cautiously in elderly; nonacetylated salicylates, sulindac, may be alternative NSAIDS – have less inhibitory effect on prostaglandin synthesis | moderate (DrugReax) 3-moderate (CP) |
| celecoxib | anticoagulants/ aspirin/ thrombolytic agents | potential for increased gastrointestinal and bleeding adverse effects most likely due to either additive effects and/or decreased platelet function | administer combination cautiously and observe for adverse bleeding events | major (DrugReax) 2-major (CP) |
| celecoxib | corticosteroids | potential for increased gastrointestinal adverse effects with combined therapy | monitor for adverse effects; avoid prolonged concurrent administration | 3-moderate (CP) |
| celecoxib | CYP2C9 inhibitors (e.g., fluconazole, amiodarone, delavirdine) | celecoxib metabolized by CYP2C9; combination may increase celecoxib serum levels and potential for toxicity | use cautiously together with lowest effective celecoxib dose; monitor for adverse effects | moderate (DrugReax) 2-major, 3-moderate (CP) |
| celecoxib | immune suppressants | celecoxib may mask infection symptoms (e.g., fever, swelling) | use combination cautiously | 3-moderate (CP) |

| Target Drug | Interacting Drug | Interaction | Recommendation | Clinical Significance Level# |
|---|---|---|---|---|
| celecoxib | lithium | NSAIDs may decrease lithium clearance by blocking renal tubular prostaglandins (may contribute to lithium clearance; may result in increased lithium levels and potential for adverse effects | avoid combination, if possible; if concurrent therapy necessary, monitor lithium levels and signs/ symptoms of lithium toxicity; sulindac, aspirin do not affect lithium clearance -may be alternative NSAIDS | moderate (DrugReax) 3-moderate (CP) |
| celecoxib | loop diuretics (e.g., furosemide) | potential for impaired diuretic and antihypertensive activity of loop diuretic and increased risk of renal insufficiency due to NSAID-associated decreased renal prostaglandin production | administer combination cautiously; monitor for signs/symptoms of renal dysfunction and reduced diuretic/ antihypertensive efficacy | moderate (DrugReax) 3-moderate (CP) |
| celecoxib | methotrexate | adjunctive administration may lead to increased methotrexate serum levels and the potential for adverse effects (e.g., hematologic, gastrointestinal toxicity), especially with higher methotrexate doses, due to NSAID-associated reductions in renal methotrexate clearance | administer combination cautiously together; observe for enhanced methotrexate pharmacologic and adverse events | major (DrugReax) 2-major (CP) |

| Target Drug | Interacting Drug | Interaction | Recommendation | Clinical Significance Level# |
|---|---|---|---|---|
| celecoxib | SNRIs/SSRIs | concurrent administration may increase risk of enhanced bleeding activity as serotonin release from platelets necessary for adequate hemostasis | monitor for signs/symptoms of bleeding with adjunctive administration | major, moderate (DrugReax) 3-moderate (CP) |
| celecoxib | warfarin | combined therapy may result in increased INR and increased risk of gastrointestinal adverse effects, especially in elderly, most likely due to competition for metabolism through CYP2C9 | monitor anticoagulant activity, especially in first several days of combination therapy; adjust warfarin doses as necessary | major (DrugReax) 2-major (CP) |

- * Clinical Pharmacology
- ACE = angiotensin converting enzyme
- NSAIDs = nonsteroidal anti-inflammatory drugs
- SNRIs = serotonin norepinephrine reuptake inhibitors
- SSRIs = selective serotonin reuptake inhibitors

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