CONSENSI- amlodipine besylate and celecoxib tablet
Burke Therapeutics, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CONSENSI safely and effectively. See full prescribing information for CONSENSI.

CONSENSI®> (amlodipine and celecoxib) tablets, for oral administration. Initial U.S. Approval: 2018

WARNING: RISK OF SERIOUS CARDIOVASCULAR and GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.1)**
- **CONSENSI is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.1, 5.4)	05/2020

INDICATIONS AND USAGE

CONSENSI is a combination of amlodipine besylate, a calcium channel blocker, and celecoxib, a nonsteroidal anti-inflammatory drug (NSAID), indicated for patients for whom treatment with amlodipine for hypertension and celecoxib for osteoarthritis are appropriate. Lowering blood pressure reduces the risk of fatal and nonfatal CV events, primarily strokes and myocardial infarctions. (1.1)

Limitations of Use

CONSENSI is only available in a celecoxib strength of 200 mg and is only to be taken once daily. (1.1)

DOSAGE AND ADMINISTRATION

Use the lowest effective dosage of celecoxib for the shortest duration consistent with individual treatment goals. If analgesic therapy is no longer indicated, discontinue CONSENSI and initiate patient on alternative antihypertensive therapy. (2.1, 2.2)

Start at (amlodipine/celecoxib) 5 mg/200 mg (2.5 mg/200 mg for small, elderly, or frail patients or hepatic impairment) orally once daily. Titrate to 5 mg/200 mg or 10 mg/200 mg once daily as needed for blood pressure control. (2.1)

CONSENSI may be substituted for its individual components. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets (amlodipine/celecoxib): 2.5 mg/200 mg, 5 mg/200 mg, or 10 mg/200 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to amlodipine, celecoxib, or any inactive ingredients of CONSENSI (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)
- Demonstrated allergic-type reactions to sulfonamides (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity and Patients with Hepatic Failure: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.4, 7)
- Hypotension: Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. (5.5)
- Increased Angina or Myocardial Infarction: Worsening angina and acute myocardial infarction, particularly in patients with severe obstructive coronary artery disease. (5.6)
- Heart Failure and Edema: Avoid use of CONSENSI in patients with severe heart failure. (5.7)
- Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of CONSENSI in patients with advanced renal disease (5.8)

- Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.9)
- Exacerbation of Asthma Related to Aspirin Sensitivity: CONSENSI is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.10)
- Serious Skin Reactions: Discontinue CONSENSI at first appearance of skin rash or other signs of hypersensitivity. (5.11)
- Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks of gestation. (5.12, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.13, 7)

ADVERSE REACTIONS

Most common adverse reactions to celecoxib in arthritis trials (>2% and >placebo): abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, rash. (6.1)

Most common adverse reaction to amlodipine is edema which occurred in a dose related manner. Other adverse experiences to amlodipine that were not dose related but that were reported with an incidence >1.0% are fatigue, nausea, abdominal pain, and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Burke Therapeutics, LLC at 1-888-275-1264 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking CONSENSI with drugs that interfere with hemostasis. Concomitant use of CONSENSI and analgesic doses of aspirin is not generally recommended. (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with CONSENSI may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7)
- ACE Inhibitors and ARBs: Concomitant use with CONSENSI in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function. (7)
- Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects. (7)
- Digoxin: Concomitant use with CONSENSI can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)
- Simvastatin: Do not exceed 20 mg of simvastatin per day in patients taking amlodipine. (7)

USE IN SPECIFIC POPULATIONS

- Infertility: NSAIDs are associated with reversible infertility. (8.3)
- Hepatic or Renal Impairment: Not recommended in patients with moderate or severe hepatic impairment or severe renal insufficiency.
- Poor Metabolizers of CYP2C9 Substrates: Not recommended.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR and GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI), and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use *[see Warnings and Precautions (5.1)]* .**
- **CONSENSI is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4) and Warnings and Precautions (5.1)]* .**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Hypertension and Osteoarthritis

CONSENSI is indicated in adult patients for whom treatment with both amlodipine for hypertension and celecoxib for osteoarthritis are appropriate.

Amlodipine

Amlodipine is indicated for the treatment of hypertension, to lower blood pressure *[see Clinical Studies (14.1)]* . Lowering blood pressure reduces the risk of fatal and nonfatal CV events, primarily strokes and myocardial infarctions.

Amlodipine may be used alone or in combination with other antihypertensive agents *[see Drug Interactions (7)]*.

Celecoxib

Celecoxib is indicated for the management of the signs and symptoms of osteoarthritis *[see Clinical Studies (14.2)]*.

Limitations of Use

CONSENSI is inappropriate for short-term or intermittent treatment or to treat any conditions other than hypertension in patients taking celecoxib for osteoarthritis. CONSENSI is only available in a celecoxib strength of 200 mg and is only to be taken once daily.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Use the lowest effective dosage of celecoxib for the shortest duration consistent with individual patient treatment goals *[see Dosage and Administration (2.2) and Warnings and Precautions (5)]* . Only 200 mg of celecoxib once daily is available with CONSENSI.

Start CONSENSI in adults at (amlodipine/celecoxib) 5 mg/200 mg orally once daily or 2.5 mg/200 mg in small, fragile, or elderly patients, or patients with mild hepatic insufficiency. Use 2.5 mg/200 mg when adding CONSENSI to other antihypertensive therapy.

Adjust amlodipine component dosage according to blood pressure goals. In general, wait 7 to 14 days

between titration steps. If more rapid titration is clinically warranted, monitor closely. The maximum dose is 10 mg/200 mg once daily.

2.2 Discontinuation

If analgesic therapy is no longer indicated, discontinue CONSENSI and initiate patient on alternative antihypertensive therapy, such as amlodipine monotherapy. If CONSENSI is stopped and replaced with an equal dose of amlodipine, monitor blood pressure carefully.

2.3 Replacement Therapy

For patients receiving celecoxib and amlodipine from separate capsules and tablets, respectively, substitute CONSENSI containing the same component doses. Monitor blood pressure carefully.

3 DOSAGE FORMS AND STRENGTHS

CONSENSI (amlodipine and celecoxib) tablets are white and biconvex, non-coated, non-scored, with the tablet strength debossed on one side, available in the following strengths:

Amlodipine/Celecoxib	Shape
2.5 mg/200 mg	Elongated oval
5 mg/200 mg	Caplet
10 mg/200 mg	Round

4 CONTRAINDICATIONS

CONSENSI is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to amlodipine, celecoxib, or any of the inactive ingredients in CONSENSI *[see Warnings and Precautions (5.9, 5.11)]* .
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs, have been reported in such patients *[see Warnings and Precautions (5.9, 5.10)]* .
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.1)]* .
- In patients who have demonstrated allergic-type reactions to sulfonamides *[see Warnings and Precautions (5.9)]* .

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Celecoxib

Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective NSAIDs of up to three years have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

In the APC (Adenoma Prevention with Celecoxib) trial, there was about a threefold increased risk of the

composite endpoint of cardiovascular death, myocardial infarction, or stroke for the celecoxib 400 mg twice daily and celecoxib 200 mg twice daily treatment arms compared to placebo. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction *[see Clinical Studies (14.3)*].

A randomized controlled trial entitled the Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION) was conducted to assess the relative cardiovascular thrombotic risk of a COX-2 inhibitor, celecoxib, compared to the non-selective NSAIDs naproxen and ibuprofen. Celecoxib 100 mg twice daily was non-inferior to naproxen 375 to 500 mg twice daily and ibuprofen 600 to 800 mg three times daily for the composite endpoint of the Antiplatelet Trialists' Collaboration (APTC), which consists of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke *[see Clinical Studies (14.3)]* .

To minimize the potential risk for an adverse CV event in celecoxib-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as celecoxib, increases the risk of serious GI events *[see Warnings and Precautions (5.2)]* .

Status Post CABG Surgery: Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *[see Contraindications (4)]* .

Post-Myocardial Infarction Patients: Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-myocardial infarction period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-myocardial infarction was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-myocardial infarction, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of celecoxib in patients with a recent myocardial infarction unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If celecoxib is used in patients with a recent myocardial infarction, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

Celecoxib

NSAIDs, including celecoxib, cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with celecoxib. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation: Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants; or selective serotonin reuptake

inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding. Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS trial, and 2.19% for the subgroup on low-dose aspirin (ASA). Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA *[see Clinical Studies (14.3)]* .

Strategies to Minimize the GI Risks in NSAID-Treated Patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue CONSENSI until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]* .

5.3 Hepatotoxicity and Patients with Hepatic Failure

Celecoxib

Elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including celecoxib.

In controlled clinical trials of celecoxib, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the ULN) of liver associated enzymes was 6% for celecoxib and 5% for placebo, and approximately 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue CONSENSI immediately, and perform a clinical evaluation of the patient.

Amlodipine

Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) is 56 hours in patients with impaired hepatic function.

5.4 Hypertension

Celecoxib

NSAIDs, including celecoxib can lead to the new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazides diuretics or loop diuretics may have impaired response to these therapies when taking NSAIDs *[see Drug Interactions (7)]* .

See Clinical Studies (14.3) for additional blood pressure data for celecoxib.

Monitor blood pressure during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Hypotension

Amlodipine

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Monitor blood pressure carefully when switching between amlodipine and CONSENSI, and adjust dose accordingly.

5.6 Increased Angina or Myocardial Infarction

Amlodipine

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

5.7 Heart Failure and Edema

Celecoxib

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately doubling in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of myocardial infarction, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients taking NSAIDs. Use of celecoxib may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) *[see Drug Interactions (7)]* .

In the CLASS study *[see Clinical Studies (14.3)]* , the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on celecoxib 400 mg twice daily (4-fold and 2-fold the recommended osteoarthritis and rheumatoid arthritis dose, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively.

Avoid the use of celecoxib in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If celecoxib is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.8 Renal Toxicity and Hyperkalemia

Celecoxib

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors or the ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating celecoxib. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during

use of celecoxib *[see Drug Interactions (7)]* . Avoid the use of celecoxib in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If celecoxib is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia: Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

5.9 Anaphylactic Reactions

Celecoxib

Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. Celecoxib is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people *[see Contraindications (4) and Warnings and Precautions (5.10)]* .

Seek emergency help if any anaphylactic reaction occurs.

5.10 Exacerbation of Asthma Related to Aspirin Sensitivity

Celecoxib

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, celecoxib is contraindicated in patients with this form of aspirin sensitivity *[see Contraindications (4)]* . When celecoxib is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.11 Serious Skin Reactions

Celecoxib

Serious skin reactions have occurred following treatment with celecoxib, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal.

Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of celecoxib at the first appearance of skin rash or any other sign of hypersensitivity.

Celecoxib is contraindicated in patients with previous serious skin reactions to NSAIDs *[see Contraindications (4)]* .

5.12 Premature Closure of Fetal Ductus Arteriosus

Celecoxib

Celecoxib may cause premature closure of the ductus arteriosus. Avoid use of NSAIDs, including celecoxib, in pregnant women starting at 30 weeks of gestation (third trimester) *[see Use in Specific Populations (8.1)]* .

5.13 Hematological Toxicity

Celecoxib

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with celecoxib has

any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

In controlled clinical trials the incidence of anemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with celecoxib should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs, including celecoxib, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs (e.g., aspirin), SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding *[see Drug Interactions (7)]* .

5.14 Masking of Inflammation and Fever

Celecoxib

The pharmacological activity of celecoxib in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.15 Laboratory Monitoring

Celecoxib

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a complete blood count (CBC) and a chemistry profile periodically *[see Warnings and Precautions (5.2, 5.3, 5.8)]*.

In controlled clinical trials, elevated blood urea nitrogen (BUN) occurred more frequently in patients receiving celecoxib compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.1)]*
- GI Bleeding, Ulceration and Perforation *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Hypertension [see Warnings and Precautions (5.4)]
- Hypotension *[see Warnings and Precautions (5.5)]*
- Increased Angina or Myocardial Infarction *[see Warnings and Precautions (5.6)]*
- Heart Failure and Edema *[see Warnings and Precautions (5.7)]*
- Renal Toxicity and Hyperkalemia *[see Warnings and Precautions (5.8)]*
- Anaphylactic Reactions *[see Warnings and Precautions (5.9)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.11)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Celecoxib Clinical Trials

Of the celecoxib-treated patients in the pre-marketing controlled clinical trials, approximately 4,250 were patients with osteoarthritis, approximately 2,100 were patients with rheumatoid arthritis, and

approximately 1,050 were patients with post-surgical pain. More than 8,500 patients received a total daily dose of celecoxib of 200 mg (100 mg twice daily or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients received celecoxib at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Pre-Marketing Controlled Arthritis Trials

The table below lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving celecoxib from 12 controlled studies conducted in patients with osteoarthritis or rheumatoid arthritis that included a placebo and/or a positive control group. Since these 12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Adverse Events Occurring in ≥ 2% of Celecoxib Patients from Pre-Marketing Controlled Arthritis Trials

	CBX N=4146	Placebo N=1864	NAP N=1366	DCF N=387	IBU N=345
Gastrointestinal					
Abdominal Pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral Edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-Accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central, Peripheral Nervous System					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper Respiratory Infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

CBX = Celecoxib 100 – 200 mg twice daily or 200 mg once daily;
NAP = Naproxen 500 mg twice daily;
DCF = Diclofenac 75 mg twice daily;
IBU = Ibuprofen 800 mg three times daily

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving celecoxib and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the celecoxib treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of celecoxib patients,

respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The following adverse reactions occurred in 0.1 - 1.9% of patients treated with celecoxib (100 - 200 mg twice daily or 200 mg once daily):

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, vomiting

Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

General: Hypersensitivity, allergic reaction, chest pain, cyst not otherwise specified (NOS), edema generalized, face edema, fatigue, fever, hot flushes, influenza- like symptoms, pain, peripheral pain

Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, paresthesia, vertigo

Hearing and vestibular: Deafness, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary: Hepatic enzyme increased [including serum glutamic oxaloacetic transaminase (SGOT) increased, serum glutamic pyruvic transaminase (SGPT) increased]

Metabolic and nutritional: BUN increased, creatine phosphokinase (CPK) increased, hypercholesterolemia, hyperglycemia, hypokalemia, non-protein nitrogen (NPN) increased, creatinine increased, alkaline phosphatase increased, weight increased

Musculoskeletal: Arthralgia, arthrosis, myalgia, synovitis, tendinitis

Platelets (bleeding or clotting): Ecchymosis, epistaxis, thrombocythemia

Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence

Hemic: Anemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia

Skin and appendages: Alopecia, dermatitis, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Application site disorders: Cellulitis, dermatitis contact

Urinary: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

The following serious adverse events (causality not evaluated) occurred in <0.1% of patients:

Cardiovascular: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis

Gastrointestinal: Intestinal obstruction, intestinal perforation, GI bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

General: Sepsis, sudden death

Liver and biliary: Cholelithiasis

Hemic and lymphatic: Thrombocytopenia

Nervous: Ataxia, suicide *[see Drug Interactions (7)]*

Renal: Acute renal failure

The Celecoxib Long-Term Arthritis Safety Study *[see Clinical Studies (14.3)]*

Hematological Events: The incidence of clinically significant decreases in hemoglobin (>2 g/dL) was lower in patients on celecoxib 400 mg twice daily (0.5%) compared to patients on either diclofenac 75 mg twice daily (1.3%) or ibuprofen 800 mg three times daily 1.9%. The lower incidence of events with celecoxib was maintained with or without ASA use *[see Clinical Pharmacology (12.2)]* .

Withdrawals/Serious Adverse Events: Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for celecoxib, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e., causing hospitalization or felt to be life-threatening or otherwise medically significant), regardless of causality, were not different across treatment groups (8%, 7%, and 8%, respectively).

Juvenile Rheumatoid Arthritis Study

In a 12-week, double-blind, active-controlled study, 242 juvenile rheumatoid arthritis patients 2 years to 17 years of age were treated with celecoxib or naproxen; 77 juvenile rheumatoid arthritis patients were treated with celecoxib 3 mg/kg twice daily, 82 patients were treated with celecoxib 6 mg/kg twice daily, and 83 patients were treated with naproxen 7.5 mg/kg twice daily. The most commonly occurring (≥5%) adverse events in celecoxib treated patients were headache, fever (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. The most commonly occurring (≥5%) adverse experiences for naproxen-treated patients were headache, nausea, vomiting, fever, upper abdominal pain, diarrhea, cough, abdominal pain, and dizziness. Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg twice daily had no observable deleterious effect on growth and development during the course of the 12 week double-blind study. There was no substantial difference in the number of clinical exacerbations of uveitis or systemic features of juvenile rheumatoid arthritis among treatment groups.

In a 12-week, open-label extension of the double-blind study described above, 202 juvenile rheumatoid arthritis patients were treated with celecoxib 6 mg/kg twice daily. The incidence of adverse events was similar to that observed during the double-blind study; no unexpected adverse events of clinical importance emerged.

Adverse Events Occurring in ≥5% of Juvenile Rheumatoid Arthritis Patients in Any Treatment Group, by System Organ Class (% of patients with events)

System Organ Class Preferred Term	All Doses Twice Daily		
	Celecoxib 3 mg/kg N=77	**Celecoxib 6 mg/kg N=82**	**Naproxen 7.5 mg/kg N=83**
Any Event	**64**	**70**	**72**
Eye Disorders	**5**	**5**	**5**
Gastrointestinal	**26**	**24**	**36**
Abdominal pain NOS	4	7	7
Abdominal pain upper	8	6	10
Vomiting NOS	3	6	11
Diarrhea NOS	5	4	8
Nausea	7	4	11
General	**13**	**11**	**18**
Pyrexia	8	9	11
Infection	**25**	**20**	**27**
Nasopharyngitis	5	6	5
Injury and Poisoning	**4**	**6**	**5**
Investigations *	**3**	**11**	**7**
Musculoskeletal	**8**	**10**	**17**

Arthralgia	3	7	4
Nervous System	**17**	**11**	**21**
Headache NOS	13	10	16
Dizziness (excl vertigo)	1	1	7
Respiratory	**8**	**15**	**15**
Cough	7	7	8
Skin & Subcutaneous	**10**	**7**	**18**

* Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased, Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS

Other Pre-Approval Studies

Adverse Events from Ankylosing Spondylitis Studies

A total of 378 patients were treated with celecoxib in placebo- and active-controlled ankylosing spondylitis studies. Doses up to 400 mg once daily were studied. The types of adverse events reported in the ankylosing spondylitis studies were similar to those reported in the osteoarthritis/rheumatoid arthritis studies.

Adverse Events from Analgesia and Dysmenorrhea Studies

Approximately 1,700 patients were treated with celecoxib in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medication. Doses up to 600 mg/day of celecoxib were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

The APC and PreSAP Trials

Adverse Reactions from Long-Term, Placebo-Controlled Polyp Prevention Studies

Exposure to celecoxib in the Adenoma Prevention with Celecoxib (APC) and Prevention of Spontaneous Adenomatous Polyps (PreSAP) trials was 400 to 800 mg daily for up to 3 years *[see Clinical Studies (14.3)]* . Some adverse reactions occurred in higher percentages of patients than in the arthritis pre-marketing trials (treatment durations up to 12 weeks; see Adverse Events from celecoxib pre-marketing controlled arthritis trials, above). The adverse reactions for which these differences in patients treated with celecoxib were greater as compared to the arthritis pre-marketing trials were as follows:

	Celecoxib (400 to 800 mg daily) N=2285	**Placebo N=1303**
Diarrhea	10.5%	7.0%
Gastroesophageal reflux disease	4.7%	3.1%
Nausea	6.8%	5.3%
Vomiting	3.2%	2.1%
Dyspnea	2.8%	1.6%
Hypertension	12.5%	9.8%
Nephrolithiasis	2.1%	0.8%

The following additional adverse reactions occurred in ≥0.1% and <1% of patients taking celecoxib, at an incidence greater than placebo in the long-term polyp prevention studies, and were either not reported during the controlled arthritis pre-marketing trials or occurred with greater frequency in the long-term, placebo-controlled polyp prevention studies:

Nervous system disorders: Cerebral infarction

Eye disorders: Vitreous floaters, conjunctival hemorrhage

Ear and labyrinth: Labyrinthitis

Cardiac disorders: Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

Vascular disorders: Deep vein thrombosis

Reproductive system and breast disorders: Ovarian cyst

Investigations: Blood potassium increased, blood sodium increased, blood testosterone decreased

Injury, poisoning and procedural complications: Epicondylitis, tendon rupture

Amlodipine Clinical Trials

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) at doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine because of adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most commonly reported side effects more frequent than placebo are reflected in the table below. The incidence (%) of side effects that occurred in a dose related manner are as follows:

	Amlodipine			**Placebo**
	2.5 mg N=275	**5 mg N=296**	**10 mg N=268**	**N=520**
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse reactions that were not clearly dose related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

	Amlodipine (%) (N=1730)	**Placebo (%) (N=1250)**
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

	Amlodipine		**Placebo**	
	Male=% (N=1218)	**Female=% (N=512)**	**Male=% (N=914)**	**Female=% (N=336)**

Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia, [1] back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps, [1] myalgia.

Psychiatric: sexual dysfunction (male [1] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea, [1] epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus, [1] rash, [1] rash erythematous, rash maculopapular.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, uric acid, BUN, or creatinine.

In patients with angiographically documented coronary artery disease [PREVENT study: 825 patients randomized to amlodipine (5-10 mg once daily) or placebo and followed for 3 years; CAMELOT study: 1318 patients randomized to amlodipine (5-10 mg once daily) or placebo in addition to standard care and followed for mean duration of 19 months], the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema.

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[1] These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of either celecoxib or amlodipine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Celecoxib

Cardiovascular:	Vasculitis, deep venous thrombosis
General:	Anaphylactoid reaction, angioedema
Liver and biliary:	Liver necrosis, hepatitis, jaundice, hepatic failure
Hemic and lymphatic:	Agranulocytosis, aplastic anemia, pancytopenia, leucopenia
Metabolic:	Hypoglycemia, hyponatremia
Nervous:	Aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage
Renal:	Interstitial nephritis

Amlodipine

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Postmarketing reporting has also revealed a possible association between extrapyramidal disorder and amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary artery disease, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

7 DRUG INTERACTIONS

Celecoxib

Clinically significant drug interactions with celecoxib are shown in the following table:

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of celecoxib and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of celecoxib with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding *[see Warnings and Precautions (5.13)]* .
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *[see Warnings and Precautions (5.2)]* . In two studies in healthy volunteers, and in patients with osteoarthritis and established heart disease respectively, celecoxib (200-400 mg daily) has

	demonstrated a lack of interference with the cardioprotective antiplatelet effect of aspirin (100-325 mg).
Intervention:	Concomitant use of celecoxib and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.13)]* . Celecoxib is not a substitute for low dose aspirin for CV protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of celecoxib and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of celecoxib and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function *[see Warnings and Precautions (5.8)]* . • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of celecoxib with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects *[see Warnings and Precautions (5.8)]* .
Digoxin	
Clinical Impact:	The concomitant use of celecoxib with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of celecoxib and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of celecoxib and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).

	Celecoxib has no effect on methotrexate pharmacokinetics.
Intervention:	During concomitant use of celecoxib and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of celecoxib and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of celecoxib and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy *[see Warnings and Precautions (5.2)]* .
Intervention:	The concomitant use of celecoxib with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of celecoxib and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of celecoxib and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
CYP2C9 Inhibitors or Inducers	
Clinical Impact:	Celecoxib metabolism is predominantly mediated via CYP2C9 in the liver. Coadministration of celecoxib with drugs that are known to inhibit CYP2C9 (e.g. fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g. rifampin) may lead to compromised efficacy of celecoxib.
Intervention:	Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers *[see Clinical Pharmacology (12.3)]* .
CYP2D6 Substrates	
Clinical Impact:	*In vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6 (e.g. atomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs.
Intervention:	Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2D6 substrates *[see Clinical Pharmacology (12.3)]* .
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with celecoxib may increase the risk of GI ulceration or bleeding.
Intervention:	Monitor patients with concomitant use of celecoxib with corticosteroids

Intervention:	for signs of bleeding *[see Warnings and Precautions (5.2)]* .

Amlodipine

Impact of Other Drugs on Amlodipine

CYP3A Inhibitors: Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment *[see Clinical Pharmacology (12.3)]* .

CYP3A Inducers: No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

Impact of Amlodipine on Other Drugs

Simvastatin: Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily *[see Clinical Pharmacology (12.3)]* .

Immunosuppressants: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate *[see Clinical Pharmacology (12.3)]* .

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including CONSENSI, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including CONSENSI, in pregnant women starting at 30 weeks of gestation (third trimester) *(see Clinical Considerations, Data)* . There is no published literature of CONSENSI in pregnant women. No animal reproductive toxicity studies have been conducted with the combination of celecoxib and amlodipine.

Celecoxib

The available published data and case reports did not identify a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Published literature reports that use of NSAIDs, including celecoxib, during the third trimesters of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimester of pregnancy are inconclusive. *(see Clinical Considerations, Data)* . In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 6 times the maximum recommended human dose of 200 mg twice daily. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternebrae fused and sternebrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 2 times the maximum recommended human dose (MRHD). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post-implantation loss, and decreased uterine decidualization *(see Data)* .

Amlodipine

The available data from post-marketing reports and a small study with Norvasc use in pregnant women with mild to moderate chronic hypertension did not identify a drug-associated risk of major birth

defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy *(see Clinical Considerations, Data)* . In animal reproduction studies, there was no evidence of adverse developmental effects when pregnant rats and rabbits were treated orally with amlodipine maleate during organogenesis at doses approximately 10 and 20-times the MRHD, respectively. However, in rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5 fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose *(see Data)* .

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Avoid use of NSAID's in pregnant women in the third trimester because NSAIDs, including celecoxib, can cause premature closure of the fetal ductus arteriosus *(see Data)* .

Labor or Delivery

There are no studies on the effects of CONSENSI during labor or delivery. In animal studies, NSAIDs, including celecoxib, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth *(see Data)* .

Data

Human Data

Celecoxib

Published literature has concluded that the use of NSAIDs during the third trimester of pregnancy may cause constriction of the patent ductus arteriosus and premature closure of the fetal ductus arteriosus.

Animal Data

Celecoxib

Celecoxib at oral doses ≥150 mg/kg/day (approximately 2 times the human exposure at 200 mg twice daily as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for rheumatoid arthritis) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses ≥50 mg/kg/day (approximately 6 times human exposure based on the AUC_{0-24} at 200 mg twice daily for rheumatoid arthritis). Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC_{0-24} at 200 mg twice daily).

Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits

were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the MRHD based on body surface area, respectively) during their respective periods of major organogenesis. However, for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

8.2 Lactation

Risk Summary

The available published literature report the individual components of CONSENSI (celecoxib, amlodipine) are present in human breast milk at low levels. Data from 3 published reports that included a total of 12 breastfeeding women calculated the average daily infant dose of celecoxib as 10-40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events with maternal use of celecoxib. Data from a published observational clinical lactation study reports that amlodipine is present at an estimated median relative infant dose of 4.2%, approximately 1.7 to 3.3% of the recommended dose for an average 6 year old (20 kg) *(see Data)* . No adverse effects of amlodipine were observed in the breastfed infants. There is no available information on the effects of celecoxib or amlodipine on milk production.

Data

Celecoxib

A clinical lactation study in six volunteers administered a single oral dose of 200 mg celecoxib [median maternal celecoxib dose of 3.3 mg/kg (range of 2.3-3.7)] at 6.5 to 15 months postpartum (mean 11 months) and in the final stage of weaning. showed that the median total amount of celecoxib present in milk was 0.011 mg (range 0.004-0.042) or 0.04% (range 0.01-0.15) of the maternal single dose (weight adjusted). The estimated daily infant dose was 0.013 mg/kg/day (range 0.011-0.021), which is 0.13 to 0.33% of the clinically used celecoxib dose for pediatric patients.

A clinical lactation study in three breastfeeding mothers who had been taking 200 mg celecoxib orally once daily for many weeks and who were at steady state (group 1) and two breastfeeding mothers administered a single 200-mg oral dose of celecoxib (group 2) averaging 12 months post-partum (range 3-22 months). The mean average concentration of celecoxib in milk during the 8-hour interval following administration of celecoxib for all five mothers was 66 µg/L (95% CI: 41 89). The estimated mean absolute infant dose was 9.8 µg/kg/day (95% CI: 6.2-13.4), which is 0.1 to 0.25% of the dose clinically used for pediatric patients. Comparison of this to the weight-normalized maternal dose yields an estimated mean relative infant dose of 0.30% (95% CI: 0.19-0.39)

Amlodipine

An observational clinical lactation study of 31 lactating women who were receiving amlodipine within 3 weeks after delivery for pregnancy-induced hypertension showed a median concentration of amlodipine in milk 24 hours after a mean maternal oral dose of approximately 6 mg/day for 7 to 9 days of 11.5 ng/mL (interquartile range of 9.84-18.0 ng/mL). The mean maternal body weight-adjusted dose was 0.0987 ± 0.0366 mg/kg. The median plasma concentration of amlodipine was 15.5 (interquartile range of 12.0-22.8 ng/mL). The median amlodipine concentration ratio of milk to plasma was 0.85 (interquartile range of 0.743-1.08). The median estimated infant daily dose was 4.17 µg/kg/day (interquartile range of 3.05 to 6.32 µg/kg/day), approximately 1.7 to 3.3% of the recommended dose for an average 6-year old (20 kg). The median relative infant daily dose was 4.18% (interquartile range of 3.12%-7.25%).

8.3 Females and Males of Reproductive Potential

Celecoxib

Infertility

Females:

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including celecoxib, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Consider withdrawal of NSAIDs, including celecoxib, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

CONSENSI

Safety and effectiveness of CONSENSI in pediatric patients have not been established.

8.5 Geriatric Use

Combination of Celecoxib and Amlodipine

In the short-term controlled clinical trial of the combination of celecoxib and amlodipine in patients with newly diagnosed hypertension whom required pharmacological therapy to control their hypertension (Study No. KIT-302-03-01), 24.5% of patients treated with the combination were ≥65 years of age. No examinations of age subgroups were planned by protocol or performed, because of the limited sample size.

Celecoxib

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious CV, GI, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.8, 5.15)]* . Because CONSENSI is not available in lower strengths of celecoxib, CONSENSI is not recommended in patients that require dosages other than 200 mg of celecoxib once daily.

Of the total number of patients who received celecoxib in pre-approval clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the glomerular filtration rate (GFR), BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients *[see Warnings and Precautions (5.4, 5.8)]* .

Amlodipine

Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40– 60%, and a lower initial dose may be required *[see Dosage and Administration (2.1)]* .

8.6 Hepatic Impairment

Celecoxib

The daily recommended dose of celecoxib in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. Because CONSENSI is not available in lower strengths of celecoxib, CONSENSI is not recommended in patients with moderate hepatic impairment. Additionally, the use of CONSENSI in patients with severe hepatic impairment is not recommended *[see Clinical Pharmacology (12.3)]* .

8.7 Renal Insufficiency

Celecoxib

CONSENSI is not recommended in patients with severe renal insufficiency *[see Warnings and Precautions (5.8) and Clinical Pharmacology (12.3)]* .

8.8 Poor Metabolizers of CYP2C9 Substrates

In patients who are known or suspected to be poor CYP2C9 metabolizers (i.e., CYP2C9*3/*3), based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin) administer celecoxib starting with half the lowest recommended dose. Because CONSENSI is not available in lower strengths of celecoxib, CONSENSI is not recommended in patients who are known or suspected to be poor CYP2C9 metabolizers *[see Clinical Pharmacology (12.5)]* .

10 OVERDOSAGE

Celecoxib

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. GI bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.8)]* .

No overdoses of celecoxib were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose.

Manage patients by symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as

phenylephrine) with attention to circulating volume and urine output.

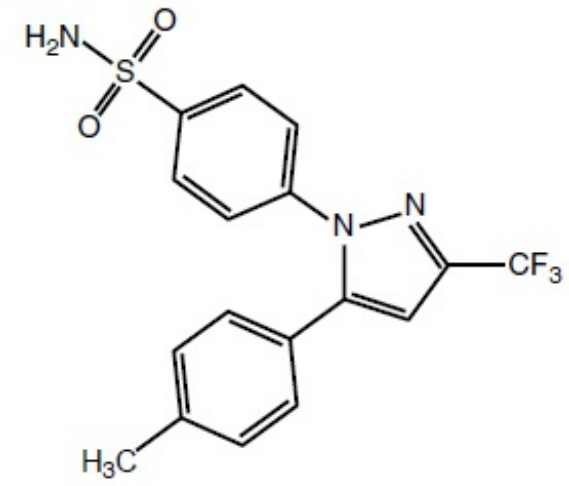
As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

CONSENSI (amlodipine and celecoxib) tablet is an NSAID and long-acting calcium channel blocker for oral administration. Each tablet contains amlodipine besylate and celecoxib 3.47 mg/200 mg, 6.93 mg/200 mg, and 13.87 mg/200 mg and is equivalent to 2.5 mg/200 mg, 5 mg/200 mg, and 10 mg/200 mg amlodipine/celecoxib respectively.

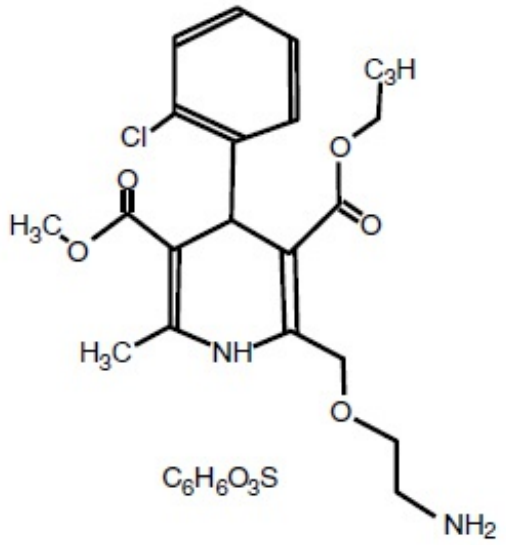
Celecoxib is chemically designated as 4-[5-(4-methylphenyl)- 3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula is $C_{17}H_{14}F_3N_3O_2S$, and the molecular weight is 381.38; the chemical structure is as follows:



Celecoxib is a white to off-white powder with a pKa of 11.1 (sulfonamide moiety). Celecoxib is hydrophobic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH range.

Amlodipine besylate is chemically designated as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.

The molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and the molecular weight is 567.1; the chemical structure is as follows:



Amlodipine besylate is a white crystalline powder. It is slightly soluble in water and sparingly soluble in ethanol.

The inactive ingredients in CONSENSI include: mannitol DC 200, croscarmellose sodium, povidone K-30, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Combination of Celecoxib and Amlodipine

The mechanism of action of CONSENSI is similar to the mechanism of action for its individual components, celecoxib and amlodipine, as described below.

Celecoxib

Celecoxib has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2.

Celecoxib is a potent inhibitor of prostaglandin synthesis *in vitro*. Celecoxib concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Amlodipine

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

12.2 Pharmacodynamics

Combination of Celecoxib and Amlodipine

The blood pressure lowering effect of the combination of celecoxib and amlodipine is similar to that seen with amlodipine alone.

Celecoxib

Platelets: In clinical trials using normal volunteers, celecoxib at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time. Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of celecoxib on platelets that may contribute to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of celecoxib.

Fluid Retention: Inhibition of prostaglandin E2 (PGE2) synthesis may lead to sodium and water retention through increased reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron. In the collecting ducts, PGE2 appears to inhibit water reabsorption by counteracting the action of antidiuretic hormone.

Amlodipine

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105–114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in GFR and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either

hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

12.3 Pharmacokinetics

CONSENSI

Following oral administration of CONSENSI tablets (amlodipine/celecoxib) 2.5 mg/200 mg or 10 mg/200 mg peak concentrations were achieved within 2 hours for celecoxib and 8 hours for amlodipine. The rate and extent of absorption of celecoxib and amlodipine were similar when CONSENSI was taken together under fed and fasting conditions.

Celecoxib

Celecoxib exhibits dose-proportional increase in exposure after oral administration up to 200 mg twice daily and less than proportional increase at higher doses. It has extensive distribution and high protein binding. It is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours.

Absorption

Peak plasma levels of celecoxib occur approximately 3 hours after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) and AUC are roughly dose-proportional up to 200 mg twice daily; at higher doses, there are less than proportional increases in C_{max} and AUC presumably due to the low solubility of the drug in aqueous media. Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or before Day 5. The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in the table below.

Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects *

Mean (%CV) Pharmacokinetic Parameter Values				
C_{max}, ng/mL	**T_{max}, hr**	**Effective t½, hr**	**Vss/F, L**	**CL/F, L/hr**
705 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)

* Subjects under fasting conditions (n=36, 19-52 yrs.)

Coadministration of celecoxib with an aluminum- and magnesium-containing antacids resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. Celecoxib, at doses up to 200 mg twice daily, can be administered without regard to timing of meals. Higher doses (400 mg twice daily) should be administered with food to improve absorption.

In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in C_{max}, T_{max}, or t½ after administration of capsule contents on applesauce.

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Elimination

Metabolism: Celecoxib metabolism is primarily mediated via CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX 1 or COX-2 inhibitors.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with little (< 3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making t½ determinations more variable. The effective half- life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Specific Populations

Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose *[see Dosage and Administration (2.1) and Use in Specific Populations (8.5)]* .

Race

Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic Impairment

A pharmacokinetic study in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, the daily recommended dose of celecoxib should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B) hepatic impairment. Because CONSENSI is not available in lower strengths of celecoxib, CONSENSI is not recommended in patients with moderate hepatic impairment. Patients with severe hepatic impairment (Child- Pugh Class C) have not been studied. The use of CONSENSI in patients with severe hepatic impairment is not recommended *[see Use in Specific Populations (8.6)]* .

Renal Impairment

In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CONSENSI is not recommended in patients with severe renal insufficiency *[see Warnings and Precautions (5.8)]* .

Drug Interaction Studies

In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4.

In vivo studies have shown the following:

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. For clinically significant drug interactions of NSAIDs with aspirin, *[see Drug Interactions (7)]* .

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg twice daily with celecoxib 200 mg twice daily as compared to subjects receiving lithium alone *[see Drug Interactions (7)]* .

Fluconazole: Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole *[see Drug Interactions (7)]* .

Other Drugs: The effects of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide, ketoconazole, methotrexate *[see Drug Interactions (7)]* , phenytoin, and tolbutamide have been studied *in vivo* and clinically important interactions have not been found.

Amlodipine

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30– 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40– 60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Drug Interactions

In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Impact of other drugs on amlodipine

Co-administered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent *[see Drug Interactions (7)]* .

Impact of amlodipine on other drugs

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone *[see Drug Interactions (7)]* .

Cyclosporine: A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine *[see Drug Interactions (7)]* .

Tacrolimus: A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed a 2.5-to 4-fold increase in tacrolimus exposure when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, a 3-fold increase in plasma exposure to tacrolimus in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension resulting in

reduction of tacrolimus dose has been reported. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs *[see Drug Interactions (7)]* .

12.5 Pharmacogenomics

Celecoxib

CYP2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*2 and CYP2C9*3 polymorphisms. Limited data from 4 published reports that included a total of 8 subjects with the homozygous CYP2C9*3/*3 genotype showed celecoxib systemic levels that were 3- to 7-fold higher in these subjects compared to subjects with CYP2C9*1/*1 or *I/*3 genotypes. The pharmacokinetics of celecoxib have not been evaluated in subjects with other CYP2C9 polymorphisms, such as *2, *5, *6, *9 and *11. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3% to 1.0% in various ethnic groups *[see Use in Specific Populations (8.8)]* .

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Combination of Celecoxib and Amlodipine

No carcinogenicity, mutagenicity or fertility studies have been conducted with the combination of celecoxib and amlodipine. However, these studies have been conducted for celecoxib and amlodipine alone.

Celecoxib

Carcinogenesis

Celecoxib was not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2-to 4-times the human exposure as measured by the AUC_{0-24} at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC_{0-24} at 200 mg twice daily) for two years.

Mutagenesis

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in vivo* micronucleus test in rat bone marrow.

Impairment of Fertility

Celecoxib had no effect on male or female fertility or male reproductive function in rats at oral doses up to 600 mg/kg/day (approximately 11-times human exposure at 200 mg twice daily based on the AUC_{0-24}). At ≥50 mg/kg/day (approximately 6-times human exposure based on the AUC_{0-24} at 200 mg twice daily) there was increased preimplantation loss.

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day (based on patient weight of 50 kg). For the rat, the highest dose was, on a mg/m^2 basis, about twice the maximum recommended human dose (based on patient weight of 50 kg).

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day [8 times the maximum recommended human dose (based on patient weight of 50 kg) of 10 mg/day on a mg/m2 basis].

13.2 Animal Toxicology

Celecoxib

An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.

14 CLINICAL STUDIES

14.1 Combination of Celecoxib and Amlodipine

During the development of this fixed-dose combination product, the central focus was to assess pharmacodynamic interactions related to blood pressure effect between celecoxib and amlodipine. There are no studies of the combination of celecoxib and amlodipine demonstrating reductions in the signs and symptoms of osteoarthritis, but one of the components, celecoxib, has demonstrated such effects. There are also no long-term studies to evaluate CV safety for the combination of celecoxib and amlodipine.

The combination of celecoxib and amlodipine was studied in a randomized, double-blind, placebo- and active-controlled study in 152 patients with newly diagnosed hypertension who required pharmacological therapy to control their hypertension. A total of 63% of patients were male, 25% were 65 years or older, 95% were white, 2% were black, and 3% were Asian. The trial used commercial celecoxib capsules and amlodipine tablets that were individually over encapsulated and then taken together or with matching placebos. The patients were randomized 1.5:1.5:1:1 to one of four treatment arms: 200 mg celecoxib + 10 mg amlodipine (celecoxib + amlodipine arm), 0 mg celecoxib + 10 mg amlodipine (amlodipine arm), 200 mg celecoxib + 0 mg amlodipine (celecoxib arm), and 0 mg celecoxib and 0 mg amlodipine (placebo arm). All drugs were administered once a day for 14 days. The trial results demonstrated that the combination of celecoxib and amlodipine provided similar blood pressure reduction to an equal dose of amlodipine.

Amlodipine

Adult Patients: The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

14.2 Osteoarthritis

Combination of Celecoxib and Amlodipine

There are no trials of the combination of celecoxib and amlodipine demonstrating reductions in the signs and symptoms of osteoarthritis, but one of the components, celecoxib, has demonstrated such effects.

Celecoxib

Celecoxib has demonstrated significant reduction in joint pain compared to placebo. Celecoxib was evaluated for treatment of the signs and the symptoms of osteoarthritis of the knee and hip in placebo- and active-controlled clinical trials of up to 12 weeks. In patients with osteoarthritis, treatment with celecoxib 100 mg twice daily or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in osteoarthritis. In three 12-week studies of pain accompanying osteoarthritis flare, celecoxib doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg twice daily or 200 mg twice daily the effectiveness of celecoxib was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200 mg once daily.

14.3 Special Studies

Celecoxib

Cardiovascular Outcomes Trial: Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen(PRECISION; NCT00346216)

Design

The PRECISION trial was a double-blind randomized controlled trial of cardiovascular safety in osteoarthritis and rheumatoid arthritis patients with or at high risk for cardiovascular disease comparing celecoxib with naproxen and ibuprofen. Patients were randomized to a starting dose of 100 mg twice daily of celecoxib, 600 mg three times daily of ibuprofen, or 375 mg twice daily of naproxen, with the option of escalating the dose as needed for pain management. Based on labeled doses, osteoarthritis patients randomized to celecoxib could not dose escalate.

The primary endpoint, the APTC composite, was an independently adjudicated composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke with 80% power to evaluate non inferiority. All patients were prescribed open-label esomeprazole (20-40 mg) for gastroprotection. Treatment randomization was stratified by baseline low-dose aspirin use.

Additionally, there was a 4-month substudy assessing the effects of the three drugs on blood pressure as measured by ambulatory monitoring.

Results

Among subjects with osteoarthritis, only 0.2% (17/7259) escalated celecoxib to the 200 mg twice daily dose, whereas 54.7% (3946/7208) escalated ibuprofen to 800 mg three times daily, and 54.8% (3937/7178) escalated naproxen to the 500 mg twice daily dose. Among subjects with rheumatoid arthritis, 55.7% (453/813) escalated celecoxib to the 200 mg twice daily dose, 56.5% (470/832) escalated ibuprofen to 800 mg three times daily, and 54.6% (432/791) escalated naproxen to the 500 mg twice daily dose; however, the rheumatoid arthritis population accounted for only 10% of the trial population.

Because relatively few celecoxib patients overall (5.8% [470/8072]) dose-escalated to 200 mg twice daily, the results of the PRECISION trial are not suitable for determining the relative CV safety of celecoxib at 200 mg twice daily compared to ibuprofen and naproxen at the doses taken.

Primary Endpoint

The trial had two prespecified analysis populations:

- Intent-to-treat population (ITT): Comprised of all randomized subjects followed for a maximum of 30 months
- Modified intent-to-treat population (mITT): Comprised of all randomized subjects who received at least one dose of study medication and had at least one post-baseline visit followed until the earlier of treatment discontinuation plus 30 days, or 43 months

Celecoxib, at the 100 mg twice daily dose, as compared with either naproxen or ibuprofen at the doses taken, met all four prespecified non-inferiority criteria ($p < 0.001$ for non-inferiority in both comparisons) for the APTC endpoint, a composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction, and non-fatal stroke. Non-inferiority was prespecified as a hazard ratio (HR) of ≤1.12 in both ITT and mITT analyses, and upper 95% confidence interval (CI) of ≤1.33 for ITT analysis and ≤1.40 for mITT analysis.

Primary Analysis of the Adjudicated APTC Composite Endpoint

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib	**Ibuprofen**	**Naproxen**
N	8,072	8,040	7,969
Subjects with Events	188 (2.3%)	218 (2.7%)	201 (2.5%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.93 (0.76, 1.13)	0.86 (0.70, 1.04)	1.08 (0.89, 1.31)
Modified Intent-To-Treat Analysis (mITT, on treatment plus 30 days, through month 43)			
	Celecoxib	**Ibuprofen**	**Naproxen**
N	8,030	7,990	7,933
Subjects with Events	134 (1.7%)	155 (1.9%)	144 (1.8%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.90 (0.72, 1.14)	0.81 (0.64, 1.02)	1.12 (0.89, 1.40)

Summary of the Adjudicated APTC Components *

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib	Ibuprofen	Naproxen
N	8,072	8,040	7,969
CV Death	68 (0.8%)	80 (1.0%)	86 (1.1%)
Non-Fatal Myocardial Infarction	76 (0.9%)	92 (1.1%)	66 (0.8%)
Non-Fatal Stroke	51 (0.6%)	53 (0.7%)	57 (0.7%)
Modified Intent-To-Treat Analysis (mITT, on treatment plus 30 days, through month 43)			
	Celecoxib	Ibuprofen	Naproxen
N	8,030	7,990	7,933
CV Death	35 (0.4%)	51 (0.6%)	49 (0.6%)
Non-Fatal Myocardial Infarction	58 (0.7%)	76 (1.0%)	53 (0.7%)
Non-Fatal Stroke	43 (0.5%)	32 (0.4%)	45 (0.6%)

* A patient may have experienced more than one component; therefore, the sum of the components is larger than the number of patients who experienced the composite outcome

In the ITT analysis population through 30 months, all-cause mortality was 1.6% in the celecoxib group, 1.8% in the ibuprofen group, and 2.0% in the naproxen group.

Ambulatory Blood Pressure Monitoring (ABPM) Substudy

In the PRECISION-ABPM substudy, among the total of 444 analyzable patients at Month 4, celecoxib dosed at 100 mg twice daily decreased mean 24-hour systolic blood pressure (SBP) by 0.3 mmHg, whereas ibuprofen and naproxen at the doses taken increased mean 24-hour SBP by 3.7 and 1.6 mmHg, respectively. These changes resulted in a statistically significant and clinically meaningful difference of 3.9 mmHg (p=0.0009) between celecoxib and ibuprofen and a non statistically significant difference of 1.8 (p=0.119) mmHg between celecoxib and naproxen.

Adenomatous Polyp Prevention Studies (NCT00005094 and NCT00141193)

Cardiovascular safety was evaluated in two randomized, double-blind, placebo-controlled, three year studies involving patients with Sporadic Adenomatous Polyps treated with celecoxib: the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint (adjudicated) of CV death, myocardial infarction, or stroke with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated):

- In the APC trial, the hazard ratios compared to placebo for a composite endpoint (adjudicated) of CV death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) with placebo treatment. The increases in both celecoxib dose groups versus placebo-treated patients were mainly due to an increased incidence of myocardial infarction.
- In the PreSAP trial, the hazard ratio for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively.

Clinical trials of other COX-2 selective and non-selective NSAIDs of up to three-years duration have shown an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal. As a result, all NSAIDs are considered potentially associated with this risk.

Celecoxib Long-Term Arthritis Safety Study (CLASS)

This was a prospective, long-term, safety outcome study conducted post-marketing in approximately 5,800 osteoarthritis patients and 2,200 rheumatoid arthritis patients. Patients received celecoxib 400 mg twice daily (4-fold and 2-fold the recommended osteoarthritis and rheumatoid arthritis doses, respectively), ibuprofen 800 mg three times daily or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for celecoxib (n = 3,987) and diclofenac (n = 1,996) were 9 months while ibuprofen (n = 1,985) was 6 months. The primary endpoint of this outcome study was the incidence of complicated ulcers (GI bleeding, perforation or obstruction). Patients were allowed to take concomitant low-dose (≤ 325 mg/day) ASA for CV prophylaxis (ASA subgroups: celecoxib, n = 882; diclofenac, n = 445; ibuprofen, n = 412). Differences in the incidence of complicated ulcers between celecoxib and the combined group of ibuprofen and diclofenac were not statistically significant.

Patients on celecoxib and concomitant low-dose ASA (N=882) experienced 4-fold higher rates of complicated ulcers compared to those not on ASA (N=3105). The Kaplan-Meier rate for complicated ulcers at 9 months was 1.12% versus 0.32% for those on low-dose ASA and those not on ASA, respectively *[see Warnings and Precautions (5.4)]* .

The estimated cumulative rates at 9 months of complicated and symptomatic ulcers for patients treated with celecoxib 400 mg twice daily are described in the table below. The table also displays results for

patients less than or greater than 65 years of age. The difference in rates between celecoxib alone and celecoxib with ASA groups may be due to the higher risk for GI events in ASA users.

Complicated and Symptomatic Ulcer Rates in Patients Taking Celecoxib 400 mg Twice Daily (Kaplan- Meier Rates at 9 months [%]) Based on Risk Factors

All Patients	
Celecoxib alone (n=3105)	0.78
Celecoxib with ASA (n=882)	2.19
Patients <65 Years	
Celecoxib alone (n=2025)	0.47
Celecoxib with ASA (n=403)	1.26
Patients ≥ 65 Years	
Celecoxib alone (n=1080)	1.40
Celecoxib with ASA (n=479)	3.06

In a small number of patients with a history of ulcer disease, the complicated and symptomatic ulcer rates in patients taking celecoxib alone or celecoxib with ASA were, respectively, 2.56% (n=243) and 6.85% (n=91) at 48 weeks. These results are to be expected in patients with a prior history of ulcer disease *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]* .

Cardiovascular safety outcomes were also evaluated in the CLASS trial. Kaplan-Meier cumulative rates for investigator-reported serious CV thromboembolic adverse events (including myocardial infarction, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic cerebrovascular accidents) demonstrated no differences between the celecoxib, diclofenac, or ibuprofen treatment groups. The cumulative rates in all patients at nine months for celecoxib, diclofenac, and ibuprofen were 1.2%, 1.4%, and 1.1%, respectively. The cumulative rates in non ASA users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in non-ASA users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased the risk to a similar degree. In the CLASS study, the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on celecoxib 400 mg twice daily (4-fold and 2-fold the recommended osteoarthritis and rheumatoid arthritis doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.9% and 4.7%, respectively. The rates of hypertension from the CLASS trial in the celecoxib, ibuprofen and diclofenac-treated patients were 2.4%, 4.2% and 2.5%, respectively.

Endoscopic Studies

The correlation between findings of short-term endoscopic studies with celecoxib and the relative incidence of clinically significant serious upper GI events with long-term use has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving celecoxib in controlled and open-labeled trials *[see Warnings and Precautions (5.4) and Clinical Studies (14.3)]* .

A randomized, double-blind study in 430 rheumatoid arthritis patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking celecoxib 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily. However, celecoxib was not statistically different than diclofenac for clinically relevant GI outcomes in the CLASS trial *[see Clinical Studies (14.3)]* .

The incidence of endoscopic ulcers was studied in two 12-week, placebo-controlled studies in 2157 osteoarthritis and rheumatoid arthritis patients in whom baseline endoscopies revealed no ulcers. There was no dose relationship for the incidence of gastroduodenal ulcers and the dose of celecoxib (50 mg to 400 mg twice daily). The incidence for naproxen 500 mg twice daily was 16.2 and 17.6% in the two

studies, for placebo was 2.0 and 2.3%, and for all doses of celecoxib the incidence ranged between 2.7%-5.9%. There have been no large, clinical outcome studies to compare clinically relevant GI outcomes with celecoxib and naproxen.

In the endoscopic studies, approximately 11% of patients were taking aspirin (≤ 325 mg/day). In the celecoxib groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

16 HOW SUPPLIED/STORAGE AND HANDLING

CONSENSI tablets are white and biconvex, non-coated, non-scored, with the tablet strength debossed on one side, available as follows:

Amlodipine	Celecoxib	Shape	NDC	
			Bottle of 30 tablets	Bottle of 500 tablets
2.5 mg	200 mg	Elongated oval	69101- **502**-30	69101- **502**-50
5 mg	200 mg	Caplet	69101- **505**-30	69101- **505**-50
10 mg	200 mg	Round	69101- **510**-30	69101- **510**-50

Storage

Store at room temperature 20°C to 25°C (68°F to 77°F); [see USP Controlled Room Temperature]. Dispense in tight, light-resistant containers (USP).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with CONSENSI and periodically during therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately *[see Warnings and Precautions (5.1)]* .

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding *[see Warnings and Precautions (5.2)]* .

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop CONSENSI and seek immediate medical therapy *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6)]* .

Hypotension

Instruct patients to return to their healthcare provider if symptoms of hypotension (e.g., lethargy, light headedness, or syncope) develop *[see Warnings and Precautions (5.5)]*.

Increased Angina or Myocardial Infarction

Warn patients that worsening of their angina or myocardial infarction can develop after starting CONSENSI or switching to a higher strength amlodipine formulation of CONSENSI, particularly in patients with severe obstructive coronary artery disease *[see Warnings and Precautions (5.6)]* .

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *[see Warnings and Precautions (5.7)]* .

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur *[see Contraindications (4) and Warnings and Precautions (5.9)]* .

Serious Skin Reactions

Advise patients to stop CONSENSI immediately if they develop any type of rash and to contact their healthcare provider as soon as possible *[see Warnings and Precautions (5.11)]* .

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including CONSENSI, may be associated with a reversible delay in ovulation *[see Use in Specific Populations (8.3)]* .

Fetal Toxicity

Advise pregnant women to avoid use of CONSENSI and other NSAIDs starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus. Advise females of reproductive potential to contact their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.1)]* .

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of CONSENSI with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of GI toxicity, and little or no increase in efficacy *[see Warnings and Precautions (5.2) and Drug Interactions (7)]* . Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with CONSENSI until they talk to their healthcare provider *[see Drug Interactions (7)]* .

Discontinuation of CONSENSI

Inform patients not to discontinue CONSENSI without discussing with their healthcare provider because an alternative blood pressure lowering drug should be started to control blood pressure *[see Dosage and Administration (2.2)]* .

Distributed by
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Hot Springs, AR 71913, USA

Revised: 05/2020

Medication Guide
CONSENSI ® (con-sen-see)
(amlodipine and celecoxib)
tablets

What is the most important information I should know about CONSENSI?

CONSENSI contains celecoxib, a nonsteroidal anti-inflammatory drug (NSAID), and amlodipine, a calcium channel blocker (CCB). NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

Do not take CONSENSI right before or after a heart surgery called a "coronary artery bypass graft" (CABG).

Avoid taking CONSENSI after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach, and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called "corticosteroids", "antiplatelet drugs", "anticoagulants", "selective serotonin reuptake inhibitors (SSRIs)", or "serotonin norepinephrine reuptake inhibitors (SNRIs)"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

You should not take other medicines that contain NSAIDs or salicylates during treatment with CONSENSI because of increased risk of stomach problems. Taking other medicines that contain NSAIDs or salicylates during treatment with CONSENSI will not provide increased relief of symptoms of osteoarthritis.

CONSENSI should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What is CONSENSI?

CONSENSI is a prescription medicine used in adults who need treatment:

- with amlodipine for high blood pressure (hypertension), to lower blood pressure, **and**
- with celecoxib for the management of the signs and symptoms of osteoarthritis.

It is not known if CONSENSI is safe and effective in children.

Who should not take CONSENSI?

Do not take CONSENSI:

- if you are allergic to amlodipine, celecoxib or any of the inactive ingredients in CONSENSI. See the end of this Medication Guide for a complete list of ingredients in CONSENSI.
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.
- if you have had an allergic reaction to sulfonamides.

Before taking CONSENSI, tell your healthcare provider about all your medical conditions, including if you:

- have heart problems.
- have liver or kidney problems.
- have asthma.
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking CONSENSI during pregnancy. **You should not take CONSENSI after 29 weeks of pregnancy.**
- are breastfeeding or plan to breastfeed. CONSENSI can pass into your breast milk. It is not known if CONSENSI will harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take CONSENSI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements. CONSENSI and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

How should I take CONSENSI?

- Take CONSENSI exactly as your healthcare provider tells you to.
- Take 1 CONSENSI tablet orally each day.
- **If your pain stops, do not stop taking CONSENSI until your healthcare provider prescribes a different medicine to treat your blood pressure.** Your healthcare provider will monitor your blood pressure when changing to the new medicine.
- **If you take too much CONSENSI, call your healthcare provider or get medical help right away.**

What are the possible side effects of CONSENSI?

CONSENSI can cause serious side effects, including:

See " What is the most important information I should know about CONSENSI?".

- liver problems, including liver failure
- worsening chest pain (angina) or heart attack, particularly in people with severe obstructive coronary artery disease
- heart failure
- swelling of your arms, legs, hands and feet (peripheral edema) is common with CONSENSI but can sometimes be serious.
- kidney problems, including kidney failure
- increased potassium levels (hyperkalemia)
- life-threatening allergic reactions
- life-threatening skin reactions
- low red blood cells (anemia)

Your healthcare provider will monitor your blood pressure and do blood tests to check you for side effects during treatment with CONSENSI.

CONSENSI may cause fertility problems in females that is reversible when treatment with CONSENSI is stopped. Talk to your healthcare provider if this is a concern for you.

The most common side effects of CONSENSI include:

- swelling of the arms, legs, hands, and feet
- joint swelling
- dizziness
- stomach pain
- diarrhea
- headache
- frequent urination
- hot or warm feeling in your face (flushing)
- gas
- tiredness

- diarrhea
- heartburn
- extreme sleepiness

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking CONSENSI and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- your skin or eyes look yellow
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

These are not all the possible side effects of CONSENSI.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CONSENSI?

- Store CONSENSI at room temperature between 68° and 77°F (20°C to 25°C).

Keep CONSENSI and all medicines out of the reach of children.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of CONSENSI

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CONSENSI for a condition for which it was not prescribed. Do not give CONSENSI to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information about CONSENSI ®, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about CONSENSI that is written for health professionals.

What are the ingredients in CONSENSI?

Active ingredients: amlodipine and celecoxib

Inactive ingredients: mannitol DC 200, croscarmellose sodium, povidone K-30, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

Manufactured by: Dexcel Pharma Technologies, Ltd., Yokneam, Israel

Distributed by: Burke Therapeutics, LLC., Hot Springs, AR 71913

For more information, go to www.consensi.com or call 1-888-275-1264

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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PRINCIPAL DISPLAY PANEL - 2.5 mg / 200 mg Tablet Bottle Label

NDC 69101-502-50

CONSENSI ®
(amlodipine and celecoxib)

2.5 mg / 200 mg*

Rx only

Dispense the enclosed Medication
Guide to each patient.

500 Tablets

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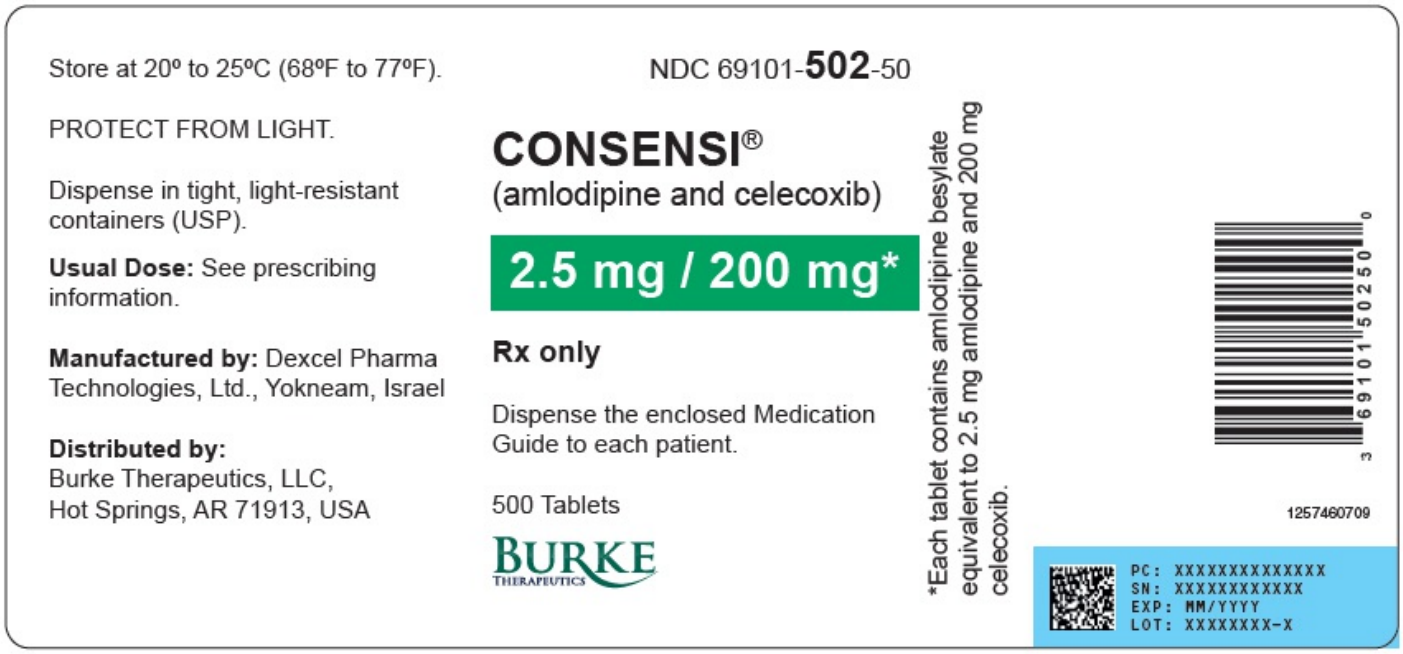


PRINCIPAL DISPLAY PANEL - 5 mg / 200 mg Tablet Bottle Label

NDC 69101-505-50

CONSENSI ®
(amlodipine and celecoxib)

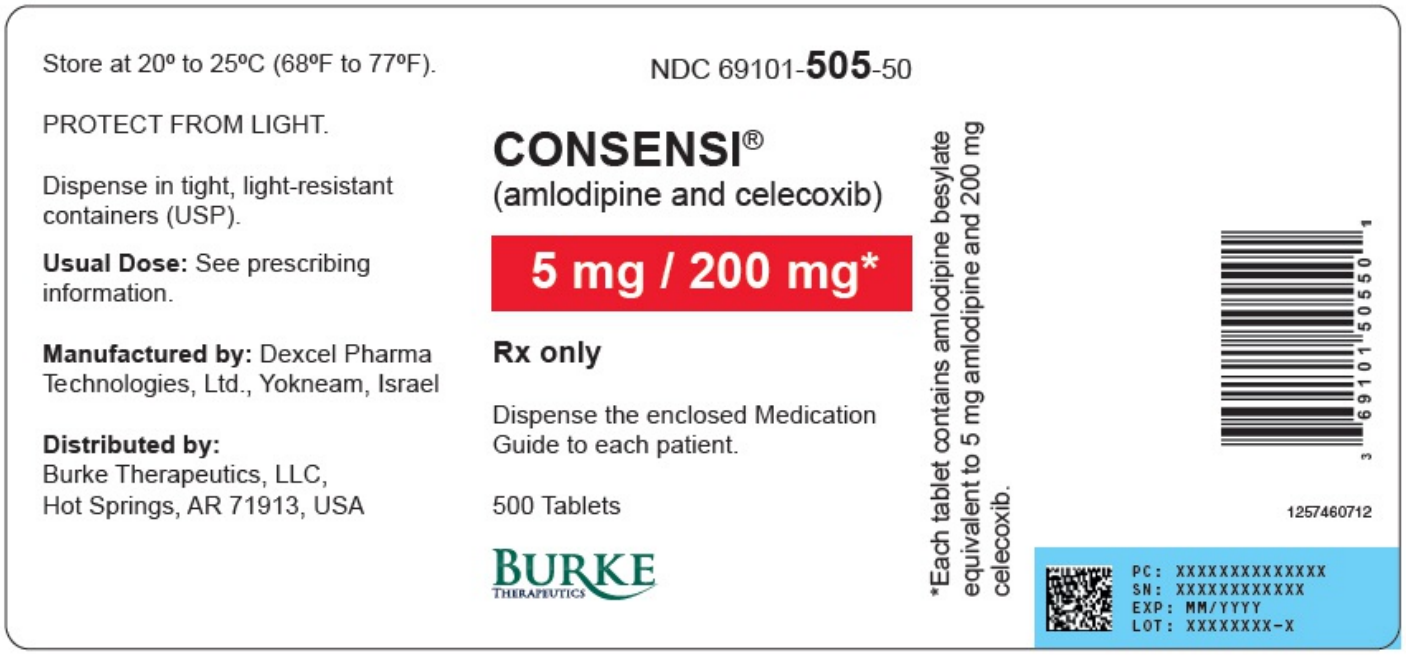
5 mg / 200 mg*

Rx only

Dispense the enclosed Medication
Guide to each patient.

500 Tablets

BURKE
THERAPEUTICS



PRINCIPAL DISPLAY PANEL - 10 mg / 200 mg Tablet Bottle Label

NDC 69101-510-50

CONSENSI ®
(amlodipine and celecoxib)

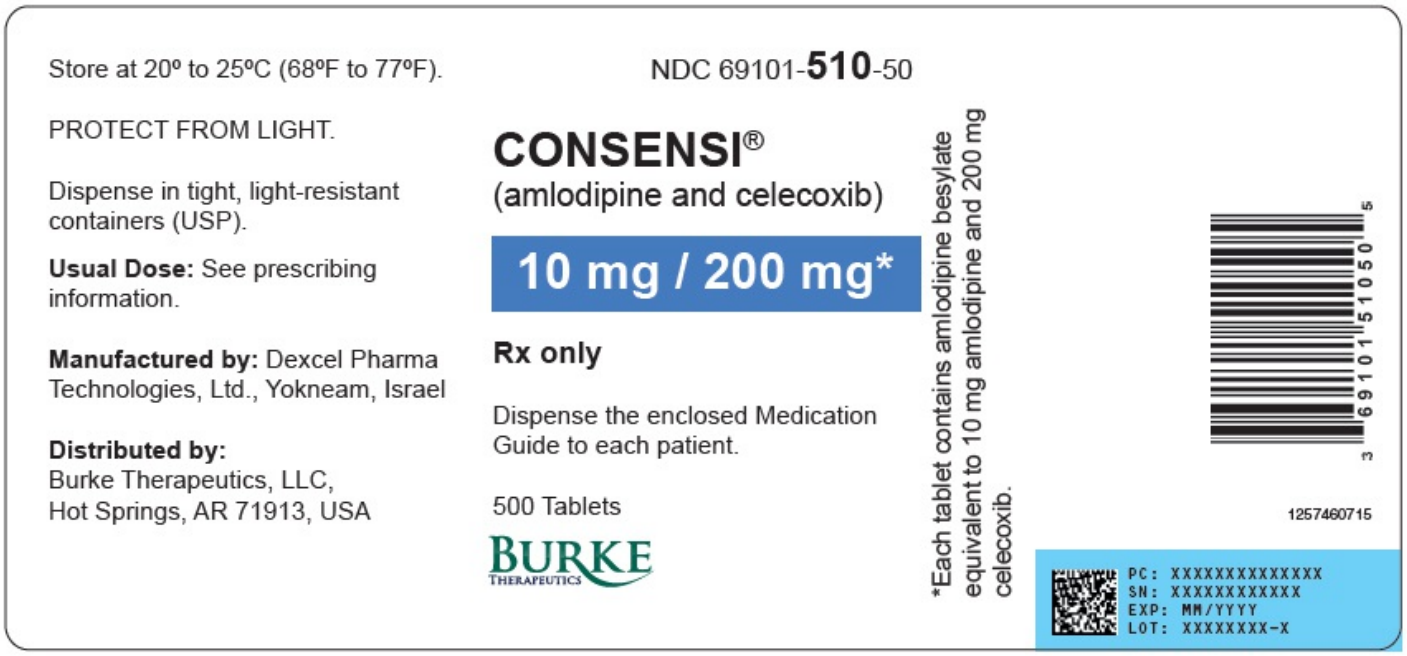
10 mg / 200 mg*

Rx only

Dispense the enclosed Medication
Guide to each patient.

500 Tablets

BURKE
THERAPEUTICS



CONSENSI

amlodipine besylate and celecoxib tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69101-502
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	2.5 mg
CELECOXIB (UNII: JCX84Q7J1L) (CELECOXIB - UNII:JCX84Q7J1L)	CELECOXIB	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITOL (UNII: 3OWL53L36A)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	white	**Score**	no score
Shape	OVAL (elongated oval)	**Size**	14mm
Flavor		**Imprint Code**	2;5;200
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69101-502-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/17/2019	
2	NDC:69101-502-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	12/17/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210045	12/17/2019	

CONSENSI

amlodipine besylate and celecoxib tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:69101-505
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	5 mg
CELECOXIB (UNII: JCX84Q7J1L) (CELECOXIB - UNII:JCX84Q7J1L)	CELECOXIB	200 mg

Inactive Ingredients	
Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	white	Score	no score
Shape	OVAL (caplet)	Size	14mm
Flavor		Imprint Code	5;200
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:69101-505-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/17/2019	
2	NDC:69101-505-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	12/17/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210045	12/17/2019	

CONSENSI

amlodipine besylate and celecoxib tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69101-510
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE	10 mg
CELECOXIB (UNII: JCX84Q7J1L) (CELECOXIB - UNII:JCX84Q7J1L)	CELECOXIB	200 mg

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
POVIDONE K30 (UNII: U725QWY32X)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics

Color	white	**Score**	no score
Shape	ROUND	**Size**	10mm
Flavor		**Imprint Code**	10;200
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69101-510-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	12/17/2019	
2	NDC:69101-510-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	12/17/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210045	12/17/2019	

Labeler - Burke Therapeutics, LLC (079259903)

Revised: 5/2020 Burke Therapeutics, LLC