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 is a fixed drug combination of amlodipine and celecoxib, 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. (5.6)
- CONSENSI is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (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 history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)

INDICATIONS AND USAGE

1 INDICATIONS AND USAGE

- Hypertension and Osteoarthritis

CONSENSI is only available in a celecoxib strength of 200 mg and is only to be taken 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)

CONSENSI is available in a celecoxib strength of 200 mg and may 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) once daily as needed for blood pressure control. (2.1)

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

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

DOSE FORMS AND STRENGTHS

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

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

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)

WARRANTS 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 liver disease develops. (5.13, 8.1)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.4, 7)

FULL PRESCRIBING INFORMATION: CONTENTS*

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. (5.6)
- CONSENSI is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (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 history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)

WARNINGS AND PRECAUTIONS

1 WARNINGS AND PRECAUTIONS

- Hypertension: Symptomatic hypotension is possible, particularly in patients with severe hepatic disease. (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)
- Gastrointestinal Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.9)
- Exacerbation of Asthma Related to Aspirin Sensitivity: CONSENSI is contraindicated in patients who have 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)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate promptly. (5.12)
- Fetal Toxicity: Limit use of NSAIDs, including CONSENSI, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios-fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios-fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.13, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.14, 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)

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

- Concomitant use of CONSENSI with other drugs that interfere with Hepatic Enzymes (e.g., anastrozole, ketoconazole, itraconazole, fluconazole, nefazodone, ritonavir, saquinavir) may increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)
- Poor Metabolizers of CYP2C9 Substrates: Not recommended.

USE IN SPECIFIC POPULATIONS

- Infertility: NSAIDs are associated with reversible infertility. (8.3)
- Hepatitis 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: 04/2021

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 4787356
**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, particularly in the first year of treatment. In a large meta-analysis of randomized controlled trials involving over 190,000 patients, the risk of CV death, MI, and stroke was increased by 1.2- to 3-fold in patients treated with NSAIDs compared to placebo.[1]

**Renal Toxicity and Hyperkalemia**
- Avoid the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction.

**Hepatotoxicity and Patients with Hepatic Failure**
- Avoid the use of celecoxib in patients with severe hepatic failure.

**Renal Toxicity and Hyperkalemia**
- Avoid the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction.

**Hypertension**
- Avoid the use of celecoxib in patients with severe hepatic failure.

**Renal Toxicity and Hyperkalemia**
- Avoid the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction.

**Hypertension**
- Avoid the use of celecoxib in patients with severe hepatic failure.

**Renal Toxicity and Hyperkalemia**
- Avoid the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction.

**Hypertension**
- Avoid the use of celecoxib in patients with severe hepatic failure.

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- Avoid the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction.

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**Renal Toxicity and Hyperkalemia**
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**Hypertension**
- Avoid the use of celecoxib in patients with severe hepatic failure.

**Renal Toxicity and Hyperkalemia**
- Avoid the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction.

**Hypertension**
- Avoid the use of celecoxib in patients with severe hepatic failure.

**Renal Toxicity and Hyperkalemia**
- Avoid the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction.
Correct volume status in dehydrated or hypovolemic patients prior to initiating celecoxib. Monitor renal function/monitor renal or hepatic impairment; heart failure exacerbation; and hypovolemia during use of celecoxib [see Drug Interactions (7)]. Avoid the use of celecoxib in patients receiving dialysis or with severe renal impairment. Celecoxib may be used in patients who have experienced worsening renal function. If celecoxib is used in patients with advanced renal disease, monitor patients for signs of worsening renal function. Patients who develop markedly increased BUN or serum creatinine during celecoxib should have their use of celecoxib evaluated. 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, adverse events have been attributed to a hyperreninemic-hypaldosteronism state. 

5.9 Anaphylactic Reactions

Celecoxib

Anaphylactic reactions have 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 sulfonamides and NSAIDs may cause anaphylactoid reactions including anaphylactic shock and anaphylactic reactions including anaphylactic shock and anaphylactic reactions including anaphylactic shock. Co-morbid conditions such as cardiovascular disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs, or other drugs that impair hemostasis may increase the risk of bleeding events. Co-morbid conditions such as cardiovascular disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs, or other drugs that impair hemostasis may increase the risk of bleeding events. 

6.1 Clinical Trials Experience

In controlled clinical trials of celecoxib in patients with osteoarthritis or rheumatoid arthritis that included a placebo and/or a positive control group, the incidence of serious adverse events was approximately 2% for patients receiving celecoxib. The incidence of serious adverse events was approximately 2% for patients receiving celecoxib. Celecoxib was well tolerated in these clinical studies. 

6.2 Clinical Pharmacology

5.8 Laboratory Monitoring

Use of NSAIDs, including celecoxib, at the first appearance of skin rash or any other sign of hypersensitivity. Anaphylactic Reactions

Increased Angina or Myocardial Infarction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Celecoxib

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as CONSENSI. Some of these events have been fatal or life-threatening. DRESS, also known as TINU syndrome, is characterized by a severe rash, fever, eosinophilia, and multiorgan involvement. It may also include involvement of the liver, lungs, kidneys, and nervous system. The rash is often not apparent at the time of presentation. The rash is often not apparent at the time of presentation. 

5.11 Skin Reactions

Skin reactions are seen after hospitalization, forming papules and plaques, and other skin symptoms. The rash is often not apparent at the time of presentation. 

5.13 Fetal Toxicity

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 sulfonamides and NSAIDs may cause anaphylactoid reactions including anaphylactic shock and anaphylactic reactions including anaphylactic shock. Co-morbid conditions such as cardiovascular disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs, or other drugs that impair hemostasis may increase the risk of bleeding events. Co-morbid conditions such as cardiovascular disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs, or other drugs that impair hemostasis may increase the risk of bleeding events. 

5.14 Hematological Toxicity

Celecoxib

Anemia has occurred in NSAID-treated patients. The risk may be due to 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, the hemoglobin or hematocrit level should be checked. If they exhibit any signs or symptoms of anemia or blood loss. 

5.15 Masking of Inflammation and Fever

On use of NSAIDs in patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis with or without 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 some patients with aspirin-sensitive celecoxib, it is contraindicated in patients with a history of asthma and/or aspirin intolerance (see Contraindications (4)). 

7.4.3 Rash

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

7.4.4 Skull

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

7.4.5 Pulmonary

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

7.4.6 Gastrointestinal Tract

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

7.4.7 Skin and Appendages

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

7.4.8 Urinary Tract

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

7.4.9 DERMATOVASCULAR

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

8.1 Pregnancy

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

8.2 Lactation

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

8.3 Pediatric Use

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

8.4 Geriatric Use

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

8.5 Drug Interactions

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

8.6 Overdose

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

8.7 Contraindications

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

8.8 Black Box Warning

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

8.9 Warnings and Precautions

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

8.10 Adverse Reactions

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

8.11 Use in Specific Populations

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

8.12 Pregnancy/Lactation

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

9.2 Preclinical Toxicology

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

9.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

9.4 Non-Clinical Safety Studies

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

9.5 Human Pharmacology and Pharmacodynamics

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

9.6 Preclinical Pharmacology

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

9.7 Clinical Trials

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

9.8 Human Experience

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

9.9 Following the administration of celecoxib, patients may experience a flush, flushing, and nausea, which may persist for several days. 

9.10 Special Populations

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

9.11 Other Information

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

9.12 Description

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

9.13 Standards of Care

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

9.14 Indications

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

9.15 Warnings

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

9.16 Precautions

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

9.17 Adverse Reactions

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

9.18 Overdosage

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

9.19 Contraindications

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

9.20 Interactions

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

9.21 Use in Special Populations

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

9.22 Patient Counseling

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

9.23 Dosage and Administration

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

9.24 How Supplied

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

9.25 Pharmacokinetics

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

9.26 Clinical Pharmacology

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

9.27 Nonclinical Pharmacology

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

9.28 Clinical Studies

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

9.29 Preclinical Studies

The following adverse reactions are discussed in greater detail in other sections of the labeling:
Vascular disorders: Deep vein thrombosis

Infective and parasitic disorders and breast disorders: Ovarian cyst

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

Injury, poisoning and procedural complications: Epicondylitis, tendon rupture

The most commonly occurring (≥5%) adverse events in placebo-treated patients were headache, fever (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrrhea, and vomiting. The most commonly occurring (≥5%) adverse experiences in 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, 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 patients treated with celecoxib were headache, fever (pyrexia), upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrrhea, and vomiting. The most commonly occurring (≥5%) adverse experiences in 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.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Celecoxib 3 mg/kg N=82</th>
<th>Celecoxib 6 mg/kg N=83</th>
<th>Naproxen 7.5 mg/kg N=83</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>13 11 18</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Headache NOs</td>
<td>13 10 16</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness (excl vertigo)</td>
<td>1 1 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>8</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Cough</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Skin &amp; Subcutaneous</td>
<td>10 7 18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 analyses abnormal NOS

Other Pre-Approval Studies

Adverse Reactions 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/day 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 adverse events studies.

Adverse Events from Anagrelide and Dysmenorrhea Studies

Approximately 1,700 patients were treated with celecoxib in anagrelide and dysmenorrhea studies. All patients in post-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 patients. The types of adverse events in the anagrelide 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-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 the 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 in placebo-controlled arthritis trials above). The adverse reactions for which these differences were observed in patients treated with celecoxib were greater as compared to the arthritis pre-marketing trials were as follows: Diarrhea, Gastroesophageal reflux disease, Nausea, Vomiting, Dyspepsia, Hypertension, Hyperlithiasis.

The following additional adverse reactions occurred in ≥5% 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 bradyarrhythmia, ventricular hypertrophy

Other adverse reactions that were not clearly dose related but were reported with an incidence greater than 0.1% in placebo-controlled clinical trials include the following:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Male% (N=1218)</th>
<th>Female% (N=512)</th>
<th>Male% (N=914)</th>
<th>Female% (N=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>5.6</td>
<td>14.6</td>
<td>1.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Flushing</td>
<td>1.5</td>
<td>4.5</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1.4</td>
<td>3.3</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.3</td>
<td>1.6</td>
<td>0.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Other adverse reactions that were not clearly dose related but were reported with an incidence greater than 1% in placebo-controlled clinical trials include the following:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Male% (N=11730)</th>
<th>Female% (N=11250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Male% (N=1194)</th>
<th>Female% (N=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>5.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Flushing</td>
<td>1.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.3</td>
<td>1.6</td>
</tr>
</tbody>
</table>

The following adverse reactions occurred 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.

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

### DRUG INTERACTIONS

#### Clinical Impact:
- Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of celecoxib and anticoagulants has 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 reports and case series suggest that the concomitant use of NSAIDs and celecoxib may result in more bleeding than an NSAID alone.

### Intervention:
- Monitor patients with concomitant use of celecoxib with anticoagulants (e.g., heparin, aspirin, SSRIs, and SNRIs for signs of bleeding [see Warnings and Precautions (5.14)])

#### Aspirin

Clinical Impact:
- Celecoxib and aspirin should be avoided for a period of two days before, the day of, and two days after surgery or dental procedures. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.

### Intervention:
- Concomitant use of celecoxib and aspirin is not generally recommended due to the increased risk of bleeding [see Warnings and Precautions (5.14)].
- Celecoxib is not a substitute for low dose aspirin for CV protection.

#### ACE Inhibitors, Angiotensin-Receptor Blockers, and Betablockers

Clinical Impact:
- NSAIDs may diminish the antihypertensive effects of ACE inhibitors, angiotensin-receptor blockers, and betablockers (including propranolol).
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with 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:
- Concomitant use of celecoxib and ACE-inhibitors, ARBs, or beta-blockers is not recommended to ensure that the desired blood pressure is maintained.
- 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:
- Monitor patients who are taking diuretics with celecoxib for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see Warnings and Precautions (5.8)].
- During concomitant use of celecoxib and other NSAIDs, monitor patients for signs of worsening renal function.

#### Ureteral Obstruction

Clinical Impact:
- Concomitant use of celecoxib and dihydroergotamine may increase the risk of ureteral obstruction.

### Intervention:
- Concomitant use of celecoxib and dihydroergotamine should be avoided unless necessary to treat severe pain.

#### NSAIDs and Saliylates

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 (5.8)].

### Intervention:
- The concomitant use of celecoxib with other NSAIDs or salicylates is not recommended.

#### Pemexedex

Clinical Impact:
- Concomitant use of celecoxib and pemexedex may increase the risk of pemexedex-associated myelosuppression, renal, and GI toxicity [see Clinical Pharmacology (12.3)]

### Intervention:
- Concomitant use of celecoxib and pemexedex is not recommended.

#### CYP2C9 Inhibitors or Inducers

Clinical Impact:
- The co-administration of celecoxib with CYP2C9 inhibitors (e.g., fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g., rifampin) may decrease the exposure 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 vitro drug interaction with CYP2D6 substrates (e.g., quinidine, venlafaxine, and 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:
- Concomitant use of corticosteroids with celecoxib may increase the risk of GI ulceration or bleeding.

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**Reference ID:** 4787356
transient and reversible with cessation of the drug. There have been a limited number of case reports of transient neonatal renal dysfunction without oliguria or anuria, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, including dialysis or continuous renal replacement therapy. Methodological limitations of these postmarketing studies and reports include lack of a control group, limited information regarding dose, duration, and timing of drug exposure, and the use of case reports. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal exposure to NSAIDs. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to term infants is uncertain. In conclusion, the available published literature reports the individual components of CONSENSI (celecoxib, amlodipine) are present in human breast milk at low levels. Data from 3 published reports that included 12 breastfeeding mothers quantified human milk concentration of celecoxib in term infants. The mean concentration of celecoxib in milk for all five mothers was 104 μg/mL (95% CI: 59-197 μg/mL), which is 0.13 to 0.33% of the dose clinically used for pediatric patients. Comparison of this to the mean concentration of amlodipine in milk (mean 11 months) and in the final stage of weaning showed that the median total amount of amlodipine reached during therapy has produced no apparent adverse effects on the neonatal cardiovascular system. Clinical studies of CONSENSI did not include sufficient numbers of subjects aged 65 and over to establish whether they respond differently to treatment with CONSENSI compared to younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, and titrating upward based on clinical response until a response is apparent. Age-related differences in plasma protein binding, renal function, and metabolism may affect the choice of dose in the elderly. Amlodipine is not recommended in patients with moderate hepatic impairment. Low-dose aspirin, 325 mg daily, can be used to prevent the occurrence of ischemic complications in patients with a history of transient ischemic attack or stroke. Celecoxib is contraindicated in patients with a history of aspirin-induced gastrointestinal intolerance or in patients at increased risk of aspirin intolerance, including those with a history of asthma, bronchospastic reactions, urticaria, angioedema, or nasal polyps. Celecoxib has not been studied in patients with hepatic impairment. It is not known whether CONSENSI is distributed in breast milk. 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 a racemic mixture of the S(+)- and R(-)-enantiomers of amlodipine (85% and 15%, respectively). It has a molecular formula of C20H25CIN2O5•C6H6O3S, and the molecular weight is 480.43. Celecoxib is a white crystalline powder. It is slightly soluble in water and sparingly soluble in ethanol. Celecoxib is hydrophobic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH range. Amlodipine is a white, odorless, crystalline, anhydrous powder. The chemical name of amlodipine is N-[2-(dimethylamino)ethyl]-N-[(4-methylphenyl)-3-[trifluoromethyl]-1H-pyrazol-1-yl]-benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula is C17H14F3N3O2S, and the molecular weight is 381.38; the chemical structure is as follows:

CONSENSI (amlodipine and celecoxib) tablet is an NSAID and long-acting calcium channel blocker for oral administration. Each tablet contains celecoxib (3.47 mg) and amlodipine (1 mg). CELECOXIB is a white to off-white, tablet-shaped, coated tablet, debossed with “CELEX” and ‘64’. AMLODIPINE is a white, round, coated tablet, debossed with “A 20”. The generic names of the active ingredients are listed below.

**BENEFICIAL EFFECTS**

### Clearance of Amlodipine

Celecoxib is a white crystalline powder. It is slightly soluble in water and sparingly soluble in ethanol. Celecoxib is hydrophobic (log P is 3.5) and is practically insoluble in aqueous media at physiological pH range. Amlodipine besylate is a racemic mixture of the S(+)- and R(-)-enantiomers of amlodipine (85% and 15%, respectively). It has a molecular formula of C20H25CIN2O5•C6H6O3S, and the molecular weight is 480.43. The chemical structure is as follows:

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inhibit water reabsorption by counteracting the action of antidiuretic hormone. In the collecting ducts, PGE2 appears to be a vasodilator that reduces the net reabsorption of water, leading to a decrease in blood pressure.

Celecoxib:

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that is primarily excreted unchanged in the urine and excreted in feces. Absorption of celecoxib is reduced in patients with moderate hepatic impairment. In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. It is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours.

**Pharmacokinetics:**

Celecoxib is rapidly absorbed after oral administration, with peak plasma concentrations occurring within 2 hours. It has a high protein binding and is extensively (about 90%) converted to inactive metabolites via hepatic metabolism. Three metabolites, a flavonol glycoside, a flavone, and a flavonol, are detected in the urine after oral administration.

**Drug Interactions:**

Celecoxib is an inhibitor of cytochrome P450 2C9, and concomitant administration of celecoxib and amlodipine results in a two-fold increase in the AUC of celecoxib and amlodipine. The rate and extent of absorption of celecoxib and amlodipine were similar when co-administered with celecoxib. Co-administration of celecoxib with an aluminum- and magnesium-containing antacid resulted in a decrease in the absorption of celecoxib and concomitant block of the calcium channel receptor.

**Use in Specific Populations:**

- **Renal Impairment:** Celecoxib is not recommended in patients with moderate renal impairment. Patients with severe renal impairment have not been studied. Similar to other NSAIDs, CONSENSI is not recommended in patients with severe renal insufficiency.
- **Hepatic Impairment:** Celecoxib is not recommended in patients with severe hepatic impairment.
- **Malignancies:** Celecoxib is not carcinogenic in Sprague-Dawley rats given oral doses up to 200 mg/kg for males and 100 mg/kg for females (approximately 2-4 times the human exposure as measured by the AUC in males at 200 mg twice daily) or in mice given oral doses up to 25 mg/kg for males.

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

<table>
<thead>
<tr>
<th>Mean (%CV) Pharmacokinetic Parameter Values</th>
<th>Cmax, ng/mL</th>
<th>Tmax, hr</th>
<th>Effective T1/2, hr</th>
<th>Vss/F, L</th>
<th>CL/F, L/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>(20.9-325)</td>
<td>(2.6-37)</td>
<td>(11.2-13)</td>
<td>(425-34)</td>
<td>(27.2-28)</td>
</tr>
</tbody>
</table>

*Subjects under fasting conditions (n=30, 19-62 yrs.)*

 Celecoxib exhibits dose-proportional increases 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, as 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, the peak plasma levels (Cmax) and AUC are roughly dose-proportional up to 200 mg twice daily, but increases are proportionate due to lower solubility of the drug in aqueous media. Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or perhaps other segments of the distal nephron.

Inhibitors and Inducers:

- Inhibitors of CYP2C9: Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in the AUC of celecoxib and amlodipine. Co-administration of cimetidine, magnesium- and aluminum hydroxide antacids, sildenafil, and nilotinib with celecoxib resulted in no clinically significant changes in the blood pressure.

**Elimination**

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. It is primarily metabolized by CYP2C9 with a half-life of approximately 11 hours. There were no significant alterations in Cmax, Tmax, or T1/2 after administration of capsule contents on distribution.

**Drug Interactions**

- **Hepatic Impairment:** Celecoxib is not recommended in patients with severe hepatic impairment.

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

- **Carcinogenesis:** Celecoxib has been studied in combination with celecoxib and amlodipine. Although there has been an estimated to be between 64 and 90%.

- **Mutagenesis:** Celecoxib is not mutagenic. It 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.

**13.2 Pharmacogenomics**

- **CYP2C9:** Celecoxib is an inhibitor of cytochrome P450 2C9, and coadministration of celecoxib with amlodipine results in a two-fold increase in the AUC of celecoxib and amlodipine. The rate and extent of absorption of celecoxib and amlodipine were similar when co-administered with celecoxib.

**13.3 Pharmacokinetics**

Celecoxib is an inhibitor of cytochrome P450 2C9, and concomitant administration of celecoxib and amlodipine results in a two-fold increase in the AUC of celecoxib and amlodipine. The rate and extent of absorption of celecoxib and amlodipine were similar when co-administered with celecoxib. Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in the AUC of celecoxib and amlodipine.
50 mg/kg for females (approximately equal to human exposure as measured by the AUCo = 200 mg/kg/day twice daily) and 1% of body weight for males (approximately equal to human exposure as measured by the AUCo = 50 mg/kg/day twice daily).

**Mutagenesis**

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, or clastogenic in a chromosome aberration assay in CHO cells and in 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 1,000 mg/kg/day. Male fertility was impaired in 11-times the maximum human exposure (at 200 mg twice daily based on the AUCo) at 250 mg/kg/day (approximately 6 times human exposure based on the AUCo). The maximum daily dose (200 mg twice daily) in human osteoarthritis treatment (i.e., 50 mg/kg in humans) was below the no-observed-effect level.

**Adequal therapy with amiodipine maleate in the diet for up to 2 years, at concentrations calculated to provide daily dosages of 0.5, 1.25, and 2.5 mg amiodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/kg basis, similar to the maximum dose tolerated in humans (10 mg amiodipine/kg/day; male rat body weight of 50 kg). For the rat, the highest dose was, on a mg/m² basis, about twice the maximum recommended human dose (i.e., on a body weight basis).

**Mutagenic studies conducted with amiodipine 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 amiodipine maleate (males for 64 days and females for 14 days) at up to 50 mg/kg (i.e., near the maximum recommended human dose based on body weight of 50 kg) or 10 mg/kg (i.e., on a mg/m² basis).

13.2. Animal Toxicology

Celecoxib

There were no studies of the combination of celecoxib and amiodipine demonstrating reductions in cardiac parameters in the absence of concomitant reduction in systolic pressure. However, a statistically significant reduction in cardiac parameters (SBP and DBP) was observed in clinical studies of celecoxib in combination with amlodipine. Celecoxib had no effect on male or female fertility in rats at oral doses up to 100 mg/kg/day (approximately equal to human exposure as measured by the AUC0-24 at 10 mg/kg/day). Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, or clastogenic in a chromosome aberration assay in CHO cells and in an in vivo micronucleus test in rat bone marrow.

13.3. Clinical Studies

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 reduction, effect between celecoxib and amiodipine. There are no studies of the combination of celecoxib and amiodipine demonstrating reductions in cardiac parameters in the absence of concomitant reduction in systolic pressure. However, a statistically significant reduction in cardiac parameters (SBP and DBP) was observed in clinical studies of celecoxib in combination with amlodipine. Celecoxib had no effect on male or female fertility in rats at oral doses up to 100 mg/kg/day (approximately equal to human exposure as measured by the AUC0-24 at 10 mg/kg/day). Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, or clastogenic in a chromosome aberration assay in CHO cells and in an in vivo micronucleus test in rat bone marrow.

4.1. Combination of Celecoxib and Amlodipine

In the PRECISION trial, there was a dose-related increase in the composite endpoint of cardiovascular death, myocardial infarction, or stroke with celecoxib compared to placebo over 3 years of treatment. The PREPAS trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated).

14.2. Osteoarthritis

14.2.1. Comparison 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. The combination of celecoxib and amlodipine was studied in a randomized, double-blind, placebo- and active-controlled clinical trial in 152 patients with osteoarthritis who were randomly assigned to treatment with celecoxib 100 mg twice daily or 200 mg once daily, and amlodipine 5 mg once daily. The combination of celecoxib and amlodipine 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 in placebo- and active-controlled clinical trials of up to 12 weeks, in patients with osteoarthritis, taken.

14.2.2. Adult Patients

The antihypertensive efficacy of celecoxib has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amiodipine and 5/3 doses of celecoxib. Celecoxib statistically significantly 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.

14.3. Special Studies

**Carotid Artery Disease**

Carotid Artery Disease

**Primary Endpoint**

There were two prespecified analysis populations:

- Intent-to-treat population (ITT): Comprised of all randomized subjects followed for a maximum of 36 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 or 36 months.

Celecoxib, at the 100 mg twice daily dose, as compared with either naproxen or ibuprofen at the 500 mg twice daily dose, resulted in statistically significantly greater reductions in the signs and symptoms of osteoarthritis, but one of the components, celecoxib, has demonstrated such effects. The combination of celecoxib and amiodipine was studied in a randomized, double-blind, placebo- and active-controlled clinical trial in 152 patients with osteoarthritis who were randomly assigned to treatment with celecoxib 100 mg twice daily or 200 mg once daily, and amlodipine 5 mg once daily. The combination of celecoxib and amiodipine 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 in placebo- and active-controlled clinical trials of up to 12 weeks, in patients with osteoarthritis, taken.

**Secondary Endpoint**

14.3.1. Analysis of Safety vs. Ibuprofen Or Naproxen (PRECISION; NCT00346216)

Cardiovascular Outcomes Trial: Prospective Randomized Evaluation of Celecoxib and Other Osteoarthritis and Rheumatoid Arthritis Patients

Clinical trials of other COX-2 selective and non-selective NSAIDs of up to three-years duration for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively.

In the PRECISION-ABPM substudy, among the total of 444 analyzable patients at Month 4, completing the trial at 100 mg twice daily, 6% (17/300) of subjects in the celecoxib arm had CV death, myocardial infarction, or stroke with celecoxib compared to placebo over 3 years of treatment. The PREPAS trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated).

14.3.2. Analysis of Safety vs. Ibuprofen Or Naproxen (PRECISION; NCT00346216)

Cardiovascular Outcomes Trial: Prospective Randomized Evaluation of Celecoxib and Other Osteoarthritis and Rheumatoid Arthritis Patients

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 PREPAS trial did not demonstrate a statistically significant increased risk for the same composite endpoint (adjudicated).

**Primary Endpoint**

1. 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 arm and 1.8% in the ibuprofen arm in the non-T1D selected group.

**Summary of the Adjudicated APTC Components**

<table>
<thead>
<tr>
<th>Component</th>
<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Naproxen</th>
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<tr>
<td>CV Death</td>
<td>68 (8.5%)</td>
<td>80 (10.1%)</td>
<td>86 (11.1%)</td>
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<tr>
<td>Non-Fatal Myocardial Infarction</td>
<td>76 (9.9%)</td>
<td>92 (11.1%)</td>
<td>66 (8.6%)</td>
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<td>Non-Fatal Stroke</td>
<td>51 (0.6%)</td>
<td>53 (0.7%)</td>
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</table>

**Modified Intent-To-Treat Analysis (mITT, on treatment plus 30 days, through month 43)**

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<thead>
<tr>
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<th>Naproxen</th>
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</table>
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 the 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

<table>
<thead>
<tr>
<th>All Patients</th>
<th>Patients &lt;65 Years</th>
<th>Patients &gt;65 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib alone</td>
<td>0.78</td>
<td>0.47</td>
</tr>
<tr>
<td>Celecoxib with ASA</td>
<td>2.19</td>
<td>3.06</td>
</tr>
</tbody>
</table>

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, 2.5% (n=243) and 6.8% (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 evaluated in the CLASS trial using 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 for 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 celecoxib and rheumatoid arthritis doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.5% 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. The previous clinically significant upper GI bleeding was 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. 16% in the 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 celecoxib and rheumatoid arthritis doses, respectively), ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were 4.5%, 6.5% 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.

### Gastrointestinal Bleeding, Ulceration, and Perforation

Advising 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 aspirin for cardiac prophylaxis, inform patients of the increased risk for and the symptoms of GI bleeding [see Warnings and Precautions (5.5)].

### Hepatic Toxicity

Inform patients of the warning signs and symptoms of hepatic toxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these symptoms develop, DISCONTINUE CONSENSI immediately medical therapy [see Warnings and Precautions (5.3), Use in Specific Populations (8.6)].

### Hypersensitivity

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)].

### Pregnancy

Advising 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)].

### Female Fertility

Advising 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)].

### Contraindications

Inform patients that the concomitant use of CONSENSI with other NSAIDs or salicylates (e.g., aspirin, ibuprofen, and naproxen) 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)].

### 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)].
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. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 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
• headache
• frequent urination
• dizziness
• stomach pain
• diarrhea
• heartburn

• hot or warm feeling in your face (flushing)
• gas
• tiredness
• 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

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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