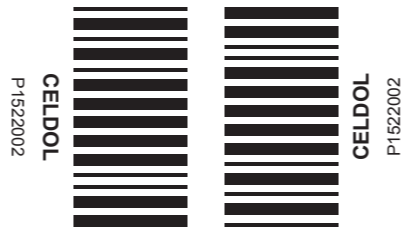


Pharmacode position may change as per the supplier’s m/c requirement



SUMMARY OF PRODUCT CHARACTERISTICS

CEL DOL

Celecoxib Capsules 100 mg and 200 mg

R, Only

NAME OF DRUG PRODUCT : Celecoxib Capsules 100 mg  
Celecoxib Capsules 200 mg

(TRADE) NAME OF PRODUCT : CELDOL 100  
CELDOL 200

STRENGTH : 100 mg and 200 mg.

PHARMACEUTICAL DOSAGE FORM: Capsules.

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Celecoxib Capsules 100 mg:  
Each hard gelatin capsule contains Celecoxib Ph.Eur. 100 mg.

Celecoxib Capsules 200 mg:  
Each hard gelatin capsule contains Celecoxib Ph.Eur. 200 mg.

\*Not all strength is marketed locally\*.

PHARMACEUTICAL FORM:

Celecoxib Capsules 100 mg:

White cap and White body, Size '4' hard gelatin capsule filled with white to off white granular powder, imprinted with 'Y' on cap and '100' on body with blue ink.

Celecoxib Capsules 200 mg

White cap and White body, Size '2' hard gelatin capsule filled with white to off white granular powder, imprinted with 'Y' on cap and '200' on body with gold ink.

CLINICAL PARTICULARS:

Therapeutic indications

- Symptomatic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA).
- Management of acute pain in adults.
- Treatment of primary dysmenorrhea.
- Relief of signs and symptoms of ankylosing spondylitis (AS).
- Management of chronic low back pain

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks, taking into consideration other available therapeutic options.

Posology and method of administration

Celecoxib capsules, at doses up to 200 mg twice per day, can be taken with or without food.

As the cardiovascular (CV) risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.

**Symptomatic Treatment of Osteoarthritis (OA):** The recommended dose of celecoxib is 200 mg administered as a single dose or as 100 mg twice per day.

**Symptomatic Relief in the Treatment of Rheumatoid Arthritis (RA):** The recommended daily dose of celecoxib is 100 mg or 200 mg twice per day.

**Ankylosing Spondylitis (AS):** The recommended dose of celecoxib is 400 mg administered as a single dose or as 100 mg twice per day.

The maximum recommended daily dose is 400 mg for above indications.

**Management of Acute Pain in Adults:** The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily, as needed.

**Management of Chronic Low Back Pain in Adults:** The recommended dose of celecoxib is 200 or 400 mg daily, administered as a 200 mg single dose, or as 100 or 200 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.

**Treatment of Primary Dysmenorrhea:** The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily, as needed.

**Elderly:** No dosage adjustment is generally necessary. However, for elderly patients weighing less than 50 kg, it is advisable to initiate therapy at the lowest recommended dose.

Method of Administration

For patients who have difficulty swallowing capsules, the contents of a celecoxib capsule can be added to apple sauce, rice gruel, yogurt or mashed banana. To do so, the entire capsule contents must be carefully emptied onto a level teaspoon of cool or room temperature apple sauce, rice gruel, yogurt or mashed banana and should be ingested immediately with water. The sprinkled capsule contents on apple sauce, rice gruel or yogurt are stable for up to 6 hours under refrigerated conditions (2-8 °C). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions and should be ingested immediately.

**Hepatic Impairment:** No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). Treatment should be initiated at half the recommended dose in patients with moderate hepatic impairment (with serum albumin 25-35 g/L) or Child- Pugh Class B).

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of celecoxib in this patient population is not recommended.

**Renal Impairment:** No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment. The use of celecoxib in this patient population is not recommended.

**Co-administration with Fluconazole:** Celecoxib should be introduced at half the recommended dose in patients receiving fluconazole, a CYP2C9 inhibitor. Caution is advised when co-administering celecoxib with other CYP2C9 inhibitors.

**Pediatric Patients:** Celecoxib has not been studied in subjects under 18 years of age.

**CYP2C9 Poor Metabolizers:** Patients who are known, or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose.

Contraindications

Celecoxib is contraindicated in:

- Patients with known hypersensitivity to celecoxib or any other ingredient of the product.
- Patients with known sulfonamide hypersensitivity.
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients who have experienced asthma, Urticaria or allergic-type reactions after taking acetylsalicylic acid (ASA [aspirin]) or other non-steroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Congestive heart failure (NYHA II-IV).
- Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

Special warnings and precautions for use

Cardiovascular Effects

**Cardiovascular Thrombotic Events:** Celecoxib may cause an increased risk of serious CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with dose and duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimize the potential risk for an adverse CV event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and symptoms of serious CV toxicity and the steps to take if they occur.

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke.

Celecoxib is not a substitute for acetylsalicylic acid for prophylaxis of CV thromboembolic diseases because of the lack of effect on platelet function. Because celecoxib does not inhibit platelet aggregation, anti-platelet therapies (e.g., acetylsalicylic acid) should not be discontinued.

**Hypertension:** As with all NSAIDs, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. NSAIDs, including celecoxib, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

**Fluid Retention and Edema:** As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking celecoxib. Therefore, patients with pre-existing congestive heart failure (CHF) or hypertension should be closely monitored. Celecoxib should be used with caution in patients with compromised cardiac function, pre-existing edema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.

Gastrointestinal (GI) Effects

Upper and lower GI perforations, ulcers or bleeds (PUBS)], some of them resulting in fatal outcome, have occurred in patients treated with celecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with CV disease, patients using concomitant glucocorticoids, antiplatelet drugs (such as aspirin) or other NSAIDs, patients using alcohol or patients with a prior history of, or active, GI disease, such as ulceration, GI bleeding or inflammatory conditions. Most spontaneous reports of fatal GI events have been in elderly or debilitated patients.

Use with Oral Anticoagulants

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g., apixaban, dabigatran, and rivaroxaban). In patients on concurrent therapy with warfarin or similar agents, serious bleeding events, some of them fatal, have been reported. Because increases in prothrombin time (INR) have been reported, anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant after initiating treatment with celecoxib or changing the dose.

Renal Effects

NSAIDs including celecoxib may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Celecoxib is not recommended in patients with severe renal impairment. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.

Caution should be used when initiating treatment in patients with dehydration. It is advisable to rehydrate patients first and then start therapy with celecoxib.

Advanced Renal Disease

Renal function should be closely monitored in patients with advanced renal disease who are administered celecoxib.

Hepatic Effects

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of celecoxib in patients with severe hepatic impairment is not recommended. Celecoxib should be used with caution when treating patients with moderate hepatic impairment (Child- Pugh Class B or serum albumin of 25-35 g/L), and initiated at half the recommended dose. Rare cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis, and hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib.

A patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to celecoxib.

Serious Skin Reactions

Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Patients with a history of sulphonamide allergy or any allergy may be at greater risk of serious skin reactions or hypersensitivity reactions. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Intolerance in Galactose

Celecoxib 100 mg and 200 mg capsules contain lactose (149.7 mg and 49.8 mg, respectively). Patients with rare hereditary problems of galactose intolerance, the Lapp- lactase deficiency or glucose-galactose malabsorption should not take this medicine.

General

By reducing inflammation, celecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections.

The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.

CYP2D6 Inhibition

Celecoxib has shown to be a moderately potent CYP2D6 inhibitor. For drugs that are metabolized by CYP2D6, a dose reduction during initiation of celecoxib treatment or a dose increase upon termination of celecoxib treatment may be necessary.

Interaction with other medicinal products and other forms of interaction

General

Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Consider starting treatment at half the lowest recommended dose.

Concomitant administration of celecoxib with inhibitors of CYP2C9 can lead to increases in plasma concentrations of celecoxib. Therefore, a dose reduction of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inhibitors.

Concomitant administration of celecoxib with inducers of CYP2C9, such as rifampicin, carbamazepine and barbiturates can lead to decreases in plasma concentrations of celecoxib. Therefore, a dose increase of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inducers.

Clinical pharmacokinetics study and *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.

Drug-specific

Interaction of Celecoxib with Warfarin or Similar Agents.

**Fluconazole and Ketoconazole:** Concomitant administration of fluconazole at 200 mg once daily resulted in a 2-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via CYP2C9 by fluconazole. Celecoxib should be introduced at half the recommended dose in patients receiving the CYP2C9 inhibitor fluconazole. Ketoconazole, a CYP3A4 inhibitor, showed no clinically relevant inhibition in the metabolism of celecoxib.

**Anti-hypertensives including Angiotensin-converting Enzyme Inhibitors (ACEIs), Angiotensin II Antagonists (also known as Angiotensin Receptor Blockers, [ARBs]), Diuretics and Beta-blockers:** Inhibition of prostaglandins may diminish the effect of anti-hypertensives including ACEIs, and/or ARBs, diuretics and beta-blockers. This interaction should be given consideration in patients taking celecoxib concomitantly with ACEIs and/or ARBs, diuretics and beta-blockers. These effects are usually reversible. Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the clinical need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

**Results from Lisinopril Study:** In a 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients co-administered with celecoxib 200 mg BID, 48% were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic blood pressure increased >10% compared to baseline), compared to 27% of patients co-administered with placebo, this difference was statistically significant.

**Cyclosporine:** Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with cyclosporine.

**Dextromethorphan and Metoprolol:** Concomitant administration of celecoxib 200 mg twice daily resulted in a 2.6-fold and a 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib inhibition to the CYP2D6 substrate metabolism via CYP2D6. Therefore, the dose of drugs as CYP2D6 substrate may need to be reduced when treatment with celecoxib is initiated or increased when treatment with celecoxib is terminated.

**Diuretics:** Clinical studies have shown that NSAIDs, in some patients, can reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.

**Methotrexate:** No pharmacokinetic and clinically important interactions have been observed in a clinical study between celecoxib and methotrexate.

**Oral Contraceptives:** In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of a prototype combination oral contraceptive (1 mg norethindrone/0.035 mg ethinyl estradiol).

**Lithium:** In healthy subjects, lithium plasma levels increased approximately 17% in subjects receiving lithium together with celecoxib. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

**Aspirin:** Celecoxib does not interfere with the anti-platelet effect of low-dose aspirin. Because of its lack of platelet effects, celecoxib is not a substitute for aspirin in the prophylactic treatment of CV disease.

**Other Drugs:** No clinically important interactions have been observed with celecoxib and antacids (aluminum and magnesium), omeprazole, glibendamide (glyburide), phenytoin, or tobutamide.

Fertility, pregnancy and lactation

Fertility

Based on the mechanism of action, the use of NSAIDs, including celecoxib, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including celecoxib, should be considered.

Pregnancy

Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

There are no studies in pregnant women. Studies in animals have shown reproductive toxicity. The relevance of these data for humans is unknown.

Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during the third trimester of pregnancy.

Celecoxib should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post- implantation loss.

If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on celecoxib should be closely monitored for amniotic fluid volume.

Lactation

Studies in rats show that celecoxib is excreted in milk at concentrations similar to those in plasma. Administration of celecoxib to lactating women has shown very low transfer of celecoxib into breast milk. Because of the potential for adverse reactions in nursing infants from celecoxib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the expected benefit of the drug to the mother.

Effects on ability to drive and use machines

The effect of celecoxib on ability to drive or use machinery has not been studied, but based on its pharmacodynamic properties and overall safety profile it is unlikely to have an effect.

Undesirable effects

Clinical Trial Experience

The following adverse drug reactions (ADRs) in Table 1 were identified with incidence rates greater than 0.01% in celecoxib group and greater than those reported in placebo group, during 12 placebo- and/or active-controlled clinical trials of treatment duration up to 12 weeks at daily doses from 100 mg up to 800 mg in adults.

The frequencies on the ADRs in Table 1 are updated based on a more recent pooling of 89 randomized, controlled clinical trials data representing clinical exposure in 38,102 patients taking celecoxib. ADR frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%). The ADRs in Table 1 are listed by system organ class and ranked by frequency in descending order.

Table 1. Adverse Drug Reactions (ADRs) in 12 Placebo- and/or Active-Controlled Clinical Trials and ADR Frequency from 89 Pain and Inflammation Randomized, Controlled Clinical Trials with Daily Doses of 25 mg to 800 mg, in Adult Populations

System Organ Class Frequency	Adverse Drug Reaction
<b>Infections and infestations</b>	
Common	Bronchitis, sinusitis, upper respiratory tract infection, urinary tract infection
Uncommon	Pharyngitis, rhinitis
<b>Blood and lymphatic system disorders</b>	
Uncommon	Anemia
Rare	Thrombocytopenia
<b>Immune system disorders</b>	
Uncommon	Hypersensitivity
<b>Psychiatric disorders</b>	
Common	Insomnia
Uncommon	Anxiety
Rare	Confusional state
<b>Nervous system disorders</b>	
Common	Dizziness
Uncommon	Hypertonia, somnolence
<b>Eye disorders</b>	
Uncommon	Vision blurred
<b>Ear and labyrinth disorders</b>	
Uncommon	Tinnitus
<b>Cardiac disorders</b>	
Uncommon	Palpitations
Rare	Cardiac failure congestive, arrhythmia, tachycardia
<b>Vascular disorders</b>	
Common	Hypertension (including aggravated hypertension)
Rare	Flushing
<b>Respiratory, thoracic and mediastinal disorders</b>	
Common	Cough
<b>Gastrointestinal disorders</b>	
Common	Vomiting, abdominal pain, diarrhea, dyspepsia, flatulence
Uncommon	Gastric ulcer, tooth disorder
Rare	Duodenal ulcer, esophageal ulcer
Very rare	Intestinal perforation, pancreatitis
<b>Hepatobiliary disorders</b>	
Uncommon	Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)
<b>Skin and subcutaneous tissue disorders</b>	
Common	Pruritus (includes pruritus generalized), rash
Uncommon	Urticaria, ecchymosis
Rare	Angioedema, alopecia
Very rare	Dermatitis bullous
<b>General disorders and administration site conditions</b>	
Common	Edema peripheral
Uncommon	Face edema, influenza-like illness
<b>Injury, poisoning and procedural conditions</b>	
Uncommon	Injury

The following additional adverse drug reactions\* in Table 2 were identified with incidence rates greater than placebo in long-term poly/p prevention studies of duration up to 3 years at daily doses from 400 mg up to 800 mg.

Frequencies of ADRs in Table 2 were determined based on these long-term poly/p prevention studies and defined as: very common (≥10%), common (≥1% and <10%), uncommon (<0.1% and <1%). The ADRs in Table 2 are listed by system organ class and ranked by frequency in descending order.

Table 2. Adverse Reactions from Poly/p Prevention Studies of Duration up to 3 Years and Daily Doses of 400 mg to 800 mg

System Organ Class Frequency	Adverse Drug Reaction
<b>Infections and infestations</b>	
Common	Ear infection, fungal infection
Uncommon	Helicobacter infection, herpes zoster, erysipelas, wound infection, gingivitis, labyrinthitis, bacterial infection
<b>Neoplasms benign, malignant, and unspecified</b>	
Uncommon	Lipoma
<b>Psychiatric disorders</b>	
Uncommon	Sleep disorder
<b>Nervous system disorders</b>	
Uncommon	Cerebral infarction
<b>Eye disorders</b>	
Uncommon	Conjunctival hemorrhage, vitreous floaters
<b>Ear and labyrinth disorders</b>	
Uncommon	Hypacusis
<b>Cardiac disorders</b>	
Common	Myocardial infarction, angina pectoris
Uncommon	Angina unstable, aortic valve incompetence, arteriosclerosis coronary artery, sinus bradycardia, ventricular hypertrophy
<b>Vascular disorders</b>	
Very Common	Hypertension*
Uncommon	Deep vein thrombosis, hematoma
<b>Respiratory, thoracic, and mediastinal disorders</b>	
Common	Dyspnea
Uncommon	Dysphonia
<b>Gastrointestinal disorders</b>	
Very Common	Diarrhea*
<b>Common</b>	Vomiting*, dysphagia, irritable bowel syndrome, gastroesophageal reflux disease, nausea, diverticulitis
Uncommon	Hemorrhoidal hemorrhage, frequent bowel movements, mouth ulceration, stomatitis
<b>Hepatobiliary disorders</b>	
Common	Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)*
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon	Dermatitis allergic
<b>Musculoskeletal and connective tissue disorders</b>	
Common	Muscle spasms
Uncommon	Synovial cyst
<b>Renal and urinary disorders</b>	
Common	Nephrolithiasis
Uncommon	Nocturia
<b>Reproductive system and breast disorders</b>	
Common	Vaginal hemorrhage, prostatitis, benign prostatic hyperplasia
Uncommon	Ovarian cyst, menopausal symptoms, breast tenderness, dysmenorrhea
<b>General disorders and administration site conditions</b>	
Uncommon	Edema
<b>Investigations</b>	
Common	Blood creatinine increased, prostatic specific antigen increased, weight increased
Uncommon	Blood potassium increased, blood sodium increased, blood testosterone decreased, hematocrit decreased, hemoglobin increased
<b>Injury, poisoning and procedural complications</b>	
Uncommon	Foot fracture, lower limb fracture, fracture, epicondylitis, tendon rupture

\*Hypertension, vomiting, diarrhea, and hepatic enzyme increased are included in Table 2 because these events were reported more frequently in these studies, which were of 3-year duration, compared to Table 1, which includes adverse reactions from studies of 12-week duration.

\*Fungal infections were primarily non-systemic.

Post-marketing Experience

Adverse reactions identified from post-marketing experience are provided below. Even though these were identified as reactions from post-marketing reports, trial data was consulted to estimate frequency. As above, frequencies are based on a pooling of trials representing exposure in 38,102 patients. Frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%), not known (cannot be estimated from the available data).

**Immune system disorders:** Very rare: anaphylactic reaction.

**Psychiatric disorders:** Rare: hallucination (includes hallucination and hallucination, visual).

**Nervous system disorders:** Very rare: cerebral hemorrhage, meningitis aseptic, aguesia, anosmia.

**Eye disorders:** Uncommon: conjunctivitis.

**Vascular disorders:** Very rare: vasculitis.

**Respiratory, thoracic and mediastinal disorders:** Rare: pulmonary embolism, pneumonitis.

**Gastrointestinal disorders:** Rare: gastrointestinal hemorrhage.

**Hepato-biliary disorders:** Rare: hepatitis. Very rare: hepatic failure, hepatitis fulminant, hepatic necrosis, cholestasis, hepatitis cholestatic, jaundice.

**Skin and subcutaneous tissue disorders:** Rare: photosensitivity reaction. Very rare: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, DRESS, acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative.

**Renal and urinary disorders:** Rare: renal failure acute, hyponatremia. Very rare: tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion.

**Reproductive system and breast disorders:** Rare: menstrual disorder. Not known: infertility female (female fertility decreased).

**General disorders and administration site conditions:** Uncommon: chest pain.

Women intending to become pregnant are excluded from all trials, thus consultation of the trial database for the frequency of this event was not reasonable.

Overdose

Clinical experience of overdose is limited. Single oral doses up to 1,200 mg and multiple oral doses up to 1,200 mg twice daily have been administered to healthy subjects without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be

<sup>b</sup> The primary efficacy measure in these studies was the percentage of patients who experienced at least 30% improvement on the Numerical Rating Scale (NRS) Pain Assessment, for which results in both studies showed statistical superiority for celecoxib over tramadol.  
<sup>c</sup> Based on least-squares means from Analysis of Covariance models, with changes in pain intensity calculated by subtracting baseline value from end-of-treatment value; p-values were calculated based on least-squares mean differences between treatment groups.  
*Further information from Clinical Studies*

*Endoscopic Studies*

Five randomized double-blind controlled trials have been conducted including scheduled upper gastrointestinal endoscopy in over 4,000 patients with OA and RA in which ulceration rates on celecoxib have been compared to those on placebo and non-specific inhibitors of both COX-1 and COX-2. In 12-week endoscopy studies celecoxib (100 mg + 800 mg/day) was associated with a significantly lower risk of gastroduodenal ulcers compared with naproxen (1,000 mg/day) and ibuprofen (2,400 mg/day). The data were inconsistent in comparison with diclofenac (150 mg/day). In 2 of the 12-week studies, the percentage of patients with endoscopic gastroduodenal ulceration was not significantly different between placebo and celecoxib 200 mg twice daily and 400 mg twice daily.

Table 3 summarizes the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

**Table 3. Incidence of Gastroduodenal Ulcers from Endoscopic Studies in Osteoarthritis and Rheumatoid Arthritis Patients**

3-Month Studies			
	Study 1 (N = 1,108)		Study 2 (N = 1,049)
Placebo	2.3% (5/217)		2.0% (4/200)
Celecoxib 50 mg twice daily	3.4% (8/233)		---
Celecoxib 100 mg twice daily	3.1% (7/227)		4.0% (9/223)
Celecoxib 200 mg twice daily	5.9% (13/221)		2.7% (6/219)
Celecoxib 400 mg twice daily	---		2.1% (8/197)
Naproxen 500 mg twice daily	16.2% (34/210)*		17.6% (37/210)*

\*p<0.05 vs. all other treatments.

Table 4 summarizes data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

**Table 4. Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in Osteoarthritis and Rheumatoid Arthritis Patients**

	Week 4	Week 8	Week 12	Final
<b>Study 3 (N = 523)</b>				
Celecoxib	4.0%	2.2%	1.5%	7.5%
200 mg twice daily	(10/252)*	(5/227)*	(3/196)*	(20/266)*
Naproxen	19.0%	14.2%	9.9%	34.6%
500 mg twice daily	(47/247)	(26/182)	(14/141)	(89/257)
<b>Study 4 (N = 1,062)</b>				
Celecoxib	3.9%	2.4%	1.8%	7.0%
200 mg twice daily	(13/337) <sup>†</sup>	(7/296) <sup>†</sup>	(5/274) <sup>†</sup>	(25/356) <sup>†</sup>
Diclofenac	5.1%	3.3%	2.9%	9.7%
75 mg twice daily	(18/350)	(10/306)	(8/278)	(36/372)
Ibuprofen	13.0%	8.2%	9.6%	23.3%
400 mg three times daily	(42/323)	(15/241)	(21/219)	(78/334)

<sup>†</sup>p<0.05 celecoxib vs. naproxen based on interval and cumulative analyses.

<sup>‡</sup>p<0.05 celecoxib vs. ibuprofen based on interval and cumulative analyses.

One randomized and double-blind 6-month study in 430 RA 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 (p<0.001).

In 4 of the 5 endoscopic studies, approximately 11% of patients (440/4,000) 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.

The correlation between findings of endoscopic studies, and the relative incidence of clinically significant serious upper GI events has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving celecoxib in controlled and open-labeled trials, albeit infrequently.

*Gastrointestinal Safety Meta-Analysis from Osteoarthritis and Rheumatoid Arthritis Studies*

An analysis of 31 randomized controlled clinical studies in OA and RA, involving 39,605 patients with OA (N = 25,903), RA (N = 3,322), or patients with either condition (N = 10,470) compared the incidence of GI adverse events in celecoxib-treated patients to the incidence in patients administered placebo or NSAIDs (including naproxen, diclofenac and ibuprofen). The incidence of clinical ulcers and ulcer bleeds with celecoxib 200 mg to 400 mg total daily dose was 0.2% compared to an incidence of 0.6% with NSAIDs (RR = 0.35; 95% CI 0.22 - 0.56).

*Cardiovascular Safety – Long-term Studies Involving Patients with Sporadic Adenomatous Polyps*

Two studies involving patients with sporadic adenomatous polyps were conducted with celecoxib, i.e., 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 of CV death, myocardial infarction, or stroke (adjudicated) 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.

In the APC trial, the hazard ratios compared to placebo for a composite endpoint of CV death, myocardial infarction, or stroke (adjudicated) 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) and 2.5% (17/685) for 400 mg twice daily and 200 mg twice daily celecoxib treatment groups, respectively, compared to 0.9% (6/679) for placebo group. The increases for both celecoxib dose groups versus placebo were mainly driven by myocardial infarction.

In the PreSAP trial, the hazard ratio compared to placebo for this same composite endpoint was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily. Cumulative rate for this composite endpoint over 3 years was 2.3% (21/933), compared to 1.9% (12/620) for placebo group.

*Cardiovascular Safety – Long-term Study of Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT)*

Data from the ADAPT study did not show a significantly increased CV risk with celecoxib 200 mg twice daily compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61 - 2.15) with celecoxib 200 mg twice daily.

*Cardiovascular Safety – Meta-Analysis from Chronic Usage Studies*

A meta-analysis of safety data (adjudicated, investigator-reported serious adverse events) from 39 completed celecoxib clinical studies of up to 65 weeks duration has been conducted, representing 41,077 patients; 23,030 (56.1%) patients exposed to celecoxib 200 mg to 800 mg total daily dose (TDD); 13,990 (34.1%) patients exposed to non-selective NSAIDs; and 4,057 (9.9%) patients exposed to placebo.

In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was similar between celecoxib (N = 19,773; 0.96 events/100 patient-years) and non-selective NSAIDs (N = 13,990; 1.12 events/100 patient-years) treatment (RR = 0.90, 95% CI 0.60 - 1.33). This pattern of effect was maintained with or without ASA use (≤ 325 mg). The adjudicated event rate of non-fatal myocardial infarction trended higher (RR = 1.76, 95% CI 0.93 - 3.35); however, that of non-fatal stroke trended lower (RR = 0.51, 95% CI 0.23 - 1.10), and that of CV death was comparable (RR = 0.57, 95% CI 0.28 - 1.14) for celecoxib compared to combined non-selective NSAIDs.

In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was 1.42/100 patient-years for celecoxib (N = 7,462) and 1.20/100 patient-years for placebo (N = 4,057) treatment (RR = 1.11, 95% CI 0.47 - 2.67). This pattern of effect was maintained with or without ASA use (≤325 mg). The incidence of non-fatal myocardial infarction trended higher (RR = 1.56, 95% CI 0.21 - 11.90), as did that of CV death (RR = 1.26, 95% CI 0.33 - 4.77), and that of non-fatal stroke was similar (RR = 0.80, 95% CI 0.19 - 3.31) for celecoxib compared to placebo.

*Cardiovascular Safety*

CV safety outcomes were evaluated in the CLASS trial (see above for description of trial). Kaplan-Meier cumulative rates for investigator-reported serious CV thromboembolic adverse events (including MI, 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.

*The Celecoxib Long-term Arthritis Safety Study (CLASS) Including Use with Aspirin*

In a prospective long-term safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients, patients received celecoxib 400 mg twice daily (4-fold and 2-fold the recommended OA and RA 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 Kaplan-Meier cumulative rates at 9 months are provided for all analyses. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation, or obstruction). Patients were allowed to take concomitant low-dose (≤ 325 mg/day) aspirin (ASA) for CV prophylaxis: 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. Those patients on celecoxib and concomitant low-dose ASA experienced 4-fold higher rates of complicated ulcers compared to those not on ASA. The results for celecoxib are displayed in Table 5.

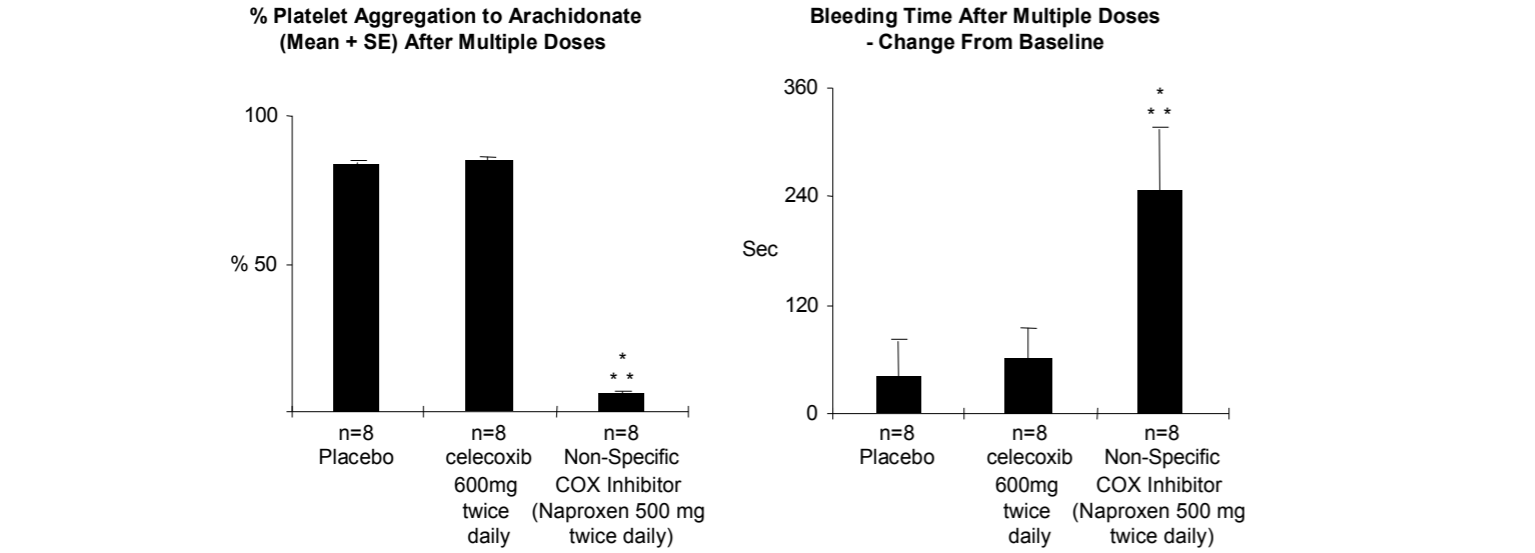
**Table 5. Effects of Co-administration of Low-dose Aspirin on Complicated Ulcer Rates with Celecoxib 400 mg Twice Daily (Kaplan-Meier Rates at 9 months [%])**

	Non-Aspirin Users N = 3105	Aspirin Users N = 882
Complicated Ulcers	0.32	1.12

*Platelet Function*

In healthy volunteers, celecoxib at therapeutic doses and at multiple doses of 600 mg twice daily (three times the highest recommended dose) had no effect on platelet aggregation and bleeding time compared to placebo. Active controls (non-specific COX inhibitors) all significantly reduced platelet aggregation and prolonged bleeding time (see Figure 1).

**Figure 1. Effect of high dose celecoxib (600 mg twice daily) on platelet aggregation and bleeding time in healthy individuals**



\*Significantly different from placebo; p < 0.05.  
\*\*Significantly different from celecoxib; p < 0.05.

*Celecoxib versus Omeprazole and Diclofenac for At-Risk Osteoarthritis and Rheumatoid Arthritis Patients (CONDOR) Trial*

In a prospective randomized 24-week safety study in patients who were aged ≥60 years or had a history of gastroduodenal ulcers (users of ASA excluded), the percentages of patients with decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of defined or presumed GI origin were lower in patients treated with celecoxib 200 mg twice daily (N = 2,238) compared to patients treated with diclofenac SR 75 mg twice daily plus omeprazole 20 mg once daily (N = 2,246) [0.2% vs. 1.1% for defined GI origin, p = 0.004; 0.4% vs. 2.4% for presumed GI origin, p = 0.0001]. The rates of clinically detected GI complications such as perforation, obstruction, or hemorrhage were very low with no differences between the treatment groups (4-5 per group). Results for the individual components of this composite endpoint were as follows:

	Celecoxib 200 mg Twice Daily (N = 2238)	Diclofenac SR 75 mg Twice Daily + Omeprazole 20 mg Once Daily (N = 2246)
<b>Pre-defined Composite GI Endpoint</b>		
<b>Components</b>	<b>N (%) of Patients</b>	
Gastroduodenal hemorrhage	3 (0.1)	3 (0.1)
Large bowel hemorrhage	1 (<0.1)	1 (<0.1)
Acute GI hemorrhage of unknown origin	1 (<0.1)	0 (0.0)
Clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of defined GI origin	5 (0.2)	24 (1.1)
Clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of presumed occult GI origin	10 (0.4)	53 (2.3)
<b>Total*</b>	<b>20 (0.9)</b>	<b>81 (3.6)</b>

For the following components of the pre-defined composite GI endpoint, there were no events in either treatment group: gastric outlet obstruction; gastroduodenal, small bowel, or large bowel perforation; small bowel hemorrhage. All events comprising the composite GI endpoint were adjudicated by an independent, expert panel blinded to randomized treatment assignments.

\*In a time-to-event analysis using life-table techniques, p<0.0001 for the comparison between the celecoxib treatment group and the diclofenac plus omeprazole treatment group for this endpoint.

*Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen (PRECISION)*

*Design*

The PRECISION study was a double-blind study of cardiovascular safety in OA or RA patients with or at high risk for cardiovascular disease comparing Celecoxib (200-400 mg daily) with Naproxen (750-1000 mg daily) and Ibuprofen (1800-2400 mg daily). The primary endpoint, Antiplatelet Trialists Collaboration (APTC), was an independently adjudicated composite of cardiovascular death (including hemorrhagic death), non-fatal myocardial infarction or non-fatal stroke. The study was planned with 80% power to evaluate non-inferiority. All patients were prescribed open-label esomeprazole (20-40 mg) for gastro protection. Patients who were taking low-dose Aspirin were permitted to continue therapy. Other independently adjudicated secondary and tertiary endpoints included cardiovascular, gastrointestinal and renal outcomes. Additionally, there was a 4-month substudy focusing on the effects of the three drugs on blood pressure as measured by ambulatory monitoring (ABPM).

*Results*

**Table 6. Population and Treatment Dose**

Analysis Set	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid	Total
Randomized (ITT)	8,072	8,040	7,969	24,081
On-Treatment (mITT)	8,030	7,990	7,933	23,953
Average Dose <sup>†</sup> (mg/day)	209±37	2,045±246	852±103	NA

<sup>†</sup>Average dose dispensed

ITT – Intent to Treat; All randomized subjects

mITT – Modified Intent to Treat; All randomized subjects with at least one dose of study medication and one post baseline visit

bid – Twice a day

tid – Three a day

NA – Not Applicable

*Primary Endpoint*

Celecoxib, as compared with either naproxen or ibuprofen, met all four prespecified non-inferiority requirements (p<0.001 for non-inferiority in both comparisons). Non-inferiority was established when the hazard ratio (HR) ≤1.12 in both ITT and mITT analyses, and upper 95% CI ≤1.33 for ITT analysis and ≤1.40 for mITT analysis.

The primary analysis for the ITT and mITT are described below in Table 7.

**Table 7. Primary Analysis of the Adjudicated APTC Composite Endpoint**

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid
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)
<b>Modified Intent-To-Treat Analysis (mITT, on treatment through month 43)</b>			
	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid
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 (0.889, 1.40)

*Key Secondary and Tertiary Endpoints*

The analysis of Major Adverse Cardiovascular Events (MACE)\* for mITT are described below in Table 8.

**Table 8. On-treatment Adjudicated Major Adverse CV Events**

	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid
N	8,030	7,990	7,933
<b>Number of Subjects with Events (%)</b>			
<b>MACE</b>	247 (3.1%)	284 (3.6%)	253 (3.2%)
CV death	35 (0.4%)	51 (0.6%)	49 (0.6%)
Nonfatal MI	56 (0.7%)	76 (1.0%)	53 (0.7%)
Nonfatal stroke	43 (0.5%)	32 (0.4%)	45 (0.6%)
Hospitalization for unstable angina	46 (0.6%)	49 (0.6%)	44 (0.6%)
Revascularization	132 (1.6%)	158 (2.0%)	122 (1.5%)
Hospitalization for TIA	12 (0.1%)	21 (0.3%)	16 (0.2%)
<b>Pairwise Comparison HR (95% CI)</b>	<b>Celecoxib vs. Naproxen</b>	<b>Celecoxib vs. Ibuprofen</b>	<b>Ibuprofen vs. Naproxen</b>
MACE	0.95 (0.80, 1.13)	0.82 (0.69, 0.97)	1.17 (0.98, 1.38)
CV death	0.69 (0.45, 1.07)	0.64 (0.42, 0.99)	1.08 (0.73, 1.60)
Nonfatal MI	1.06 (0.73, 1.54)	0.72 (0.51, 1.01)	1.48 (1.04, 2.11)
Nonfatal stroke	0.93 (0.61, 1.42)	1.26 (0.79, 1.98)	0.74 (0.47, 1.16)
Hospitalization for unstable angina	1.02 (0.67, 1.54)	0.89 (0.59, 1.33)	1.16 (0.77, 1.74)
Revascularization	1.06 (0.83, 1.35)	0.78 (0.62, 0.99)	1.35 (1.07, 1.72)
Hospitalization for TIA	0.73 (0.35, 1.55)	0.54 (0.26, 1.09)	1.38 (0.72, 2.64)

\*MACE = APTC composite endpoint plus coronary revascularization, or hospitalization for unstable angina or transient ischemic attack.

In the ITT population for the MACE endpoint there were no significant differences, in the pairwise comparisons between treatment regimens.

The analysis of Gastrointestinal Events for mITT are described below in Table 9.

**Table 9. On-treatment Adjudicated Gastrointestinal Endpoints**

	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid
N	8,030	7,990	7,933
<b>Subjects with Events, n(%)</b>			
CSGIE	27 (0.3%)	59 (0.7%)	52 (0.7%)
IDA of GI Origin	27 (0.3%)	58 (0.7%)	66 (0.8%)
<b>Pairwise Comparison, HR (95% CI)</b>	<b>Celecoxib vs. Naproxen</b>	<b>Celecoxib vs. Ibuprofen</b>	<b>Ibuprofen vs. Naproxen</b>
CSGIE	0.51 (0.32, 0.81)	0.43 (0.27, 0.68)	1.16 (0.80, 1.69)
IDA of GI Origin	0.39 (0.25, 0.62)	0.43 (0.27, 0.68)	0.91 (0.64, 1.29)

\*CSGIE (Clinically Significant Gastrointestinal Events) = composite of the following: gastroduodenal hemorrhage; gastric outlet obstruction; gastroduodenal, small bowel or large bowel perforation; large bowel hemorrhage; small bowel hemorrhage; Acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage; symptomatic gastric or duodenal ulcer

\*\*IDA (Iron Deficiency Anemia) = clinically significant iron deficiency anemia of GI origin or decrease in Hct (Hematocrit) and/or Hgb (Hemoglobin) (defined as Hct ≥10 points and or Hgb of ≥2 g/dl from baseline

In the ITT population for the CSGIE endpoint there were no significant differences, in the pairwise comparisons between treatment regimens (data not shown). For the endpoint of iron deficiency anemia of GI origin, significant differences (celecoxib vs. naproxen; celecoxib vs. ibuprofen) and non-significant differences (ibuprofen vs. naproxen) were observed in a manner consistent with the data presented above.

The analysis of clinically significant renal events\*, hospitalization for CHF and hypertension for mITT are described below in Table 10.

**Table 10. On-treatment Adjudicated Renal Events, Hospitalization for CHF and Hypertension**

	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid
N	8,030	7,990	7,933
<b>Subjects with Events, n(%)</b>			
Renal events	42 (0.5%)	73 (0.9%)	62 (0.8%)
Hospitalization for CHF	28 (0.3%)	38 (0.5%)	35 (0.4%)
Hospitalization for hypertension	25 (0.3%)	37 (0.5%)	32 (0.4%)
Any of the Above	89 (1.1%)	130 (1.7%)	120 (1.5%)
<b>Pairwise Comparison, HR (95% CI)</b>	<b>Celecoxib vs. Naproxen</b>	<b>Celecoxib vs. Ibuprofen</b>	<b>Ibuprofen vs. Naproxen</b>
Renal events	0.66 (0.44, 0.97)	0.54 (0.37, 0.79)	1.21 (0.86, 1.70)
Hospitalization for CHF	0.77 (0.47, 1.27)	0.70 (0.43, 1.13)	1.12 (0.71, 1.77)
Hospitalization for hypertension	0.76 (0.45, 1.28)	0.64 (0.38, 1.07)	1.16 (0.74, 1.90)
Any of the Above	0.72 (0.55, 0.95)	0.60 (0.46, 0.79)	1.19 (0.93, 1.52)

\*N.B. Renal events included a composite of predefined rises in creatinine levels (verified serum creatinine of ≥2.0 mg/dL,

(177 µmol/L) and an increase of ≥0.7 mg/dL (62 µmol/L), or hospitalization for acute renal failure (defined as a doubling in serum creatinine, or confirmation of hyperkalemia with ≥ 5.0% elevation in serum creatinine), or the initiation of hemodialysis or peritoneal dialysis.

In the ITT population for the endpoint of clinically significant renal events, only the pairwise comparison between celecoxib and ibuprofen was significant, HR 0.61 (0.44, 0.85), no significant differences were observed between treatment regimens in the incidence of hospitalization for congestive heart failure, and a significantly lower incidence of hospitalization for hypertension was observed between celecoxib and ibuprofen, HR 0.59 (0.36, 0.99).

*All-cause Mortality*

In the mITT populations celecoxib, naproxen and ibuprofen were associated with 53 (0.7%), 79 (1.0%), and 73 (0.9%) deaths, respectively. Significant differences were observed in the pairwise comparisons between celecoxib and either naproxen HR 0.65 (0.46, 0.92) or celecoxib and ibuprofen HR 0.68 (0.48, 0.97). In the ITT population the celecoxib, naproxen and ibuprofen were associated with 132 (1.6%), 163 (2.0%) and 142 (1.8%) deaths, respectively. No significant differences were observed in pairwise comparisons between treatments.

*ABPM Substudy*

In the PRECISION-ABPM substudy, among the total of 444 adjudicated patients, at Month 4, celecoxib-treated patients had the smallest change in 24-hour ambulatory systolic blood pressure (SBP) compared to ibuprofen and naproxen: celecoxib produced a slight reduction of 0.3 mmHg while ibuprofen and naproxen 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; a non-significant difference of -1.8 (p<0.119) mmHg between celecoxib and naproxen, and a non-significant difference of -2.1 mmHg (p=0.0787) between naproxen and ibuprofen.

*Pharmacokinetic properties*

*Absorption*