PRODUCT MONOGRAPH

Pr CELECOXIB

Celecoxib capsules

100 mg and 200 mg

Non-steroidal anti-inflammatory drug (NSAID)

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	Capsules, 100 mg and 200 mg	Croscarmellose sodium, lactose, magnesium stearate, povidone and sodium lauryl sulfate talc. Capsule contains gelatin, sodium lauryl sulphate and titanium dioxide. 100 mg ink (ammonia, FD&C blue aluminum lake, propylene glycol and shellac). 200 mg ink (ammonia, propylene glycol, shellac and yellow iron oxide).

INDICATIONS AND CLINICAL USE

CELECOXIB (celecoxib) is indicated for relief of symptoms associated with:

- Osteoarthritis,
- Adult Rheumatoid Arthritis, and
- Ankylosing Spondylitis

CELECOXIB is also indicated for the short-term (≤ 7 days) management of moderate to severe acute pain in adults in conditions such as the following:

- Musculoskeletal and/or soft tissue trauma including sprains,
- Postoperative orthopaedic, and
- Pain following dental extraction

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Use of CELECOXIB should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

CELECOXIB, as a NSAID, does NOT treat clinical disease or prevent its progression.
CELECOXIB, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (>65 years of age):

Evidence from clinical studies and postmarket experience suggests that use in geriatric population is associated with differences in safety (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics).

Paediatrics (<18 years of age*)*:

Safety and Efficacy have not been established in the paediatric population (see CONTRAINDICATIONS).

CONTRAINDICATIONS

CELECOXIB (celecoxib) is contraindicated in:

- The peri-operative setting of Coronary Artery Bypass Graft Surgery (CABG). Although celecoxib has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications (see CLINICAL TRIALS - Cardiovascular Safety).
- The third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants
- Severe uncontrolled heart failure
- Known hypersensitivity to celecoxib or to any of the components/excipients
- Demonstrated allergic-type reactions to sulfonamides
- History of asthma, urticaria, or allergic-type reactions after taking Acetylsalicylic Acid (ASA) or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see WARNINGS AND PRECAUTIONS - Hypersensitivity Reactions - Anaphylactoid Reactions).
- Active gastric / duodenal / peptic ulcer, active gastrointestinal bleeding
- Cerebrovascular bleedings
- Inflammatory bowel disease
- Severe liver impairment or active liver disease
- Severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see WARNINGS and PRECAUTIONS - Renal)
- Known hyperkalemia (see WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance)
- Safety and efficacy of celecoxib have not been established in the paediatric population under 18 years of age.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (see WARNINGS AND PRECAUTIONS - Cardiovascular; CLINICAL TRIALS – Cardiovascular Safety).

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing celecoxib to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as celecoxib, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see also WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance).
Randomized clinical trials with celecoxib have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing celecoxib.

Risk of Gastrointestinal (GI) Adverse Events (see WARNINGS AND PRECAUTIONS – Gastrointestinal System).

Use of NSAIDs, such as celecoxib, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

Risk in Pregnancy: Caution should be exercised in prescribing celecoxib during the first and second trimesters of pregnancy. Celecoxib is CONTRAINDICATED for use during the third trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see CONTRAINDICATIONS).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Celecoxib is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions (see DRUG **INTERACTIONS - Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs).**

Carcinogenesis and Mutagenesis

See **PART II - TOXICOLOGY – Carcinogenesis and Mutagenesis.**

Cardiovascular

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal (see ADVERSE REACTIONS). The risk may increase with dose and duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see CLINICAL TRIALS - Cardiovascular Safety - Meta-analysis from Chronic Usage Studies).

Caution should be exercised in prescribing CELECOXIB to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAIDs, such as celecoxib, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus blood pressure should be monitored regularly. Consideration should be given to discontinuing celecoxib should hypertension either develop or worsen with its use.

Use of NSAIDs, such as celecoxib, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renal-mediated mechanism (see WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

One of three randomized clinical trials of about 3 years duration showed a dose-related increase in serious cardiovascular events (mainly myocardial infarction), detectable at doses of celecoxib 200 mg twice daily or more, compared to placebo.

Endocrine and Metabolism

Corticosteroids: celecoxib is not a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids (see DRUG INTERACTIONS - Drug-Drug Interactions - Glucocorticoids).

Gastrointestinal System (GI)

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as celecoxib. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with celecoxib, even in the absence of previous GI tract symptoms. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high-risk patients, alternate therapies that do not involve NSAIDs should be considered (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using celecoxib and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

Caution should be taken if prescribing celecoxib to patients with a prior history of peptic / duodenal ulcer disease and/or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, paroxetine, fluoxetine, sertraline)

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of celecoxib when and if these adverse reactions appear.

Celecoxib exhibited a low incidence of gastroduodenal ulceration and serious clinically significant GI events within clinical trials (see ADVERSE REACTIONS - Clinical Trial Adverse

Drug Reactions). In a prospective long-term outcome study (CLASS), there were no significant differences in the incidence of complicated ulcers between patients who received a higher-than-therapeutic dose of celecoxib (400 mg BID) for OA and RA, in the presence of concomitant ASA (N = 882 patients), compared to ibuprofen 800mg TID and diclofenac 75 mg BID. The incidence of complicated and symptomatic ulcers was lower for celecoxib than for Ibuprofen in patients not taking ASA. In active-controlled studies, the endoscopic gastroduodenal ulceration rate observed with all doses of celecoxib was less than what was seen with the NSAID comparator and, in placebo-controlled studies, was similar to that seen with placebo (see PART II - CLINICAL TRIALS - Endoscopic Studies).

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Should urinary symptoms occur, in the absence of alternate explanation, treatment with celecoxib should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from hemophilia or platelet disorders should be carefully observed when celecoxib is administered.

Celecoxib does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see CLINICAL TRIALS - Special Studies - Platelets).

Anti-coagulants: Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of bleeding. Concurrent therapy of celecoxib with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects: NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike Acetylsalicylic Acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible. Celecoxib does not appear to inhibit platelet aggregation at indicated dosages (see CLINICAL TRIALS - Special Studies - Platelets).

Celecoxib and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA (see DRUG INTERACTIONS - Drug-Drug Interactions - Acetylsalicylic Acid or other NSAIDs).

Concomitant administration of celecoxib with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias: Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including celecoxib. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including celecoxib, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

In controlled clinical trials the incidence of anemia was 0.6% with celecoxib and 0.4% with placebo. Serious potentially fatal bleeding events have been reported, predominantly in the elderly, in patients receiving celecoxib concurrently with warfarin or similar agents (see DRUG INTERACTIONS - Drug-Drug Interactions and ADVERSE REACTIONS - Post-Market Adverse Drug Reactions).

Hepatic / Biliary / Pancreatic

As with other NSAIDs, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continuing therapy.

In controlled clinical trials of celecoxib, the incidence of borderline elevations of liver tests was 6% for celecoxib and 5% for placebo, and approximately 0.2% of patients taking celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib. Severe hepatic reactions, including liver necrosis and hepatic failure (with fatal outcomes or requiring liver transplant), fulminant hepatitis (with fatal outcome), cholestatic hepatitis (with fatal outcome) and jaundice have been reported with celecoxib.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g., eosinophilia, associated with rash, etc.), celecoxib should be discontinued (see CONTRAINDICATIONS).

If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Hypersensitivity Reactions

Allergies to Sulfonamides: See CONTRAINDICATIONS.

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occured in patients without known prior exposure to celecoxib. In post-marketing experience, very rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving celecoxib. Celecoxib should NOT be given to patients with the ASA-triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without

nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see CONTRAINDICATIONS).

ASA-Intolerance: Celecoxib should not be given to patients with the complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see CONTRAINDICATIONS).

Cross-Sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAID as well.

Serious Skin Reactions: see WARNINGS AND PRECAUTIONS- Skin.

Immune

See WARNINGS AND PRECAUTIONS - Infection - Aseptic Meningitis.

Infection

Celecoxib in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis: Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissues diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs, such as celecoxib. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop celecoxib should be discontinued and an ophthalmologic examination performed. Ophthalmic examination should be carried out at periodic intervals in any patient receiving celecoxib for an extended period of time.

Peri-Operative Considerations

Coronary Artery Bypass Graft Surgery: See CONTRAINDICATIONS.

Psychiatric

See WARNINGS AND PRECAUTIONS - Neurologic.

Renal

Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria and occasionally nephrotic syndrome and acute glomerulonephritis.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and those who are elderly. In such patients, renal function should be monitored. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs (see CONTRAINDICATIONS).

Caution should be used when initiating treatment with NSAIDS, such as celecoxib, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

Advanced Renal Disease: No information is available from controlled clinical studies regarding the use of celecoxib in patients with advanced kidney disease. In post-marketing experience, serious renal failure, including the need for dialysis, and fatalities have been reported in patients with impaired renal function. Therefore, treatment with celecoxib, as with NSAIDs, is not recommended in these patients with advanced renal disease. Kidney function should be monitored, especially in high-risk populations, such as the elderly, patients with cardiovascular disease and diabetes mellitus, as well as in the setting of concomitant use of diuretics and ACE inhibitors (see CONTRAINDICATIONS).

Fluid and Electrolyte Balance: Use of NSAIDs, such as celecoxib, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing celecoxib in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see WARNINGS AND PRECAUTIONS - Cardiovascular).

Use of NSAIDs, such as celecoxib, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (see CONTRAINDICATIONS).

Fluid retention has been observed in 2.1% of patients taking celecoxib in clinical trials (see ADVERSE REACTIONS –Clinical Trials Adverse Drug Reactions). In a prospective long-term outcome study (CLASS), hypertension was observed in 2.0%, 3.1% and 2.0% of patients receiving 400 mg BID celecoxib (N=3987), 800 mg TID ibuprofen (N=1985) and 75 mg BID diclofenac (N=1996), respectively. The corresponding rates for edema were: 3.7%, 5.2% and 3.5%, respectively (see ADVERSE REACTIONS - Clinical Trials Adverse Drug Reactions).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function / Reproduction

The use of celecoxib, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of celecoxib should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life threatening but may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib (see ADVERSE REACTIONS - Post-Market Adverse Drug Reactions). Patients appear to be at higher 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. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Special Populations

Pregnant Women: CELECOXIB is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see PART II - TOXICOLOGY).

Caution should be exercised in prescribing CELECOXIB during the first and second trimesters of pregnancy (see PART II - DETAILED PHARMACOLOGY - TOXICOLOGY).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Nursing Women: (See CONTRAINDICATIONS).

Paediatrics (<18 years of age): (See CONTRAINDICATIONS).

Geriatrics (>65 years of age): Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Celecoxib has been studied in elderly patients. Of the total number of patients who received celecoxib in clinical trials, more than 3,300 patients (25 %) were 65-74 years of age, while approximately 1,300 additional patients (10 %) were 75 years and over (see ADVERSE REACTIONS). While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger patients (see WARNINGS AND PRECAUTIONS - Gastrointestinal System (GI) and ADVERSE REACTIONS - Adverse Drug Reaction Overview).

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. The maximum recommended dose in CYP2C9 poor metabolizers is 100 mg daily (see DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION sections).

Monitoring and Laboratory Tests

Cardiovascular: (Hypertension): Blood pressure should be monitored regularly during therapy with celecoxib.

Hematologic: Patients on long-term treatment with NSAIDs, including celecoxib, should have their hemoglobin, hematocrit, and blood cell count checked if they exhibit any signs or symptoms of anemia or blood loss.

Concurrent therapy of celecoxib with warfarin requires close monitoring of the international normalized ratio (INR).

Hepatic: 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. If abnormal liver tests persist or worsen, celecoxib should be discontinued.

Renal: Renal function (serum creatinine and serum urea etc.) should be monitored in high-risk populations, such as the elderly, patients with advanced renal disease, patients with cardiovascular disease and diabetes mellitus, as well as in the setting of concomitant use of diuretics and ACE inhibitors (see **CONTRAINDICATIONS**). If abnormal renal tests persist or worsen, celecoxib should be discontinued.

Patients on long-term treatment with NSAIDs, including celecoxib, should have their electrolytes, such as serum potassium, checked regularly if they exhibit any signs or symptoms of renal disease.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Of the celecoxib treated patients in controlled trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 were patients with post-surgical pain. More than 8,500 patients have received a total daily dose of celecoxib of 200 mg (100 mg BID or 200 mg QD) or more, including more than 400 treated at 800 mg (400 mg BID). Approximately 3,900 patients have received celecoxib at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Celecoxib has been studied in elderly patients. Of the total number of patients who received celecoxib in clinical trials, more than 3,300 patients were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger patients. In GI endoscopy studies involving over 800 elderly patients, the rate of gastroduodenal ulceration was not different in elderly patients compared to the young. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In clinical studies comparing renal function as measured by the GFR, urea and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

Clinical Trial Adverse Drug Reactions - New Drug Submission (NDS) Arthritis Trials

Table 1 lists all adverse events, regardless of causality, occurring in ≥ 2% of patients receiving celecoxib from 12 controlled studies conducted in patients with osteoarthritis and rheumatoid arthritis that included a placebo and/or a positive control group.

Table 1 - Events Occurring in ≥ 2% of Celecoxib Patients From Original NDS Arthritis Trials

	Celecoxib 100-200 mg BID and 200 mg QD	Placebo	Naproxen 500 mg BID	Ibuprofen 800 mg TID	Diclofenac 75 mg BID
	(n=4146)	(n=1864)	(n=1366)	(n=387)	(n=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a Whole					
Back pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral edema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and Peripheral Nervous System					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving celecoxib and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the celecoxib treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of celecoxib patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The adverse event profile from the long-term outcomes trial (at 4- and 2-fold the recommended doses for Osteoarthritis (OA) and Rheumatoid Arthritis (RA), respectively) is similar to those reported in the arthritis-controlled trials. In the arthritis-controlled trials, the celecoxib endoscopic gastroduodenal ulceration rate was consistently less than what was seen with the NSAID comparators. In the long-term outcome study however, there was no statistically significant difference for the incidence of complicated ulcers (perforation, obstruction, or bleeding) among the celecoxib 400mg BID and NSAID comparators (see CLINICAL TRIALS - Special Studies). The major differences in study design and patient populations preclude direct comparison between the GI endpoint results in the arthritis controlled and the long-term outcome trials.

The incidences of withdrawals due to adverse events and the incidences of selected serious adverse events (i.e., those causing hospitalization or felt to be life-threatening or otherwise medically significant) observed in this trial are shown in Table 2. No significant differences were seen across treatment groups in the incidences of serious adverse events (see Table 2).

Table 2 - Summary of Withdrawal and Serious Cardiovascular Adverse Event Data From the CLASS Trial Incidence Rates (%) in all OA and RA Patients and in Patients Without ASA

	Celecoxib 400 mg BID	**Diclofenac 75 mg BID**	**Ibuprofen 800 mg TID**
All Patients	**(n=3987)**	**(n=1996)**	**(n=1985)**
All withdrawals	22.4	26.5*	23.0
Withdrawals for GI Symptoms	12.2	16.6*	13.4
Serious adverse events	6.8	5.6	6.0
Myocardial infarction (fatal and non-fatal)	0.5	0.2	0.5
Deep vein thrombosis	0.2	0.3	0.0
Cardiac failure	0.2	0.1	0.5
Unstable angina	0.2	0.2	0.0
Cerebrovascular disorder	0.1	0.3	0.3
Patients Without ASA	**(n=3105)**	**(n=1551)**	**(n=1573)**
All withdrawals	21.2	25.4*	22.5
Withdrawals for GI Symptoms	11.5	15.4*	13.2
Serious adverse events	5.0	4.2	4.3
Myocardial infarction (fatal and non-fatal)	0.2	0.1	0.1
Deep vein thrombosis	0.2	0.2	0.0
Cardiac failure	0.1	<0.1	0.3
Unstable angina	<0.1	0.0	0.0
Cerebrovascular disorder	<0.1	0.3	0.1

*p<0.05 vs. celecoxib

The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality:

CELECOXIB
(100 - 200 mg BID or 200 mg QD)

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

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

General: Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Resistance Mechanism Disorders: Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media

Central, Peripheral Nervous System:	Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo
Female Reproductive:	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis
Male Reproductive:	Prostatic disorder
Hearing and Vestibular:	Deafness, ear abnormality, earache, tinnitus
Heart Rate and Rhythm:	Palpitation, tachycardia
Liver and Biliary System:	ALT increased, AST increased, hepatic function abnormal
Metabolic and Nutritional:	Urea increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase
Musculoskeletal:	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
Platelets (bleeding or clotting):	Ecchymosis, epistaxis, thrombocythemia
Psychiatric:	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Hemic:	Anemia
Respiratory:	Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia
Skin and Appendages:	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
Application Site Disorders:	Cellulitis, dermatitis contact, injection site reaction, skin nodule
Special Senses:	Taste perversion
Urinary System:	Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
Vision:	Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Adverse Events From Ankylosing Spondylitis Studies:

A total of 896 patients were treated with celecoxib in placebo- and active- controlled ankylosing spondylitis studies for a maximum duration of 12 weeks. Celecoxib was also studied in one long-term open label extension study up to 2 years in 215 patients with ankylosing spondylitis. The average daily dose was 200 mg. The types of adverse events reported in the ankylosing spondylitis studies were generally similar to those reported in the arthritis studies. The percentage of patients with hypertension (6.1%) and serious GI adverse events (3.7%) in the 2-year, open-label extension study, were greater than those reported in the 12-week studies, respectively of

0.7% and 0.0 %. The most common GI disorders reported in the 2-year extension study compared to those reported in the 12-week studies include Diarrhea (15.0% vs. 4.5%), Abdominal Pain upper (13.6 % vs. 3.8%), Dyspepsia (9.8% vs. 3.7%), Nausea (5.6% vs. 2.8%) and Abdominal Pain (5.6% vs. 1.5%). The percentage of patients with cardio-vascular events (1.4%) in the 2-year, open-label extension study was similar to that observed in the CLASS trials.

Adverse Events From Analgesia and Dysmenorrhea Studies

Approximately 1,700 patients were treated with celecoxib in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose (up to 400 mg) of study medication. Doses up to 600 mg/day of celecoxib were studied in primary dysmenorrhea and post-orthopaedic surgery pain studies. The types of adverse experiences in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only new adverse event reported was alveolar osteitis (dry socket) in the post-oral surgery pain studies.

In approximately 700 patients treated with celecoxib in the post-general and orthopaedic surgery pain studies, the most commonly reported adverse experiences were nausea, vomiting, headache, dizziness and fever.

Other serious adverse reactions which occur rarely (estimated <0.1%) regardless of causality: the following adverse events have occurred rarely in patients taking celecoxib.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis
Gastrointestinal:	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, cholelithiasis, ileus
Hemic and Lymphatic:	Thrombocytopenia
Liver and Biliary System:	Cholelithiasis, hepatitis, jaundice, liver failure
Metabolic:	Hypoglycemia
Nervous System:	Ataxia
Renal:	Acute renal failure
General:	Sepsis, sudden death

Serious Cardiovascular Adverse Events: Long-term Studies Involving Patients with Sporadic Adenomatous Polyps

Two studies involving patients with sporadic adenomatous polyps were conducted with celecoxib: the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Colorectal Sporadic Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint of cardiovascular 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, as shown below:

Serious Cardiovascular Adverse Events in the APC and PreSAP Trials

Number (%) **of Subjects** [Hazards Ratio[a] (95% Confidence Interval) Compared to Placebo]

	APC Trial			PreSAP Trial	
Adjudicated Endpoint[b]	**Placebo N = 679**	**Celecoxib 200 mg BID N = 685**	**Celecoxib 400 mg BID N = 671**	**Placebo N = 628**	**Celecoxib 400 mg QD N = 933**
CV death	**1 (0.1)**	**5 (0.7)** [4.9 (0.6, 42.2)]	**6 (0.9)** [6.2 (0.7, 51.4)]	**4 (0.6)**	**4 (0.4)** [0.7 (0.2, 2.7)]
CV death or MI	**4 (0.6)**	**14 (2.0)** [3.5 (1.1, 10.6)]	**15 (2.2)** [3.9 (1.3, 11.7)]	**7 (1.1)**	**13 (1.4)** [1.3 (0.5, 3.2)]
CV death, MI, or stroke (APTC endpoint)	**6 (0.9)**	**17 (2.5)** [2.8 (1.1, 7.2)]	**20 (3.0)** [3.4 (1.4, 8.5)]	**12 (1.9)**	**21 (2.3)** [1.2 (0.6, 2.4)]

BID = Twice daily; QD = Once daily; N = Number of subjects treated; CV = Cardiovascular; MI = Myocardial infarction; APTC = Antiplatelet Trialists' Collaboration; HF = Heart failure.

[a] Hazards ratios are based on event rates per subject-year of exposure to study medication.

[b] Includes only serious adverse events, for all randomized subjects, adjudicated and categorized according to a pre-specified scheme by an independent Cardiovascular Safety Committee blinded to randomized treatment assignments.

Investigator Reports of Adverse Reaction from Long-term, Placebo-controlled Polyp Prevention Studies

Indications and dosages of the PreSAP and APC trials are not approved in Canada. Exposure to celecoxib in the APC and PreSAP trials was 400 to 800 mg daily for up to 3 years. Among adverse reactions that occurred in higher percentages of patients than in the arthritis pre-marketing trials (treatment durations up to 12 weeks (see ADVERSE REACTIONS - Clinical Trial Adverse Drug Reactions), hypertension was reported at an incidence of 12.5 % in the celecoxib group (400-800 mg daily dose) compared to 9.8 % in the placebo group.

Abnormal Hematologic and Clinical Chemistry Findings

During the controlled clinical trials, there was an increased incidence of hyperchloremia in patients receiving celecoxib compared with patients on placebo. Other laboratory abnormalities that occurred more frequently in the patients receiving celecoxib included hypophosphatemia, and elevated urea. These laboratory abnormalities were also seen in patients who received comparator NSAIDs in these studies. The clinical significance of these abnormalities has not been established.

Post-Market Adverse Drug Reactions

Additional reports of serious adverse events temporally associated with celecoxib during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to celecoxib exposure.

Blood and Lymphatic System Disorders: Pancytopenia, agranulocytosis, aplastic anemia, leukopenia*

Immune System Disorders: Serious allergic reactions, anaphylactic shock

Psychiatric Disorders: Confusion*, hallucination

Nervous System Disorders: Aggravated epilepsy, aseptic meningitis, ageusia, anosmia

Ear and Labyrinth Disorders:	Decreased hearing
Eye Disorders:	Conjunctivitis
Cardiac Disorders:	Congestive heart failure, heart failure, myocardial infarction, arrhythmia[**], syncope[**]
Vascular Disorders:	Vasculitis, cerebral hemorrhage, pulmonary embolism (some with fatal outcome), flushing[**]
Respiratory, Thoracic and Mediastinal Disorders:	Bronchospasm
Gastrointestinal Disorders:	Gastrointestinal hemorrhage, acute pancreatitis, gastric ulcer[**], duodenal ulcer[**], esophageal ulcer[**]
Hepatobiliary Disorders:	Liver failure (with fatal outcome), fulminant hepatitis (with fatal outcome), liver necrosis, cholestasis, cholestatic hepatitis (with fatal outcome), hepatitis, jaundice
Skin and Subcutaneous Tissue Disorders:	Angioedema, isolated reports of skin exfoliation including: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, drug rash with eosinophilia and systemic symptoms (DRESS, or hypersensitivity syndrome), acute generalized exanthematous pustulosis (AGEP), bullous eruption, dermatitis bullous[**]
Reproductive System and Breast Disorders:	Menstrual disorder, female fertility decreased (See WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction)
Musculoskeletal and Connective Tissue Disorders:	Myositis
Renal and Urinary Disorders:	Acute renal failure, interstitial nephritis, nephrotic syndrome, acute glomerulonephritis, minimal change disease, hyponatremia
General Disorders and Administration Site Conditions	Chest pain

[*]Noted in both cumulative review of clinical trial data set and post-market adverse drug reactions
[**] Identified in cumulative review of clinical trial data set

Serious bleeding events (some of them fatal) have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin or similar agents (see **DRUG INTERACTIONS**).

DRUG INTERACTIONS

Overview

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver (commonly used drugs which are also substrates and/or inhibitors for cytochrome P450 2C9

include warfarin, fluoxetine, fluconazole, phenytoin, and tolbutemide). Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. Furthermore, 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.

In vitro studies indicate that celecoxib, although not a substrate, is a relatively weak inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by P450 2D6.

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

Drug-Drug Interactions

Acetylsalicylic Acid (ASA) or other NSAIDs: The use of celecoxib in addition to any other NSAID, including over-the-counter ones (such as ASA and ibuprofen), for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

As with all other NSAIDs, the concomitant administration of ASA with celecoxib results in an increased rate of GI ulceration or other complications, compared to use of celecoxib alone (see CLINICAL TRIALS - Special Studies). In the long-term outcomes study (at 4- and 2-fold the recommended doses for OA and RA, respectively), there was no statistically significant difference for the incidence of complicated ulcers between celecoxib and comparator groups in patients taking ASA. Concomitant low dose ASA use increased the rate of complicated ulcers to four times that of patients not taking ASA. Resulting incidence rate for complicated ulcers in patients taking celecoxib and ASA was 1.02%.

Antacids: Co-administration of celecoxib with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC.

Pharmacokinetic parameters at steady state such as AUC and C_{max} for both celecoxib and omeprazole were comparable when administered alone or together in healthy volunteers (n=36). However increased Gastrointestinal (GI) and skin adverse events such as diarrhoea, abdominal pain, pruritis and rash were observed in combined arm of celecoxib+omeprazole.

Anticoagulants: Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing celecoxib therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily

doses of 2-5 mg of warfarin (dose sufficient to prolong prothrombin times to 1.2 to 1.7 times their baseline values). In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, serious bleeding events (some of them fatal) have been reported, predominantly in the elderly, in association with increases in prothrombin time, in patients receiving celecoxib concurrently with warfarin or similar agents (see ADVERSE REACTIONS Post-Market Adverse Drug Reactions).

Anti-Hypertensives: NSAIDs may diminish the anti-hypertensive effects of Angiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration. Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might result in deterioration of renal function, including increased risk for acute renal failure and hyperkalemia, especially in patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

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 treated 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 treated with placebo; this difference was statistically significant.

Anti-platelet Agents: There is an increased risk of bleeding, via inhibition of platelet function, where anti-platelet agents are combined with NSAIDs. Celecoxib does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see CLINICAL TRIALS - Special Studies and Platelets; WARNINGS AND PRECAUTIONS - Hematologic - Anti-platelet Effects).

Cyclosporin and Tacrolimus: Although this interaction has not been studied with celecoxib, co-administration of cyclosporin or tacrolimus and any NSAID may increase the nephrotoxic effect of cyclosporin or tacrolimus due to the NSAID's effect on renal prostaglandins. Renal function should be monitored when celecoxib and either of these drugs is used in combination.

Digoxin: No interaction data is available for the co-administration of celecoxib and digoxin. However an increase in serum digoxin level has been noted with some NSAIDS.

Diuretics: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the effects of diuretics. This response has been attributed to inhibition of renal prostaglandin synthesis. Although prospective studies of celecoxib with diuretics have not been conducted, no adverse reactions indicative of elevations in blood pressure were seen in clinical trials in which arthritis patients were taking celecoxib concurrently with diuretics (n=485). No adverse reactions indicative of sodium retention or renal impairment were seen in clinical trials in patients taking celecoxib concurrently with diuretics.

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib

metabolism via P450 2C9 by fluconazole (see ACTION AND CLINICAL PHARMACOLOGY Pharmacokinetics - Metabolism). Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.

Glucocorticoids: Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increase the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (> 65 years of age) individuals.

Ketoconazole: Celecoxib did not have a significant effect on the pharmacokinetics of ketoconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with Celecoxib 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Methotrexate: Celecoxib did not have a significant effect on the pharmacokinetics of 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).

Oral Hypoglycemics: The effect of celecoxib on the pharmacokinetics and/or pharmacodynamics of glyburide and tolbutemide has been studied and clinically important interactions have not been found.

Phenytoin: Celecoxib did not have a significant effect on the pharmacokinetics of phenytoin.

Other Drug Interactions: No drug interaction data are available for celecoxib and the co-administration of the following products: acetaminophen, alcohol, aminoglycosides, bone marrow depressants, butemide, cholestyramine, colchicine, corticosteroids, gold compounds, indapamide, insulin, nephrotoxic agents, nonsteroidal anti-inflammatory agents, potassium supplements, probenecid, valproic acid, zidovudine.

Drug-Food Interactions

When celecoxib capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media.

Drug-Herb Interactions

The interaction of celecoxib with herbal medications or supplements has not been studied.

Drug-Laboratory test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Hepatic Impairment: CELECOXIB (celecoxib) capsules should be introduced at the lowest dose in patients with mild hepatic impairment (Child-Pugh 5-6). The daily recommended dose of CELECOXIB capsules in patients with moderate hepatic impairment (Child-Pugh 7-9) should be reduced by 50% and should be given at the lowest dose of 100 mg once daily (see ACTION AND CLINICAL PHARMACOLOGY- Special Populations and Conditions). CELECOXIB is contraindicated in patients with severe hepatic impairment (Child-Pugh >9) (see **CONTRAINDICATIONS**).

Renal Insufficiency: No dosage adjustment is necessary for patients with creatinine clearance > 30 mL/min (see ACTION AND CLINICAL PHARMACOLOGY - Special Populations and Conditions). CELECOXIB is contra-indicated in patients with severe renal impairment (estimated creatinine clearance < 30 mL/min) (see CONTRAINDICATIONS).

Elderly (> **65 years of age):** In the elderly, frail and debilitated, the dosage should be reduced to the lowest level providing control of symptoms, and adjusted when necessary (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics).

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. The maximum recommended dose in CYP2C9 poor metabolizers is 100 mg daily (see DRUG INTERACTIONS and WARNINGS AND PRECAUTIONS - Special Populations sections).

Recommended Dose and Dosage Adjustment - 18 years of age and older

Use of CELECOXIB should be limited to the lowest effective dose for the shortest possible duration of treatment (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Osteoarthritis: The recommended daily dose of CELECOXIB is 200 mg administered as a single dose or as two divided doses (100 mg twice per day). Maximum dose = 200 mg a day.

Rheumatoid Arthritis: The recommended starting dose of CELECOXIB is 100 mg twice per day, which may be increased to 200 mg twice per day if necessary. Maximum dose = 200 mg twice a day.

Ankylosing Spondylitis: The recommended daily dose of CELECOXIB is 200 mg administered as a single dose or as two divided doses (100 mg twice a day). Maximum dose = 200 mg a day.

Management of Acute Pain: The recommended dose of CELECOXIB is 400 mg as a single dose on the first day followed by 200 mg once daily on subsequent days up to a maximum of 7 days. Patients may be instructed to take an additional dose of 200 mg on any given day, if needed. Maximum dose = 400 mg a day for up to 7 days.

Administration

Capsules should be swallowed whole. DO NOT open, divide, crush, or chew the capsules.
CELECOXIB can be taken with or without food.

Missed Dose

Patients who miss one or more doses of CELECOXIB should not increase the dose of CELECOXIB to compensate for the missed dose or doses, but should continue therapy as soon as possible, then take the next dose at the scheduled time.

OVERDOSAGE

No overdoses of celecoxib were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity.

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animals. The mechanism of action of celecoxib is believed to be related to inhibition of cyclooxygenase-2 (COX-2). COX-2 is expressed at high levels in inflamed tissues where it is induced by mediators of inflammation. COX-2 also plays physiological roles in a limited number of tissues, including those of the female reproductive tract, the kidney and possibly the vascular endothelium. COX-2 has the same catalytic activity as COX-1. COX-1 is expressed constitutively in most tissues including the gastrointestinal tract, kidney, lungs, brain, and platelets. The prostaglandins produced by COX-1 play key roles in the maintenance of physiological functions such as platelet aggregation and are among the factors that maintain the GI mucosal barrier. At therapeutic concentrations (see DOSAGE AND ADMINISTRATION) celecoxib inhibits COX-2 and does not inhibit COX-1.

Pharmacokinetics

The pharmacokinetics of celecoxib have been evaluated in approximately 1500 individuals. In addition to healthy, young and elderly volunteers (male and female), pharmacokinetic

measurements have been done in patients and also in special populations including individuals with hepatic or renal impairment.

Absorption: Peak plasma levels of celecoxib occur approximately 3 hours after an oral dose. Both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional across the clinical dose range of 100-200 mg studied. Under fasting conditions, at higher doses, there is a less than proportional increase in C_{max} and AUC which is thought to be due to the low solubility of the drug in aqueous media. Because of the low solubility, absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before Day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in Table 3.

Table 3
Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Mean (%CV) Pharmacokinetic (PK) Parameter Values (95% Confidence Interval)				
C_{max}, ng/mL	**T_{max}, hr**	**Effective $t_{1/2}$, hr**	**V_{ss}/F, L**	**CL/F, L/hr**
705 (38) (484.2-925.0)	2.8 (37) (1.95-3.71)	11.2 (31) (8.3-14.0)	429 (34) (307.2-551.5)	27.7 (28) (21.3-34.1)

[1]Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects: When celecoxib capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Co-administration of celecoxib with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC. Celecoxib capsules can be administered without regard to the timing of meals.

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

Metabolism: Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*3 polymorphism. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. The maximum recommended dose in CYP2C9 poor metabolizers is 100 mg daily (see WARNINGS AND PRECAUTIONS, Special Populations, CYP2C9 Poor Metabolizers and DRUG INTERACTIONS.).

In a pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP2C9*1/*1, CYP2C9*1/*3, or CYP2C9*3/*3, the median C_{max} and AUC 0-24 of celecoxib on Day 7 were approximately 4-fold and 7-fold, respectively, in subjects

genotyped as CYP2C9*3/*3 compared to other genotypes. In three separate single dose studies, involving a total of 5 subjects genotyped as CYP2C9*3/*3, single-dose AUC 0-24 increased by approximately 3-fold compared to normal metabolizers. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3 - 1.0% among different ethnic groups.

Excretion: Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabelled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$)) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special Populations and Conditions

Geriatrics: At steady state, elderly subjects (over 65 years old) had a 40% higher C_{max} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{max} and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for elderly patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose, and as with all other NSAIDs, exercise caution in the use of higher doses.

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

Hepatic Insufficiency: A pharmacokinetic study in subjects with mild (Child-Pugh 5-6) and moderate (Child-Pugh 7-9) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, celecoxib capsules should be introduced at a reduced dose in patients with moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of celecoxib in patients with severe hepatic impairment is not recommended (see **CONTRAINDICATIONS**).

Renal Insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied (see **Contraindications**).

STORAGE AND STABILITY

Store between 15°C and 30°C.

Keep in a safe place out of reach of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CELECOXIB (celecoxib):

Capsules

100 mg: Each white to off-white, hard gelatin capsule, ink-printed in blue with a band on the cap into which "CXB" appears in white, and with another band on the body into which "100" appears in white, contains 100 mg celecoxib and the following non medicinal ingredients: croscarmellose sodium, lactose, magnesium stearate, povidone, sodium lauryl sulfate and talc. The gelatin capsule shells and caps contain: gelatin, sodium lauryl sulphate and titanium dioxide, and pharmaceutical ink (ammonia, FD&C blue aluminum lake, propylene glycol and shellac). Available in HDPE bottles of 100 and 500 capsules.

200 mg: Each white to off-white, hard gelatin capsule, ink-printed in gold with a band on the cap into which "CXB" appears in white, and with another band on the body into which "200" appears in white, contains 200 mg celecoxib and the following non medicinal ingredients: croscarmellose sodium, lactose, magnesium stearate, povidone, sodium lauryl sulfate and talc. The gelatin capsule shells and caps contain: gelatin, sodium lauryl sulphate and titanium dioxide and pharmaceutical ink (ammonia, propylene glycol, shellac and yellow iron oxide). Available in HDPE bottles of 100 and 500 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

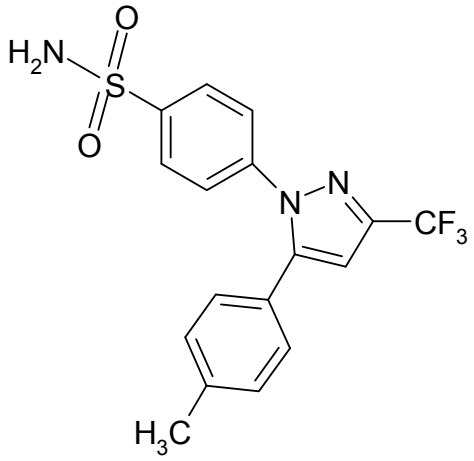
Proper name: Celecoxib

Chemical name: 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide.

Molecular formula: $C_{17}H_{14}F_3N_3O_2S$

Molecular weight: 381.38 g/mol

Structural formula:



Description: Celecoxib is a white powder.

Melting Range: The melting range of celecoxib is 160-164°C.

pH/ Solubility: Celecoxib is a neutral molecule at physiologic pH. Celecoxib is defined as "practically insoluble" in water according to the USP classification system (with an n-octanol/water partition coefficient of 10,000 at physiologic pH (7.0)).

pKa: Celecoxib is weakly acidic with a pKa of 11.1.

Chirality: Celecoxib does not contain a chiral center; therefore stereoisomer-dependent pharmacology is not relevant.

CLINICAL TRIALS

Comparative Bioavailability Studies

Single dose, single center, randomized, blinded, 2-period, 2-sequence, crossover, comparative bioavailability study of CELECOXIB 200 mg Capsules of Laboratoire Riva Inc., was performed versus CELEBREX of Pfizer Canada Inc., administered as 1 x 200 mg Capsules to 19 healthy male volunteers in the fasting state. Bioavailability data were measured and the results are summarized in the following table:

Celecoxib (1 x 200 mg capsule) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T (ng·h/mL)	5127.1 5251.5 (21.7)	4873.0 4980.4 (21.7)	105.21	98.83-112.01
AUC_I (ng·h/mL)	5400.0 5522.5 (20.8)	5207.0 5304.6 (19.9)	103.71	97.65-110.14
C_{max} (ng/mL)	563.8 621.9 (46.0)	536.7 605.7 (48.2)	105.04	90.40-122.06
T_{max}§ (h)	2.50 (1.00 – 5.00)	3.00 (2.00 – 12.00)		
$T_{½}$€ (h)	8.18 (33.5)	9.52 (37.4)		

* CELECOXIB, Laboratoire Riva Inc., Blainville, Canada
† Celebrex™, Pfizer Inc. Kirkland, Québec, Canada
§ Expressed as the median (range)
€ Expressed as the arithmetic mean (CV%)

Study results

Randomized clinical trials with celecoxib have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

Osteoarthritis: The clinical effectiveness of celecoxib in the treatment of the signs and the symptoms of osteoarthritis (OA) of the knee and hip was demonstrated in placebo- and active-controlled clinical trials of up to 12 weeks duration, involving approximately 4,200 patients. Celecoxib demonstrated significant reductions in joint pain and disease activity, and also improvement in patient functional activity and health-related quality of life compared to placebo. Clinically significant effects on joint pain were seen as early as 24 hours after the first dose of celecoxib. Doses of 200 mg BID provided no additional efficacy above that seen with 100 mg BID. In the repeated dose OA studies with 100 mg BID of celecoxib, pain was significantly decreased by the end of the first day of dosing, continued to be significantly less than placebo and was comparable to naproxen 500 mg BID, diclofenac 75 mg BID, and ibuprofen 800 mg TID.

A total daily dose of 200 mg has been shown to be equally effective when administered as 100 mg BID or 200 mg QD. Response to celecoxib was independent of age, gender, severity, or duration of OA. Celecoxib has shown continued efficacy at doses of up to 400 mg a day in a long-term (up to 12 months), open label study of 2,500 patients.

In patients with OA, treatment with celecoxib 100 mg BID or 200 mg QD resulted in improvement in functional activity as demonstrated by an improvement in pain, stiffness, function and total WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scores. Improvement in quality of life, as measured by the MOS-SF-36 (Short Form 36 Item Health Survey) has been shown by improvements in Physical Function, Role Physical, Bodily Pain, Vitality and Social Functioning domains.

Rheumatoid Arthritis: The clinical effectiveness of celecoxib in the treatment of the signs and the symptoms of rheumatoid arthritis (RA) was demonstrated in placebo- and active-controlled clinical trials of up to 24 weeks in duration, involving approximately 2,100 patients. Celecoxib demonstrated significant reductions in joint tenderness and pain, joint swelling, disease activity, and morning stiffness compared to placebo. Improvements were demonstrated in the ACR20 Index for RA (American College of Rheumatology 20% Responder Index), patient functional activity, and health-related quality of life compared to placebo. Celecoxib doses of 100 mg BID and 200 mg BID were similar in efficacy and both were comparable to naproxen 500 mg BID. Although celecoxib 100 mg BID and 200 mg BID provided similar efficacy overall, some patients derive additional benefit from the 200 mg BID dose. Doses of 400 mg BID provided no additional efficacy above that seen with 100-200 mg BID.

Additional studies demonstrated that celecoxib 200 mg BID was comparable to diclofenac 75 mg BID and ibuprofen 800 mg TID. Response to celecoxib was independent of age, gender, severity, or duration of RA. In an open label study of up to 12 months in approximately 1,900 RA patients, celecoxib has shown continued efficacy.

In patients with RA, treatment with celecoxib 200 mg BID resulted in improvement in functioning as shown by an improvement in the Health Assessment Questionnaire (HAQ) functional disability index. Improvement in quality of life as measured by the MOS-SF-36 has been shown by improvements in Physical Function, Role Physical Bodily Pain, Vitality and Social Functioning domains. Compared to celecoxib 100 mg BID, celecoxib 200 mg BID resulted in greater improvement in the HAQ disability index and the MOS-SF-36 domains of Physical Function and Bodily Pain.

Ankylosing Spondylitis: Celecoxib has been investigated in 896 patients in placebo and active (diclofenac, naproxen or ketoprofen) controlled clinical trials of 6 weeks (one trial) and 12 weeks (three trials) duration for the symptomatic treatment of Ankylosing Spondylitis. At doses of 100 mg BID, 200 mg once daily, and 400 mg once daily, celecoxib was statistically superior to placebo for all measures of efficacy including global pain intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale) and functional impairment (Bath Ankylosing Spondylitis Functional Index). Studies results for efficacy endpoints are presented in Table 4.

Table 4: Celecoxib Clinical Efficacy Parameters in Ankylosing Spondylitis Trials

	Placebo	Celecoxib 200 mg TDD[b]	Celecoxib 400 mg[1] TDD[c]	Ketoprofen 100 mg BID	Naproxen 500 mg BID	Diclofenac 150 mg TDD[d]
Study 193	**N=156**	**N=137**	**N=161**	**- -**	**N=157**	
Global Pain Intensity[a]						
Week 12	-9.9	-30.0*	-30.4*	- -	-36.3*	- -
Bath Ankylosing Spondylitis Functional Index (BASFI) scores						
Week 12 Mean Change	1.6	-8.6*	-12.5*	- -	-16.1*,[2]	- -
Global Disease Activity (VAS)						
Week 12 Mean Change	-6.0	-21.5*	-22.7*	- -	-27.8*,[2]	- -
Responder Analysis (ASAS-20 criteria)						
Week 12 Responder, n (%)	41(26)	60(44)*	86(53)*	- -	98(62) *,[2]	- -
Study 137	**N=76**	**N=80**		**N=90**		
Global Pain Intensity[a]						
Week 6	-11.9	-25.7*	- -	-22.5	- -	- -
Bath Ankylosing Spondylitis Functional Index (BASFI) scores						
Week 6 Mean Change	1.3	-11.9*	- -	-6.0*	- -	- -
Study 243 (FAS)	**- -**	**N=126 (N=151)**	**N=124 (N=147)**	**- -**	**- -**	**N=123 (N=154)**
Global Pain Intensity[a]						
Week 12	- -	-29.1**	-31.7**	- -	- -	-32.7
Bath Ankylosing Spondylitis Functional Index (BASFI) scores (FAS population)						
Week 12 Mean Change	- -	-0.8[3]	-0.9[3]	- -	- -	-0.9[3]
Responder Analysis (ASAS-20 criteria)						
Week 12 Responder, n (%)	- -	69(45.4)[3]	79(53.4)[3]	- -	- -	90(58.4)[3]
Study 247	**- -**	**N=107**	**N=108**	**- -**	**- -**	**N=115**
Global Pain Intensity[a]						
Week 12	- -	-25.8**	-30.6**	- -	- -	-28.2
Bath Ankylosing Spondylitis Functional Index (BASFI) scores						
Week 12 Mean Change	- -	-14.1[3]	-16.1[3]	- -	- -	-17.1[3]
Responder Analysis (ASAS-20 criteria)						
Week 12 Responder, n (%)	- -	55(51.4)[3]	65(60.2)[3]	- -	- -	66(57.4)[3]

[1] 400 mg TDD is not approved in Canada for this indication.

* Statistically significant difference vs. placebo ($p < 0.05$), based on Analysis of Covariance model with the effects of treatment and centre, and baseline values as covariate.

** Differences compared to diclofenac were not statistically significant ($p > 0.50$), based on Analysis of Covariance model (for Study 243, baseline value and age as covariates and treatment, gender and centers as factors; for Study 247, baseline value as a covariate and treatment and centers as factors.

[2] Statistically significant difference vs. celecoxib 200 QD ($p < 0.05$)

[3] no significant treatment groups difference

[a] As measured using 100 mm Visual Analog Scale (Patient's assessment). All values represent least squares mean changes from baseline to the end of treatment, with last observation carried forward for patients who withdrew prior to the end of treatment.

[b] Celecoxib 100 mg twice daily in study 137, or 200 mg once daily in Studies 193, 243, and 247.

[c] Celecoxib 200 mg BID (Study 243 and 247) or 400 mg QD (study 193)
[d] Diclofenac Sustained Release 75 mg twice daily in Study 243, or Diclofenac 50 mg three times daily in Study 247.
FAS=Full analysis set

Analgesia: In acute analgesic models of post-oral surgery pain and post-orthopaedic surgery pain, celecoxib relieved pain that was rated by patients as moderate to severe. Single doses of celecoxib provided pain relief within 30- 60 minutes. In replicate multiple dose studies of post-orthopaedic surgery pain, celecoxib was effective in reducing pain without additional analgesic medication.

Special Studies

Clinical Experience with Higher-than-therapeutic Dose for OA and RA (800 mg/day) in the presence of concomitant ASA: Celecoxib Long-term Arthritis Safety Study (CLASS)

Study Design: A prospective, long-term outcome study was conducted in approximately 5800 OA and 2200 RA patients. Patients received celecoxib 400 mg BID (4-fold and 2-fold greater than the daily recommended 200 mg OA and 400 mg RA doses, respectively), ibuprofen 800 mg TID or diclofenac 75 mg BID (common therapeutic doses for OA and RA) for a median exposure of 9 months for celecoxib and diclofenac, and 6 months for ibuprofen. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction). Additional protocol specified endpoints included the incidence of symptomatic ulcers (gastroduodenal ulcers identified based on UGI symptoms such as abdominal pain, dyspepsia, nausea, diarrhea or vomiting) and clinically relevant decreases in hemoglobin (>2 g/dl) and/or hematocrit (≥10 points). Patients were allowed to take concomitant low-dose ASA (≤325 mg), mostly for cardiovascular prophylaxis.

Study Results: No statistically significant differences were demonstrated for the incidence of complicated ulcers at the doses studied among the three treatment groups in all patients. Study results for the complete study duration are presented in Table 5.

Secondary analysis showed that the incidence of complicated and symptomatic ulcers was lower for celecoxib than for ibuprofen in all patients and in those patients not taking ASA. Approximately 22% of patients were taking low-dose ASA.

Concomitant low-dose ASA use increased the rates of complicated and symptomatic ulcers to four times that of patients not taking ASA (see DRUG INTERACTIONS – Drug-Drug Interactions – Acetylsalicylic Acid *(ASA)* or other NSAIDs).

Celecoxib at the doses studied had a significantly lower incidence of GI intolerability compared to diclofenac, but not ibuprofen (see ADVERSE REACTIONS).

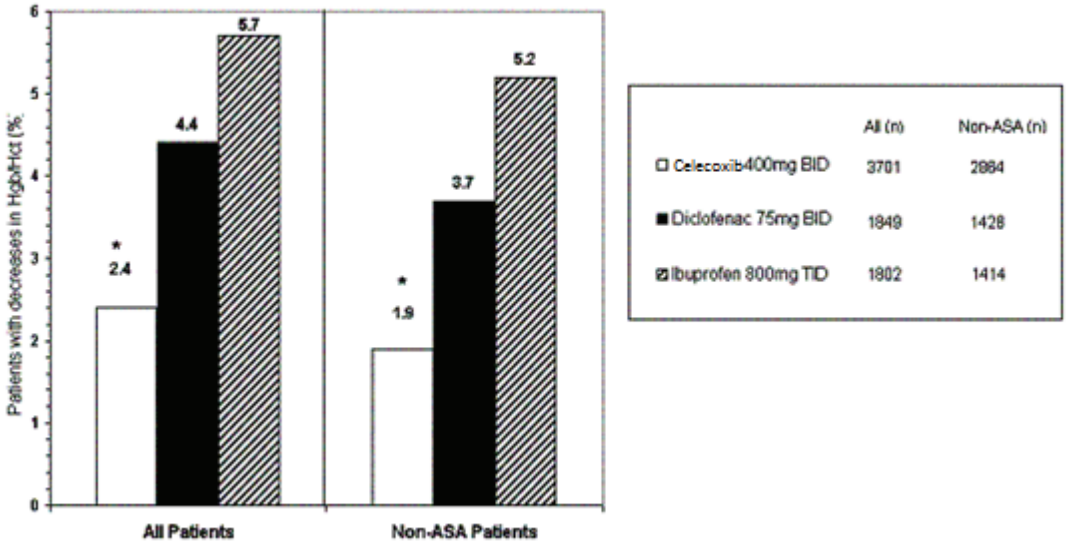
Table 5 Complicated and Symptomatic Ulcers in OA and RA Patients (Incidence rates at 12 months [%], events/patients)

	Higher-Than-therapeutic Dose (4X OA; 2X RA)	**Common Therapeutic Dose**	
	Celecoxib 400 mg BID	**Ibuprofen 800 mg TID**	**Diclofenac 75 mg BID**
All Patients (Exposure)	**2320 Pt-years**	**1112 Pt-years**	**1081 Pt-years**
Complicated ulcers	0.43 (17/3987)	0.55 (11/1985)	0.50 (10/1996)
Complicated and symptomatic ulcers	1.05* (42/3987)	1.76 (35/1985)	1.30 (26/1996)
Patients without ASA (Exposure)	**1803 Pt-years**	**874 Pt-years**	**841 Pt-years**
Complicated ulcers	0.26[1] (8/3105)	0.64 (10/1573)	0.26 (4/1551)
Complicated and symptomatic ulcers	0.68[2] (21/3105)	1.72 (27/1573)	0.64 (10/1551)
Patients with ASA (Exposure)	**517 Pt-years**	**248 Pt-years**	**240 Pt-years**
Complicated ulcers	**1.02 (9/882)**	**0.24 (1/412)**	**1.35 (6/445)**
Complicated and symptomatic Ulcers	**2.38 (21/882)**	**1.94 (8/412)**	**3.60 (16/445)**

***p=0.017 vs. ibuprofen**
[1] p=0:037 vs. ibuprofen
[2] p<0.001 vs. ibuprofen

In a prospective, long-term outcome study, celecoxib (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) also demonstrated a significantly lower incidence of clinically relevant decreases in hemoglobin (> 2 g/dl) or hematocrit (≥10 points) than ibuprofen and diclofenac (Figure 1) regardless of ASA use. The corresponding incidence rates from the controlled arthritis trials (1 to 6 months duration, most of 3 months duration) were 0.4% in placebo, 0.9% in celecoxib, and 1.7%, 3.3%, 5.2% for naproxen, diclofenac, and ibuprofen respectively. In the controlled arthritis trials Celecoxib was studied at the doses up to 400 mg BID. Similar significant differences were seen in the absence of bleeding ulcers, in patients not on ASA, and in OA and RA patients.

Figure 1
Incidence of Clinically Relevant Decreases in Hemoglobin and/or Hematocrit
(Incidence Rates at 12 Months [%], Events/Patients)



*p<0.05 vs. ibuprofen and diclofenac

Celecoxib versus Omeprazole and Diclofenac for Osteoarthritis and Rheumatoid Arthritis patients at-risk of developing GI complications (CONDOR) trial

In a prospective randomised 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=2238) compared to patients treated with diclofenac SR 75mg twice daily plus omeprazole 20 mg once daily (N=2246) [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).

Endoscopic Studies: Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomized 12-24 week trials using active comparators, two of which also included placebo controls. Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24-week endoscopic ulcer data are available on 184 patients on celecoxib at doses ranging from 50-400 mg BID. NSAID comparators included naproxen 500 mg BID, diclofenac 75 mg BID, and ibuprofen 800 mg TID.

In active-controlled studies, the endoscopic gastroduodenal ulceration rate observed with all doses of celecoxib was less than what was seen with the NSAID comparator (see Tables 6-8) and, in placebo-controlled studies, was similar to that seen with placebo (see Table 6). Studies were designed to detect differences between celecoxib and the NSAID comparator, therefore were not powered to detect small differences relative to placebo. Moreover, celecoxib doses above the highest recommended therapeutic dose of 200 mg BID were evaluated, and demonstrated that with supratherapeutic doses (2-4 times the recommended dose), the incidence of endoscopic ulcers was similar to placebo. Duration of observation had no impact on the celecoxib

gastroduodenal ulcer rate, as shown in a 24-week trial in which the celecoxib endoscopic ulcer rate was significantly lower than diclofenac SR and comparable to ulcer rates observed with placebo in other studies.

In all three studies that included naproxen 500 mg BID, and in the study that included ibuprofen 800 mg TID, celecoxib was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared celecoxib with diclofenac 75 mg BID; one study revealed a statistically significantly higher prevalence of endoscopic ulcers in the diclofenac group at the study endpoint (6 months on treatment), and one study revealed no statistically significant difference between cumulative endoscopic ulcer incidence rates in the diclofenac and celecoxib groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of celecoxib over the range studied.

Table 6 summarizes the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

Table 6 Incidence of Gastroduodenal Ulcers from Endoscopic Studies in OA and RA Patients

	3 Month Studies	
	Study 1 (n = 1108)	**Study 2 (n = 1049)**
Placebo	2.3% (5/217)	2.0% (4/200)
Celecoxib 50 mg BID	3.4% (8/233)	---
Celecoxib 100 mg BID	3.1% (7/227)	4.0% (9/223)
Celecoxib 200 mg BID	5.9% (13/221)	2.7% (6/219)
Celecoxib 400 mg BID	---	4.1% (8/197)
Naproxen 500 mg BID	16.2% (34/210)*	17.6% (37/210)*

* $p \leq 0.05$ vs all other treatments

Note: Studies were designed to detect differences between celecoxib and NSAID comparator, therefore were not powered to detect small differences relative to placebo.

Table 7 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 7 Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients

	Week 4	**Week 8**	**Week 12**	**Final**
Study 3 (n=523)				
Celecoxib 200 mg BID	4.0% (10/252)*	2.2% (5/227)*	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BID	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (89/257)
Study 4 (n=1062)				
Celecoxib 200 mg BID	3.9% (13/337)[1]	2.4% (7/296)[1]	1.8% (5/274)[1]	7.0% (25/356)[1]
Diclofenac 75 mg BID	5.1% (18/350)	3.3% (10/306)	2.9% (8/278)	9.7% (36/372)
Ibuprofen 800 mg TID	13.0% (42/323)	6.2% (15/241)	9.6% (21/219)	23.3% (78/334)

* $p \leq 0.05$ Celecoxib vs. naproxen based on interval and cumulative analyses

[1] $p \leq 0.05$ Celecoxib vs. ibuprofen based on interval and cumulative analyses

One randomized and double-blinded, 6-month study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The results are shown in Table 8.

Table 8 Incidence of Gastroduodenal Ulcers From a 6-Month Endoscopy Study in RA Patients

	6 Months
Study 5 (n = 430)	
Celecoxib 200 mg BID	4% (8/212)
Diclofenac 75 mg BID	15% (33/218)*

* Significantly different from Celecoxib; $p<0.001$

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established (see WARNINGS AND PRECAUTIONS - Gastrointestinal System).

Use With Acetylsalicylic Acid (ASA): Patients with cardiovascular risk factors, including those with a recent history of myocardial infarction or stroke and patients deemed to require low-dose ASA for cardiovascular prophylaxis were included in the long-term outcome study (see ADVERSE REACTIONS). As a result, approximately 22% of patients enrolled in the long-term outcome study were taking ASA (≤325 mg/day). As with the NSAID comparators, the incidence rate of ulcers and ulcer complications (perforations, obstructions and bleeds) in celecoxib patients was higher in ASA users as opposed to non-ASA users (see CLINICAL TRIALS - Special Studies).

Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking ASA (325 mg/day). In the celecoxib groups, the endoscopic ulcer rate appeared to be higher in subjects taking both celecoxib and ASA than in subjects taking only celecoxib. However, the increased rate of ulcers in these ASA users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without ASA.

Platelets: In four clinical trials involving 118 subjects, celecoxib did not affect platelet function. Celecoxib at single doses up to 800 mg and multiple doses of 600 mg BID for up to seven days duration (i.e., three times the highest recommended therapeutic dose), had no effect on platelet aggregation and bleeding time compared to placebo. In contrast, the NSAIDs naproxen 500 mg BID, ibuprofen 800 mg TID, and diclofenac 75 mg BID significantly reduced platelet aggregation and prolonged bleeding time.

Cardiovascular Safety - Meta-analysis from Chronic Usage Studies:

No long-term controlled clinical study specifically designed to assess the CV safety of chronic celecoxib dosing of any duration has been conducted. However, a meta-analysis of safety data from 41 completed celecoxib clinical studies of up to 1 year in duration has been conducted, representing 44,308 patients (24,933 (56.3%) patients exposed to celecoxib, 13,990 (31.6%) patients exposed to NSAIDs, 4057 (9.2%) patients exposed to placebo, and 1328 (3.0%) patients exposed to rofecoxib).

In this analysis, the incidence of the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was similar between celecoxib (N=19,773) and non-selective NSAID (N=13,990) treatment (RR=0.86, 95% CI 0.59 - 1.26). This pattern of effect was maintained with or without ASA use (=325 mg). The incidence of non-fatal myocardial infarction trended higher (RR=1.49, 95% CI 0.82 - 2.70); however that of stroke was significantly lower (RR= 0.33, 95% CI 0.14 - 0.78), and that of cardiovascular death was comparable (RR=0.72, 95% CI 0.37 - 1.39) for celecoxib compared to combined non-selective NSAIDs.

In this analysis, the incidence of the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was 0.31% for celecoxib (N=7462) and 0.20% for placebo (N=4,057) treatment (RR=1.26, 95% CI 0.57 - 2.80). This pattern of effect was maintained with or without ASA use (=325 mg). The incidence of non-fatal myocardial infarction trended higher (RR=1.24, 95% CI 0.27 - 5.76), as did that of cardiovascular death (RR=1.74, 95% CI 0.49 - 6.17), and that of stroke was similar RR=0.80, 95% CI 0.19 - 3.31) for celecoxib compared to placebo.

DETAILED PHARMACOLOGY

Animal Pharmacology

Celecoxib was evaluated in a series of preclinical pharmacology studies: 1) to examine its inhibitory kinetics and mechanism of action; 2) to determine its anti-inflammatory, analgesic and antipyretic actions *in vivo*; 3) to specifically evaluate its propensity to cause GI tract injury and to explore its potential for action on a variety of physiological systems that are targets of NSAIDs. A major goal of these studies was to understand the pharmacological action of celecoxib in relation to its ability to produce differential inhibition of COX isoforms *in vivo, ex vivo* and *in vitro.* Selective inhibition of COX-2 vs COX-1 by celecoxib was shown in a number of systems *in vivo* and *in vitro,* providing a mechanistic basis for the novel pharmacological profile of this agent. Based on these studies, celecoxib is expected to be an effective anti-inflammatory, analgesic, anti-pyretic and anti-proliferative agent in humans with a diminished potential for adverse GI, platelet and renal effects.

The analgesic actions of celecoxib were demonstrated using the rat carrageenan footpad hyperalgesia model with a thermal stimulus. Celecoxib also showed analgesic activity in the irritant dorsoflexion mouse model using two different irritants but it did not affect the CNS component of the dorsoflexion pain response. Naloxone did not reverse the analgesic actions of celecoxib, indicting an analgesic mechanism not involving the opioid receptor. The absence of an opiate receptor-mediated mechanism was suggested by the lack of activity in the mouse tail pinch model, which normally responds only to opiates such as morphine and local anaesthetics. Celecoxib was shown to achieve concentrations in brain tissue greater than 2-fold higher than those found in the plasma at the time points used for analgesic testing, demonstrating penetration of this agent into the CNS. When given intrathecally (to the lumbar spinal cord) to rats prior to injection of carrageenan into the foot pad, celecoxib prevented elevations of CSF levels of PGE_2, decreased the inflammatory foot edema and elicited analgesia to a thermal stimulus, indicating that a portion of the analgesic efficacy of celecoxib could be at the level of the spinal cord.

Human Pharmacology

Upper Gastrointestinal Mucosal Effect: See CLINICAL TRIALS - Special Studies.

Platelet Function: Four studies were conducted to investigate the effects of celecoxib on platelet function. A principal feature of these studies is that celecoxib was evaluated at doses exceeding the recommended therapeutic clinical dose range for anti-inflammatory and analgesic efficacy.

Absence of platelet effect was demonstrated by evaluation of platelet aggregation, bleeding time and measurement of blood or serum thromboxane levels. The studies showed consistently that celecoxib, after single or multiple doses up to three-fold higher than the highest recommended

dose, did not consistently or significantly reduce platelet aggregation in response to collagen or arachidonate. In contrast, the NSAIDs naproxen, ibuprofen, diclofenac and ASA all significantly reduced platelet aggregation.

Bleeding time was also evaluated in these studies and the results confirmed the findings of platelet aggregation assays. Celecoxib did not significantly increase bleeding time, whereas NSAIDs studied increased bleeding time compared to placebo.

Serum TxB_2 levels were reduced by the above comparator NSAIDs, but not consistently by celecoxib. When reductions in serum TxB_2 levels were seen with celecoxib, they were not of sufficient magnitude to affect platelet function. Linear regression analysis of celecoxib plasma concentrations did not demonstrate a pattern of correlation between plasma concentrations and platelet function in these studies.

Renal Function: Specific studies assessed the effects of celecoxib on renal function in groups of individuals deemed most at risk of adverse renal hemodynamic effects associated with NSAID treatment. Renal effects of celecoxib were assessed in healthy elderly subjects, in subjects with chronic stable renal insufficiency, and in patients undergoing sodium and volume restriction. Celecoxib was not associated with deleterious changes in glomerular filtration rate (GFR) in subgroups that are considered to be susceptible to the adverse renal hemodynamic effects of NSAIDs. Celecoxib 200 mg BID and 400 mg BID did not have a measurable effect on GFR in healthy elderly subjects, in patients with moderate renal insufficiency, or in mildly sodium-depleted patients. Celecoxib was associated with transient reductions in urinary sodium excretion. However, the effect was not reproducibly observed, the magnitude of the observed changes was small, and dietary sodium intake was often not strictly controlled.

Celecoxib was associated with a reduction in urinary 6-keto-PGF_1 excretion and decreased urinary PGE_2 excretion but did not affect serum TxB_2 levels and urinary 11-dehydroTxB_2 excretion in contrast to naproxen. These results are consistent with a lack of COX-1 inhibitory activity with celecoxib in contrast to the mixed, non-specific COX inhibitory activity of naproxen.

Analgesic Activity: See CLINICAL TRIALS - Osteoarthritis and Rheumatoid Arthritis.

TOXICOLOGY

All of the findings seen in animals treated with celecoxib are consistent with the known pharmacological action of the compound (i.e., inhibition of PG synthesis) and/or occurred at exposures and maximal plasma concentrations of the active moiety (i.e., celecoxib) that are greater than projected for therapeutic effect. Celecoxib is not mutagenic and is not carcinogenic in rodents. GI injury is seen with celecoxib only at exposures that are greater than needed for therapeutic use. Significant departures from the comparator NSAIDs are seen with celecoxib in animals, including: 1) greater margins of safety for GI injury in sensitive animal species, 2) absence of injury to the fundic stomach and large intestine when administered by gavage or capsule, 3) no effect on hemostasis, 4) absence of renal papillary necrosis in chronic rodent studies, and 5) absence of dystocia. Based on these findings, celecoxib is considered safe for use in humans.

No evidence of toxicity or adverse pharmacological effect was produced by celecoxib in animals at the expected exposures and maximal plasma concentrations of the clinical doses (200 and 400 mg/day).

No sign of GI injury was seen in 6-month chronic studies with rats at exposures that are 3- to 6-fold greater than the expected exposures with the clinical doses, or at maximal plasma concentrations that are also 3- to 6-fold the C_{max} of the clinical doses. Similarly, no sign of GI injury was seen in dogs after 12 months of dosing at mean exposures and maximal plasma concentrations that are 2- to 5-fold greater than the respective exposures and C_{max} produced by the clinical doses.

Higher exposures produced dose-limiting GI injury in rats and dogs. The morphological appearance of the GI injury produced by celecoxib is similar to that seen with NSAIDs and thus, is not a novel form of injury. Exposures in rats in the chronic toxicity study that are 6 to 12-fold greater than the exposures at the range of clinical doses produced GI injury and death. The injury was seen more frequently in females due to higher exposures associated with the dimorphism seen in rats. Exposures approximately 4- to 9-fold greater than the exposures at the clinical dose range produced GI injury and death in dogs in a 4-week subchronic study. The mucosal injury is reversible in dogs with cessation of dosing with celecoxib. GI injury is an expected consequence of COX-1 inhibition, however the requirement for high exposures of celecoxib to produce injury is consistent with the pharmacological concept of COX-2 specific inhibition within the therapeutic dosage range.

No adverse pharmacological effect of celecoxib on central nervous system or pulmonary function were seen at plasma levels of celecoxib that are 2- to 5-fold and 3- to 6-fold, respectively, greater than the maximal plasma concentrations at the clinical dose range. No effect on template bleeding time was seen in dogs at exposures sufficient to produce GI injury and death. A few cardiovascular changes were observed in anesthetized animals given celecoxib intravenously, and included small sporadic increases in left ventricular end-diastolic pressure in dogs at plasma concentrations 3- to 7-fold greater than the Cmax produced by the clinical doses, and increases in mean arterial, systolic and diastolic blood pressures in guinea pigs at plasma concentrations that are 3- to 6-fold greater than the C_{max} produced by the range of clinical doses. These changes are not suggestive of a clinically significant effect and are not expected at clinically relevant exposures in patients.

Decreased urinary sodium concentration (antinatriuresis) was seen in male and female rats at plasma concentrations at least 3-fold higher than the maximal plasma concentration produced by the clinical doses. Antinatriuresis is an expected pharmacological consequence of prostaglandin inhibition in the kidney. In studies of longer duration in rats, antinatriuresis was seen after 6 weeks of dosing at exposures that are 2- to 4-fold greater than the exposures at the range of clinical doses. No evidence of antinatriuresis was seen after 13 or 26 weeks at exposures that are 6- and 9-fold greater, respectively, than the exposure at the maximum daily clinical dose (400 mg/day).

Carcinogenesis: Carcinogenicity evaluations in rats and mice revealed no evidence of carcinogenicity or increases in the incidence of background tumors after at least 104 weeks of dosing. The carcinogenicity assessment of celecoxib was made in rats in which the average exposures throughout the study were as high as 4- to 9-fold greater in males and 5- to 10-fold greater in females than the exposures produced by the range of clinical doses. Evidence that the

Maximum Tolerated Dose (MTD) was exceeded was seen in both males and females as GI injury and death. The frequency of this injury was greater in females which were exposed to higher levels of celecoxib due to the dimorphism in rats. Significant reductions in survival were seen in the two highest male dose groups and all treated female groups as a result of the GI injury. A NOEL (No-Observed-Effect Level) for the GI injury was established in males at exposures that are 1- to 2-fold the exposures at the range of clinical doses. A NOEL could not be established in females because exposures in these animals were generally higher than the no-effect exposure in males throughout the study.

The carcinogenicity evaluation in mice was made at average exposures throughout the study which were approximately 1- to 2.5-fold greater in males and 1- to 2-fold greater in females than the exposures at the clinical dose range. Evidence that the MTD was exceeded was seen in all treated groups as injury in all segments of the GI tract resulting in significant decreases in survival in all but the lowest dose groups. The frequency of injury was comparable in males and females because differential dosages were used to compensate for the dimorphism seen in mice. The use of diet admixture to expose the animals to celecoxib may have produced direct topical exposure of the GI tract which explains the appearance of the injury throughout the GI tract and the lower systemic exposures associated with injury in mice.

No other form of toxicity or irreversible injury was seen in rats, mice or dogs treated with celecoxib. Renal papillary necrosis was not seen in rats or mice, and occurred in two dogs with severe GI injury and hemorrhage. The GI injury seen in these dogs produced septicemia, bacterial emboli and volume depletion (due to hemorrhage) which are factors that predispose the renal papilla to injury.

Reproduction and Teratology: Celecoxib does not produce any effect on male or female fertility or male reproductive function in rats at exposures that are estimated to be 3.5- to 7-fold greater in males and 19- to 38-fold greater in females than the exposures associated with the range of clinical doses. No reproducible effect on ovulation was seen, but decreased embryonic viability reflected as pre- and post-implantation loss occurred in females treated with celecoxib at exposures that are 5- to 11-fold greater than the exposures at the clinical dose range. This effect was not seen after a recovery period during which treatment was ceased. Thus, this effect is the likely consequence of disruption of PG-dependent processes critical for implantation and maintenance of pregnancy and is not the result of permanent alteration of female reproductive function. A NOEL for all effects on early reproductive function in rats was established at exposures that are 4- to 8-fold greater than the exposures at the range of clinical doses.

Teratology evaluations conducted in rats and rabbits treated with celecoxib revealed no evidence of teratogenicity at exposures that are ~ 3-fold greater than exposures at the range of clinical doses. Diaphragmatic hernias appeared at high dosages in 3 of 4 teratology studies in rats at exposures that are 6- to 12-fold greater than clinical exposures. This malformation was also seen at a lower incidence in live offspring in the perinatal evaluation. An increase in the frequency of wavy ribs was observed in one rat teratology study but was not reproduced in a second study. Wavy ribs are reversible and are not regarded as an adverse finding of significance for humans. In rabbit teratology studies, a low incidence of ventricular septal defects (VSD) and other related anomalies, including enlarged aorta and pulmonary stenosis, was observed at systemic exposures approximately 5-fold the clinical exposures. The low incidence of VSD in celecoxib studies cannot be clearly distinguished from the background historical control data thus its relationship to treatment with celecoxib is uncertain. The NOELs for teratology evaluations in rats

(10 mg/kg/day) and in rabbits (60 mg/kg/day) are associated with exposures that are ~ 3-fold greater than the clinical exposures.

Slight prolongation of gestation was seen in a perinatal evaluation in rats treated with celecoxib but was not dose-dependent and was within historical control data ranges. No evidence of dystocia or increased parturition time was seen in this study. There was no effect of celecoxib on the physical appearance of the pups with the exception of the diaphragmatic hernias previously discussed. There was no evidence of adverse effect on the survival, physical development, behavior and reproductive performance of the F_1 generation, or on the development and survival of the F2 generation pups resulting from treatment of the F0 females with celecoxib. The highest plasma levels measured in treated dams are approximately 1- to 2-fold the C_{max} of the clinical doses, while the highest plasma levels measured in neonates are approximately 5- to 10-fold greater than maximal plasma concentration of the clinical doses.

Mutagenesis: Celecoxib is not mutagenic in bacteria (Ames assay) or mammalian cells. No evidence of clastogenicity or disruption of the mitotic apparatus was seen *in vitro,* or rats *in vivo* at exposures that are 6- to 12-fold greater in males and 16- to 33-fold greater in females than the exposures produced by the clinical doses. These results are consistent with the absence of carcinogenicity in the cancer bioassays conducted with celecoxib.

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51) Product Monograph: CELEBREX®, Pfizer Canada Inc., Revision dated May 7, 2014, Control No. 171673.

PART III: CONSUMER INFORMATION

Pr CELECOXIB
Celecoxib capsules

Read this information each time you refill your prescription in case new information has been added. This leaflet is part III of a three-part "Product Monograph" published when CELECOXIB was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CELECOXIB. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Your health care provider has prescribed CELECOXIB for you for one or more of the following medical conditions:

- Osteoarthritis - relieve pain
- Rheumatoid Arthritis - relieve joint pain and swelling
- Ankylosing Spondylitis - relieve pain
- Sprains, After orthopaedic (bone and joint) surgery (NOT open heart surgery), dental extraction - to relieve short-term pain (maximum use of 7 days)

What it does:

CELECOXIB (celecoxib), as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the type of prostaglandins (chemicals), produced by your body which cause joint swelling, redness and pain. At prescribed doses, CELECOXIB does not affect the type of prostaglandins that helps maintain the protective layer of the stomach, and reduces the chances of bleeding from the stomach.

CELECOXIB, as a nonsteroidal anti-inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. CELECOXIB can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:

Do not take CELECOXIB if you have any of the following medical conditions:

- **Heart bypass surgery (planning to have or recently had)**
- **Severe, uncontrolled heart failure**
- **Allergy to celecoxib or any of the other ingredients in CELECOXIB**
- **Allergy to Sulfonamide drugs**
- **Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs)**
- **Current Pregnancy (after 28 weeks of pregnancy)**
- **Currently Breastfeeding (or planning to breastfeed)**
- **Ulcer (active)**
- **Bleeding from the stomach or gut (active)**
- **Bleeding in the brain**
- **Inflammatory Bowel Disease (Crohn's Disease or Ulcerative Colitis)**
- **Liver Disease (active or severe)**
- **Kidney Disease (severe or worsening)**
- **High potassium in the blood**

Safety and effectiveness of CELECOXIB have NOT been established in children under 18 years of age.

Patients who took a drug in the same class as CELECOXIB after a type of heart surgery (coronary artery bypass grafting) (CABG) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

What the medicinal ingredient is:

Celecoxib

What the nonmedicinal ingredients are:

Croscarmellose sodium, lactose, magnesium stearate, povidone, sodium lauryl sulfate and talc. Capsule contains gelatin, sodium lauryl sulphate and titanium dioxide.
100 mg ink: ammonia, FD&C blue aluminum lake, propylene glycol and shellac.
200 mg ink: ammonia, propylene glycol, shellac and yellow iron oxide.

What dosage forms it comes in:

Capsules: 100 mg and 200 mg

WARNINGS AND PRECAUTIONS

Before taking this medication tell your health care provider

Serious Warnings and Precautions

If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than CELECOXIB:

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

if you have any of the following:

- High Blood Pressure
- High Cholesterol
- Diabetes Mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or Ex-smoker
- Kidney Disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to sulfonamide drugs

- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyp, long-term swelling of the sinus (chronic sinusitis) or hives
- Gastrointestinal problems (problems with your stomach and/or intestine)
- Any other medical problem

Fertility may be decreased. The use of CELECOXIB is not recommended in women who have difficulty conceiving.

Also, before taking this medication, tell your health care provider if you are planning to get pregnant.

While taking this medication:

- tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking this medication, especially if you are planning to have heart surgery;
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;

INTERACTIONS WITH THIS MEDICATION

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

- Acetylsalicylic acid or other NSAIDs (e.g. ASA, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen)
- Antacids
- Antidepressants [Selective serotonin receptor uptake inhibitor (SSRIs) (e.g. citalopram, paroxetine, fluoxetine, sertraline)]
- Blood pressure medications; ACE (angiotensin converting enzyme) inhibitors (e.g. enalapril, lisinopril, perindopril, ramipril). ARBs (angiotensin II receptor blockers) (e.g. candesartan, irbesartan, losartan, valsartan)
- Blood thinners e.g. warfarin (to prevent blood clots), ASA, clopidogrel
- Corticosteroids (including glucocorticoids) e.g. prednisone
- Cyclosporin
- Digoxin
- Diuretics Furosemide, hydrochlorothiazide
- Fluconazole
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner for the prevention of having a heart attack or stroke while you are taking CELECOXIB. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both CELECOXIB and ASA than if you take CELECOXIB alone.

PROPER USE OF THIS MEDICATION

Capsules should be swallowed whole. DO NOT open, divide, crush, or chew the capsules.

Dose: 18 years of age and older only

Medical Condition	Starting Dose	Maximum Dose (per day)	Maximum Duration of Treatment (days
Osteoarthritis (18 years of age and older)	200 mg once a day or 100 mg twice a day	200 mg	not specified
Rheumatoid Arthritis (18 years of age and older)	100 mg twice a day	400 mg	not specified
Ankylosing Spondylitis (18 years of age and older)	200 mg once a day or 100 mg twice a day	200 mg	not specified
Pain (18 years of age and older)	400 mg on first day, then 200 mg once a day	400 mg	7 days

Take CELECOXIB only as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much CELECOXIB may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

If you will be using CELECOXIB for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

CELECOXIB is NOT recommended for patients under 18 year of age since safety and effectiveness have NOT been established.

CELECOXIB can be taken with or without food.

Missed Dose:

Take the dose you missed as soon as you remember, then take the next dose at the scheduled time.

Overdose:

If you take more than the prescribed dose, contact your health care provider immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

CELECOXIB may cause some side effects, especially if used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.

CELECOXIB may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking CELECOXIB, do NOT drive or operate machinery.

CELECOXIB may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your health care provider.

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect	STOP Taking Drug and Get Emergency Medical Attention IMMEDIATELY	STOP Taking Drug and Talk to Your Health Care Provider
Bloody or black tarry stools	✓	
Shortness of breath, wheezing, any trouble breathing or chest tightness	✓	
Skin rash, hives, swelling or itching	✓	
Blurred vision or other visual disturbance	✓	
Change in urine (amount or colour) (dark red or brown)	✓	
Pain or difficulty urinating		✓
Feet or lower leg swelling; weight gain		✓
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		✓
Yellow discolouration of the skin or eyes with or without itchy skin		✓
Malaise, fatigue, or loss of appetite		✓
Headaches, stiff neck		✓
Mental confusion or depression		✓
Dizziness or lightheadedness		✓
Hearing problems		✓

This is NOT a complete list of side effects. If you develop any other symptoms while taking CELECOXIB, see your health care provider.

HOW TO STORE IT

Store between 15 and 30°C.

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Keep out of reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor Laboratoire Riva Inc., at 1-800-363-7988.

This leaflet was prepared by
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