

AUSTRALIAN PRODUCT INFORMATION

CELECOXIB APOTEX (CELECOXIB) CAPSULES

1 NAME OF THE MEDICINE

Celecoxib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CELECOXIB APOTEX capsules contain 100 mg or 200 mg of celecoxib.

Excipients with known effect

Lactose monohydrate.

For the full list of excipients see section **6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

100 mg capsules: opaque, white to off-white capsules imprinted with 'CC' and '100' in black ink.

200 mg capsules: white to off-white capsules imprinted with 'CC' and '200' in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

For the treatment of primary dysmenorrhoea in adults.

For the short-term treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used (see section **5.1 Pharmacodynamic properties - Clinical trials**).

Patients on long-term treatment should be reviewed regularly, such as every three months, with regards to efficacy, risk factors and ongoing need for treatment.

Adults

The doses can be given without regard to timing of meals.

Osteoarthritis

The usual recommended daily dose is 200 mg taken once daily or in two divided doses.

Rheumatoid Arthritis

The recommended daily dose is 200 mg taken in two divided doses.

A dose of up to 400 mg daily may be used for short-term management of disease flares or exacerbations.

Ankylosing Spondylitis

The maximum recommended daily dose is 200 mg taken once daily or in two divided doses.

Primary Dysmenorrhoea

The recommended dose is 400 mg as a single dose or divided on the first day, followed by 200 mg once daily on subsequent days. Patients may be instructed to take an additional dose of 200 mg on any given day, if needed. The maximum recommended treatment duration is 5 days.

Acute Pain Following Surgery or Musculoskeletal and/or Soft Tissue Injury

The recommended dose is a loading dose of 400 mg then 200 mg once or twice daily as required for up to 5 days.

The effective dose in this patient population is 200 mg twice daily.

Elderly

No dosage adjustment is generally necessary. However, for elderly patients with a lower than average body weight (<50 kg), it is advisable to initiate therapy at the lowest recommended dose.

Hepatic impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. In arthritis patients with moderate hepatic impairment, celecoxib should be introduced at half the recommended dose.

There is no clinical experience in patients with severe hepatic impairment. Therefore, the use of celecoxib in patients with severe hepatic impairment (Child-Pugh score ≥ 10) is contraindicated (see sections **5 Pharmacological properties** and **4.3 Contraindications**).

Renal impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment (see section **5.2 Pharmacokinetic properties**).

Children and Adolescents

Celecoxib is not approved for use in patients under 18 years of age.

CYP 2C9 Poor Metabolisers

Patients who are known, or suspected to be CYP 2C9 poor metabolisers based on previous history/experience with other CYP 2C9 substrates should be administered celecoxib with caution. Consider starting treatment at a reduced dose (see sections **4.5 Interactions with other medicines and other forms of interactions** and **5.2 Pharmacokinetic properties**).

4.3 CONTRAINDICATIONS

Known hypersensitivity to celecoxib or any of the excipients contained in the CELECOXIB APOTEX capsules (see section **6.1 List of excipients**).

Demonstrated allergic-type reactions to sulfonamides.

Celecoxib should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other non-steroidal anti-inflammatory drugs, including other COX-2 specific inhibitors. Severe, rarely fatal, anaphylactoid reactions to non-steroidal anti-inflammatory drugs have been reported in such patients (see section **4.4 Special warnings and precautions for use - Anaphylactoid Reactions**).

Celecoxib should not be used with other non-steroidal anti-inflammatory drugs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

Celecoxib is contraindicated for the peri-operative treatment of pain in patients undergoing coronary artery bypass graft (CABG) surgery (see section **4.4 Special warnings and precautions for use**).

Celecoxib is contraindicated in:

- Patients with unstable ischaemic heart disease of thrombus aetiology or significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section **4.4 Special warnings and precautions for use - Cardiovascular and Thrombotic Events**).
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients with estimated creatinine clearance <30 mL/min.
- Patients with congestive heart failure (NYHA II-IV).
- Patients with severe hepatic impairment (Child-Pugh# score ≥10; see sections **5 Pharmacological properties** and **4.2 Dose and method of administration**).

Child-Pugh is a classification of the severity of liver disease.

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds over control)	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A - 100 and 85 percent; grade B - 80 and 60 percent; and grade C - 45 and 35 percent.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks and benefits of therapy (see sections **4.3 Contraindications** and **4.4 Special warnings and precautions for use**).

Cardiovascular and Thrombotic Events

COX-2 inhibitors have been associated with an increased risk of cardiovascular and thrombotic adverse events. Celecoxib is a COX-2 inhibitor (see section **5.1 Pharmacodynamic properties - Clinical trials - Cardiovascular Safety**).

All NSAIDs, both COX-2 selective and non-selective may cause an increased risk of serious cardiovascular thrombotic events. This risk may increase with duration of use.

Patients with known cardiovascular disease, history of atherosclerotic cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Celecoxib should be used with caution in patients at high risk of cardiovascular disease including those with significant *and multiple* risk factors (e.g. diabetes, hypertension, hypercholesterolaemia, cardiac failure and smokers).

To minimise the potential risk for an adverse cardiovascular event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible (see sections **5.1 Pharmacodynamic properties - Clinical trials - Cardiovascular Safety**, and **4.2 Dose and method of administration**).

Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Gastrointestinal Effects

Infrequently, serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach or intestine has been observed in patients treated with celecoxib. Physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms.

Celecoxib exhibited a low incidence of gastroduodenal ulceration and serious clinically significant GI events within clinical trials. The following information for non-steroidal anti-inflammatory drugs should be borne in mind.

Serious GI toxicity, such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine can occur at any time, with or without warning symptoms, in patients treated with non-steroidal anti-inflammatory drugs. Minor upper GI problems, such as dyspepsia, are common, and may also occur at any time during NSAID therapy. Therefore, physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% 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. However, even short-term therapy is not without risk. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

Among 5,285 patients who received celecoxib in the original arthritis trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population.

The incidences of *complicated* and *symptomatic ulcers* for patients treated with celecoxib 400 mg BD (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) from the prospective randomised controlled long-term outcomes trial in 8000 OA and RA patients in which low dose aspirin use was allowed was 0.68% on celecoxib alone and 1.08% on celecoxib with or without aspirin.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. To minimise the potential risk of an ulcer complication, the lowest effective dose of celecoxib should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors.

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.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to celecoxib. In post-marketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving celecoxib. Celecoxib should not be given to patients with the aspirin 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 aspirin or other NSAIDs (see sections **4.3 Contraindications** and **4.4 Special warnings and precautions for use - Pre-existing Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Serious Skin Reactions

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. Patients appear to be at highest risk for these events early in the course of therapy: the onset of the event occurring in the majority of cases within the first month of treatment. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hypertension

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

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Such patients should be carefully monitored while receiving treatment with celecoxib. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors (see section **4.4 Special warnings and precautions for use - Concomitant use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics**), and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs.

At the present time the relative roles of COX-1 and COX-2 in renal physiology is incompletely understood. Celecoxib reduces the urinary excretion of PGE₂ and 6-keto-PGF₁ α (a

prostacyclin metabolite) but leaves serum thromboxane B2 (TXB2) and urinary excretion of 11-dehydro-TXB2, a thromboxane metabolite (both COX-1 products) unaffected.

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

Use in renal impairment

No information is available regarding the use of celecoxib in patients with advanced kidney disease. Therefore, treatment with celecoxib is not recommended in these patients. If celecoxib therapy must be initiated, close monitoring of the patient's kidney function is advisable.

Concomitant use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics:

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time, increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the initiation of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Use with Other NSAIDs

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

Hepatic effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice, fatal fulminant hepatitis, liver necrosis, hepatic failure (some with fatal outcome), and liver transplant have been reported with NSAIDs, including celecoxib (see section **4.8 Adverse effects (Undesirable effects)**). 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.

Use in hepatic impairment

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), celecoxib should be discontinued.

The incidence of elevations in ALT and/or AST may be increased in patients treated with celecoxib at doses greater than 400 mg daily.

Haematological Effects

Anaemia is sometimes seen in patients receiving celecoxib. In controlled clinical trials the incidence of anaemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with celecoxib should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia or blood loss. 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 section **5.1 Pharmacodynamic properties - Clinical trials - Celecoxib Long-term Arthritis Safety Study** and - **Platelet Function**).

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, celecoxib should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Fluid Retention and Oedema

Fluid retention and oedema have been observed in some patients taking celecoxib (see section **4.8 Adverse effects (Undesirable effects)**). Therefore, celecoxib should be used with caution in patients with fluid retention, hypertension, heart failure, compromised cardiac function, pre-existing edema or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolaemia. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Use in Patients being Treated with Corticosteroids

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.

Use in Patients with Inflammatory Bowel Disease (IBD)

Short-term exposure of celecoxib to patients with ulcerative colitis (UC) in remission has not shown an exacerbation of IBD in spondyloarthropathies, but the implications of longer term exposure remain unknown. NSAIDs have been associated with an exacerbation of IBD associated with spondyloarthropathies.

Detecting Infections

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

Use in the elderly

Of the total number of patients who received celecoxib in clinical trials, more than 3,300 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 subjects. Other reported clinical experience including data from the Celecoxib Long-term Arthritis Safety Study have not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section **4.4 Special warnings and precautions for use - Gastrointestinal Effects**).

In clinical studies comparing renal function as measured by the GFR, BUN (Blood Urea Nitrogen) and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers

Paediatric use

Celecoxib is not approved for use in patients under 18 years of age.

Effects on laboratory tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. In controlled clinical trials elevated BUN occurred more frequently in patients receiving celecoxib compared with patients on placebo. This abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

General

Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Patients who are known or suspected to be poor CYP 2C9 metabolisers based on previous history/experience with other CYP 2C9 substrates should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. Consider starting treatment at a reduced dose (see section **4.2 Dose and method of administration**).

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

ACE-inhibitors and Angiotensin II Antagonists

Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors and/or angiotensin II antagonists. This interaction should be given consideration in patients taking celecoxib concomitantly with ACE-inhibitors and/or angiotensin II antagonists.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, may result in deterioration of renal function, including possible acute renal failure.

Fruzemide

Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of frusemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Aspirin

Celecoxib can be used with low dose aspirin. However, concomitant administration of aspirin with celecoxib may result in an increased rate of GI ulceration or other complications, compared to use of celecoxib alone (see section **5.1 Pharmacodynamic properties - Clinical trials - Celecoxib Long-term Arthritis Safety Study**).

In the long-term outcome study, the incidences of MI, stroke, unstable angina and deep thrombophlebitis in non-aspirin users were 0.2%, <0.1%, <0.1% and 0.3% respectively and in aspirin users were 1.5%, 0.6%, 0.9% and 0.3% respectively. Incidence rates with celecoxib were not different from those of the two comparators. Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole

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

metabolism via P450 2C9 by fluconazole (see section **5.2 Pharmacokinetic properties - Metabolism**). Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium

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

Oral Hypoglycaemics

The effect of celecoxib on the pharmacokinetics and/or pharmacodynamics of glibenclamide and tolbutamide has been studied and clinically important interactions have not been found.

Glucocorticoids

Oral glucocorticoids should be used with caution since they increase the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Antacids

Coadministration of celecoxib with an aluminium- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in C_{max} and 10% in AUC.

Methotrexate

Celecoxib did not have a significant effect on the pharmacokinetics of methotrexate.

Ketoconazole

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

Phenytoin

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

Warfarin

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 mg to 5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, some of them fatal, predominantly in the elderly, in association with increases in prothrombin time in patients receiving celecoxib concurrently with warfarin (see section **4.4 Special warnings and precautions for use - Gastrointestinal Effects**).

Other Drug Interactions

No drug interaction data are available for celecoxib and the co-administration of the following products: paracetamol, alcohol, aminoglycosides, bone marrow depressants, butemide, cholestyramine, colchicine, corticosteroids, cyclosporine, digoxin, gold compounds, indapamide, insulin, nephrotoxic agents, non-steroidal anti-inflammatory agents, oral contraceptives, potassium supplements, probenecid, valproic acid, zidovudine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Celecoxib did not affect male or female fertility in rats at oral doses up to 600 mg/kg/day (approximately 7-fold human exposure based on $AUC_{0-24\text{ h}}$ at 400 mg BD, which is twice the recommended maximum daily dose).

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

Use in pregnancy

Category B3

There is no information on the use of celecoxib in pregnant women. Celecoxib use is not recommended in pregnancy unless it is considered clinically essential (see information on animal studies). No studies have been done to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. In animal studies, both COX-1 and COX-2 have been shown to be present in the ductus arteriosus of fetal lambs and to contribute to maintenance of patency. Therefore, use of celecoxib during the third trimester of pregnancy should be avoided, and celecoxib should not be used during the first and second trimesters of pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. The effects of celecoxib on labour and delivery in pregnant women are not known.

In rats, celecoxib caused early embryonic death at doses greater than 30 mg/kg/day administered before mating and during early gestation (approximately 2-fold human exposure based on $AUC_{0-24\text{ h}}$ at 400 mg BD, which is twice the recommended maximum daily dose). This effect is attributable to inhibition of prostaglandin production, and is not associated with permanent alteration of reproductive function. Celecoxib was shown to cross the placenta in rats. Teratology studies disclosed an increased incidence of wavy ribs in one study in rats dosed at 100 mg/kg/day, increased incidences of diaphragmatic hernias at 30 and 100 mg/kg/day in another rat study; and increased incidences of rib and sternebral abnormalities in rabbits at doses of 60 mg/kg/day or greater and cardiovascular abnormalities in rabbits at doses of 150 mg/kg/day or greater. At the no-effect dose in rats (10 mg/kg/day), $AUC_{0-24\text{ h}}$ was similar to that in humans dosed at 400 mg BD. At the threshold dose of 60 mg/kg/day in rabbits, $AUC_{0-24\text{ h}}$ was slightly below that in humans dosed at 400 mg BD.

Celecoxib had a marginal effect on parturition in rats, causing slight prolongation of gestation and parturition and increased incidence of still births at oral doses of 10 mg/kg/day or greater (slightly greater than human exposure based on $AUC_{0-24\text{ h}}$ at 400 mg BD).

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

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Of the celecoxib treated patients in controlled trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and over 1,000 were patients with post-surgical pain. More than 8,500 patients have received a total daily dose of celecoxib of 200 mg (100 mg BD or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg BD). 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.

Adverse Events from Original Celecoxib Arthritis Trials

Table 1 lists all adverse events, regardless of causality, occurring in $\geq 2\%$ of patients receiving celecoxib from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or an active control group.

Table 1: Adverse events occurring in $\geq 2\%$ of celecoxib patients from original celecoxib arthritis trials

	Celecoxib (100 - 200 mg BD or 200 mg once daily) (N = 4146)	Placebo (N = 1864)	Naproxen 500 mg BD (N = 1366)	Diclofenac 75 mg BD (N = 387)	Ibuprofen 800 mg TDS (N = 345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhoea	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 oedema	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%

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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 Celecoxib Long-term Arthritis Safety Study (at 4- and 2-fold the recommended doses for OA and RA, respectively) was similar to those reported in the arthritis controlled trials.

The following adverse events occurred in 0.1 - 1.9% of patients taking celecoxib 100-200 mg BD or 200 mg once daily regardless of causality:

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, oesophagitis, gastritis, gastroenteritis, gastroesophageal reflux, haemorrhoids, hiatal hernia, melaena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting

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

General: Allergy aggravated, allergic reaction, asthenia, chest pain, cyst, oedema generalised, face oedema, 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, hypoaesthesia, migraine, neuralgia, neuropathy, paraesthesia, vertigo

Female reproductive: Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhoea, menstrual disorder, vaginal haemorrhage, vaginitis

Male reproductive: Prostatic disorder

Hearing and vestibular: Deafness, ear abnormality, earache, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary system: Hepatic function abnormal, AST increased, ALT increased

Metabolic and nutritional: BUN increased, CPK increased, diabetes mellitus, hypercholesterolaemia, hyperglycaemia, hypokalaemia, nonprotein nitrogen increase, creatinine increased, alkaline phosphatase increase, weight increase

Musculoskeletal: Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis

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

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

Haemic: Anaemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnoea, 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, haematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection

Vision: Blurred vision, cataract, conjunctivitis, eye pain, glaucoma.

Other Serious Adverse Events which Occur Rarely (<0.1%), Regardless of Causality

The following serious adverse events have occurred rarely in patients, taking celecoxib. Cases reported only in post-marketing experience are indicated in italics.

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

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus, ulcers (oesophageal, gastric and duodenal)

Liver and biliary systems: Cholelithiasis, *hepatitis, fulminant hepatitis, jaundice, liver failure, liver necrosis, cholestasis, cholestatic hepatitis, liver transplant, elevation of hepatic enzymes*

Haemic and lymphatic: Thrombocytopenia, *agranulocytosis, aplastic anaemia, pancytopenia, leucopenia*

Metabolic: *Hypoglycaemia*

Psychiatric: *Hallucinations*

Nervous system: Aseptic meningitis, ataxia, suicide, aggravated epilepsy, confusion, *ageusia, anosmia*

Renal: Acute renal failure, *interstitial nephritis, nephritic syndrome, minimal change disease, hyponatraemia*

Reproductive System & Breast Disorders: *Menstrual disorders, female fertility decreased*

Skin: *Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS, or hypersensitivity syndrome), acute generalised exanthematous pustulosis (AGEP)*

Ear: Decreased hearing

Eye: *Conjunctivitis*

General: Sepsis, sudden death, *anaphylactoid reaction, angioedema, bullous eruption.*

Adverse Events from the Primary Dysmenorrhoea Studies

These studies had an overall incidence of adverse events of 30.5% in the placebo treatment period, 31.2% in the celecoxib treatment period, and 36.3% in the NSAID comparator (naproxen sodium) period. Overall, nausea, headache, and dizziness were the most common adverse events in the celecoxib treatment group. These adverse events can be related to primary dysmenorrhoea.

Adverse Reactions from Polyp Prevention Trials

The following additional adverse events* in Table 2 were reported at incidence rates greater than placebo in long-term polyp prevention studies of duration up to 3 years at daily doses from 400 mg up to 800 mg (see section **5.1 Pharmacodynamic properties - Clinical trials - Cardiovascular Safety – Long-term Studies Involving Patients With Sporadic Adenomatous Polyps**). Adverse events are listed by system organ class are ranked by frequency. Frequencies are defined as: very common (>10%), common (>1% and <10%), uncommon (>0.1% and <1%).

Table 2: Adverse reactions occurring in celecoxib patients from long-term studies involving patients with sporadic adenomatous polyps

System Organ Class Frequency	Adverse Drug Events
Infections and infestations Common Uncommon	Ear infection, fungal infection (primarily non-systemic) Helicobacter infection, herpes zoster, erysipelas, wound infection, gingival infection, labyrinthitis, bacterial infection
Neoplasms benign, malignant, and unspecified Uncommon	Lipoma
Psychiatric disorders Uncommon	Sleep disorder
Nervous system disorders Uncommon	Cerebral infarction
Eye disorders Uncommon	Vitreous floaters, conjunctival haemorrhage

System Organ Class Frequency	Adverse Drug Events
Ear and labyrinth disorders Uncommon	Hypoacusis
Cardiac disorders Common Uncommon	Angina pectoris, myocardial infarction Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy
Vascular disorders Very common Uncommon	Hypertension* Deep vein thrombosis, haematoma
Respiratory, thoracic, and mediastinal disorders Common Uncommon	Dyspnoea Dysphonia
Gastrointestinal disorders Very common Common Uncommon	Diarrhoea* Nausea, gastro-oesophageal reflux disease, diverticulum, vomiting*, dysphagia, irritable bowel syndrome Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
Hepatobiliary disorders Rare	Elevation of hepatic enzymes
Skin and subcutaneous tissue disorders Uncommon	Dermatitis allergic
Musculoskeletal and connective tissue disorders Common Uncommon	Muscle spasms Ganglion
Renal and urinary disorders Common Uncommon	Nephrolithiasis Nocturia
Reproductive system and breast disorders Common Uncommon	Benign prostatic hyperplasia, prostatitis Vaginal haemorrhage, breast tenderness, dysmenorrhoea, ovarian cyst, menopausal symptoms
General disorders and administration site conditions Uncommon	Oedema
Investigations Common Uncommon	Blood creatinine increased, prostatic specific antigen increased, weight increased Blood potassium increased, blood sodium increased, blood testosterone decreased, haematocrit decreased, haemoglobin increased
Injury, poisoning and procedural complications Uncommon	Foot fracture, lower limb fracture, epicondylitis, tendon rupture, fracture

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

Other Adverse Effects

Intestinal anastomotic ulceration was observed in 3 of 58 patients enrolled in familial adenomatous polyposis clinical trials and who had prior intestinal surgery, one at 100 mg BD, and two at 400 mg BD.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems and contact Apotex Medical Information Enquiries/ Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

Clinical experience of overdose is limited. 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.

Signs and Symptoms

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, epigastric pain and other gastrointestinal adverse effects, 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.

Treatment of Overdosage

There are no specific antidotes. Patients should be managed by symptomatic and supportive care following an overdose. Monitor patients for signs and symptoms of gastrointestinal ulceration and/or haemorrhage. Monitor serum electrolytes, renal function and urinalysis after significant overdose.

Consider activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one or two hours of ingestion and may reduce absorption of the drug. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

No information is available regarding the removal of celecoxib by haemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Forced diuresis, alkalinisation of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: M01AH Coxibs

Celecoxib is a cyclooxygenase-2 (COX-2) specific inhibitor, a member of a larger class of non-steroidal anti-inflammatory drugs that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily by inhibition of COX-2. At therapeutic concentrations in humans celecoxib does not inhibit cyclooxygenase-1 (COX-1). COX-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of

inflammatory prostanoids, in particular prostaglandin E2, causing inflammation, oedema and pain. In animal models, celecoxib acts as an anti-inflammatory, analgesic, and antipyretic agent by blocking the production of inflammatory prostanoids via COX-2 inhibition. In animal colon tumour models, celecoxib reduced the incidence and multiplicity of tumours.

In-vivo and *ex-vivo* studies show that celecoxib has a very low affinity for the constitutively expressed COX-1 enzyme. Consequently at therapeutic doses celecoxib has no effect on prostanoids synthesised by activation of COX-1 thereby not interfering with normal COX-1 related physiological processes in tissues, particularly the stomach, intestine and platelets.

Clinical trials

Osteoarthritis (OA)

Celecoxib has demonstrated significant reduction in joint pain compared to placebo. Celecoxib was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with celecoxib 100 mg BD or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, celecoxib doses of 100 mg BD and 200 mg BD provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BD or 200 mg BD the effectiveness of celecoxib was shown to be similar to that of naproxen 500 mg BD. Doses of 200 mg BD provided no additional benefit above that seen with 100 mg BD. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BD or 200 mg OD.

Rheumatoid Arthritis (RA)

Celecoxib has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. Celecoxib was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. Celecoxib was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. Celecoxib doses of 100 mg BD and 200 mg BD were similar in effectiveness and both were comparable to naproxen 500 mg BD.

Although celecoxib 100 mg BD and 200 mg BD provided similar overall effectiveness, some patients derived additional benefit from the 200 mg BD dose. Doses of 400 mg BD provided no additional benefit above that seen with 100-200 mg BD.

Ankylosing Spondylitis (AS)

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 AS. At doses of 100 mg twice daily (BD), 200 mg once daily (OD), and 400 mg once daily (OD), celecoxib was statistically superior to placebo for all measures of efficacy including global pain intensity, global disease activity and functional impairment. In two 12 week studies of celecoxib at 200 mg total daily dose and 400 mg total daily dose, non-inferiority was demonstrated relative to diclofenac 150 mg total daily dose for global pain intensity. Results for global pain intensity are presented below.

Table 3: Global pain intensity^a in celecoxib ankylosing spondylitis clinical trials

Study	Placebo	Celecoxib 200 mg TDD ^b	Ketoprofen 100 mg BD	Naproxen 500 mg BD	Diclofenac 150 mg TDD ^b
Study 193 Baseline mean Mean Change, Week 12 p-value versus placebo ^c	N=156 73.5 -9.9 --	N=137 70.8 -30.0 < 0.001	-- -- --	N=157 71.7 -36.3 < 0.001	-- -- --
Study 137 Baseline mean Mean Change, Week 6 p-value versus placebo ^c	N=76 69.5 -11.9 --	N=80 70.4 -25.7 0.0068	N=90 65.7 -22.5 0.0512	-- -- --	-- -- --
Study 243 Baseline mean Mean Change, Week 12 [95% Confidence Interval] ^d	-- -- --	N=126 66.5 -29.1 [-33.6 to - 24.6]	-- -- --	-- -- --	N=123 65.9 -32.7 [-37.1 to - 28.2]
Study 247 Baseline mean Mean Change, Week 12 [95% Confidence Interval] ^d	-- -- --	N=107 66.3 -25.8 [-31.1 to - 20.6]	-- -- --	-- -- --	N=115 67.0 -28.2 [-33.1 to 23.2]

a As measured using 100 mm Visual Analogue Scale. Values for mean change 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 TDD = Total daily dose: celecoxib 200 mg TDD was administered as 100 mg twice daily (Study 137) or 200 mg once daily (Studies 193, 243, and 247); diclofenac 150 mg TDD was administered as Sustained Release 75 mg twice daily in Study 243, or 50 mg three times daily in Study 247.

c Based on Analysis of Covariance models with the effects of treatment and centre, and baseline value as covariate.

d Based on Analysis of Covariance models; for Study 243, baseline values and age as covariates and treatment, gender and centres as factors; for Study 247, baseline value as a covariate and treatment and centres as factors. Although Study 247 did not reach its target for patient enrolment, a post-hoc analysis indicated that the statistical power of the study to detect treatment differences was not significantly weakened.

Dysmenorrhoea

The analgesic efficacy of celecoxib 400 mg for the treatment of primary dysmenorrhoea has been established in replicate, single dose, controlled studies where the primary measures of efficacy were Summed Pain Intensity Difference for the first 8 hours (SPID8) and the sum of the pain relief scores for the first 8 hours (TOTPAR8). A secondary measure of efficacy was Time to Onset of Analgesia. Naproxen sodium 550 mg was included in a third arm of these studies for comparison against placebo.

On the basis of the primary measures of efficacy, Studies 129 and 130 show that celecoxib is significantly superior to placebo in the treatment of primary dysmenorrhoea. In Study 129, the median Time to Onset of Analgesia for celecoxib was significantly shorter than that observed for placebo. In Study 130, the median Time to Onset of Analgesia for celecoxib was shorter than that observed for placebo, but the difference was not significant.

Table 4: Analgesic efficacy of celecoxib for primary dysmenorrhea

Study	SPID8	TOTPAR8	Median Time to Onset of Analgesia
	Mean [SD]	Mean [SD]	(hr:min)
129			
Placebo (N = 122)	6.0 [7.2]	12.8 [10.2]	01:05
Celecoxib 400 mg (N = 122)	10.1 [7.1]*	18.3 [10.2]*	00:52*
Naproxen sodium 550 mg (N = 122)	11.5 [6.4]*	20.6 [9.2]*	00:45*
130			
Placebo	6.4 [6.8]	13.0 [10.2]	01:27
Celecoxib 400 mg	9.6 [6.3]*	18.0 [9.5]*	00:53
Naproxen sodium 550 mg	11.7 [5.6]*	21.3 [7.8]*	00:50*

*Result is statistically significantly different from placebo ($p < 0.05$)

Dental Surgery

The analgesic efficacy of celecoxib was demonstrated in five studies of patients with post oral surgery pain, a well validated pain model. In these studies 1,130 patients were evaluated including over 360 at single doses of 100 mg or 200 mg. These doses showed analgesic activity beginning by 45 minutes and continuing for approximately 8 hours.

In the placebo controlled comparative study with aspirin (650 mg), celecoxib 100 mg provided statistically significant pain relief and reduction in pain intensity compared to placebo. Although time to onset of pain relief was 0.6 hours for aspirin and 1.0 hour for celecoxib, a greater proportion of the celecoxib group completed the study without rescue medication.

Four further single dose studies compared celecoxib with placebo and either ibuprofen (400 mg) or naproxen sodium (550 mg). All active agents were statistically superior to placebo. Median time to onset of perceptible pain relief with celecoxib 100 mg was 45 and 39 mins; celecoxib 200 mg 38, 30, 44 and 40 mins; ibuprofen 33 and 28 mins, naproxen sodium 24 and 36 mins.

Post Surgery

The efficacy of celecoxib for use in acute pain post surgery has been demonstrated in three pivotal studies; all were randomised, double blind and placebo controlled trials. Two of the studies had a duration of 3 days and the third study was for 5 days post-operative. All three studies used an 11 point score for pain analysis.

The first study was conducted in 120 patients undergoing major plastic surgery e.g. breast augmentation, abdominoplasty procedure. The patients received celecoxib either as an initial 400 mg post-operative dose, then 200 mg BD for 3 days (40 patients) or 400 mg 30- 90 mins before surgery then 200 mg BD for 3 days; the remaining 40 patients received placebo. The primary variable 'opioid analgesia use' was significantly less in the post-operative and peri-operative groups compared to the placebo group for the 3 post-operative days (18 and 23 mg vs. 68 mg; 5 and 13 mg vs. 40 mg; 3 and 3 mg vs. 32 mg respectively, $p < 0.05$) as were the average pain scores. As a result, pain scores were relatively low with the greatest difference (approximately 1.75) being at 4h and 24h.

The second study was conducted in 77 patients undergoing laparoscopic surgery. The patients received either placebo (38) or 400 mg/day celecoxib (39) administered initially in the recovery room and then continued as 200 mg BD for 3 days post-surgery. The primary variable was the times to resume normal dietary (3 ± 2 vs. 2 ± 2 days), bowel (3 ± 2 vs. 2 ± 1 days) and physical

activities (6 ± 3 vs. 4 ± 2 days); these latter two were significantly and clinically different. The effects on pain management were assessed by pain score and rescue analgesia requirements. The pain scores on the first, second and third days were significantly lower in the celecoxib group vs. placebo (differences at 24, 48 and 72h = 2, 2 and 1). The corresponding percentages of patients requiring rescue analgesia were similarly significantly lower (21, 15, 12% vs. 30, 29, 27% at 24, 48 and 72h).

The third study was conducted to evaluate the management of pain after tonsillectomy. Thirty-nine patients received celecoxib 200 mg, 39 received placebo and 37 received ketoprofen 100 mg. This was initially pre-operative and then BD for 5 days and then as required. The primary outcome parameter was the consumption of rescue analgesic during the first 24h after surgery. All patients in the celecoxib group, 32 of 37 (86%) in the ketoprofen group ($p=0.024$, celecoxib vs. ketoprofen) and 37 of 39 (95%) in the placebo group were provided oxycodone for rescue analgesia during the first 4h after surgery. In the celecoxib group, the time to first dose of rescue analgesia was significantly shorter than in the ketoprofen group ($p=0.039$). All patients were provided rescue analgesia during the first 24h after surgery. The total number of oxycodone doses was 215 (mean 5 [range 2-14]) in the celecoxib group, 179 (5[1-9]) doses in the ketoprofen group and 230 (6[1-13]) doses in the placebo patients ($p=0.021$, placebo vs. ketoprofen).

Musculoskeletal Pain

The efficacy of celecoxib was demonstrated in five studies in patients with musculoskeletal pain, including ankle sprain and low back pain. In these studies over 1,822 patients were evaluated.

Four studies in ankle sprain demonstrated celecoxib 200 mg BD to be non-inferior to a variety of active comparators (naproxen, ibuprofen or diclofenac) in the treatment of acute ankle sprains in all primary measures and in most secondary measures, with one instance of inferiority to the active comparator (Physician's Global Assessment of Ankle Injury, day 4).

Finally in a further study in low back pain, the celecoxib treatment was observed to be as effective as diclofenac.

Celecoxib Long-term Arthritis Safety Study (CLASS)

Study Design

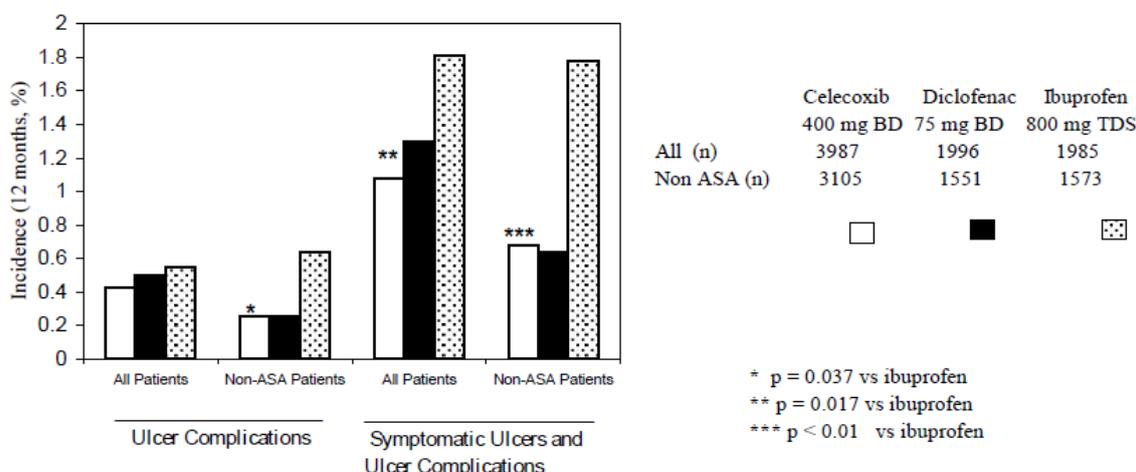
A prospective 12 month study was conducted in approximately 5,800 OA patients and 2,200 RA patients. The primary endpoint of this outcome study was the incidence of *complicated ulcers* (gastrointestinal bleeding, perforation or obstruction) in celecoxib treated patients compared to each comparator. Patients received celecoxib 400 mg BD (4-fold and 2-fold greater than the recommended OA and RA doses, respectively), ibuprofen 800 mg TDS (approved maintenance dose is 1600 mg daily) or diclofenac 75 mg BD (approved maintenance dose is 75-100 mg daily) for a median exposure of 9 months for celecoxib and diclofenac, and 6 months for ibuprofen. Patients were allowed to take concomitant low-dose aspirin ≤ 325 mg mostly for cardiovascular prophylaxis.

Study Results

No statistically significant differences were demonstrated for the incidence of complicated ulcers among the three treatment groups in all patients. In an additional non-protocol specified analysis, there was no difference in the incidence of *complicated and symptomatic ulcers* in patients on celecoxib vs. those on diclofenac, although the incidence was significantly lower for celecoxib than for ibuprofen in all patients, and in those patients not taking aspirin (ASA) (Figure 1). Approximately 22% of patients were taking low-dose aspirin. Concomitant low-dose aspirin use increased the risk of complicated and symptomatic ulcers on celecoxib, diclofenac and ibuprofen (see section **5.1 Pharmacodynamic properties - Clinical trials - Use with**

Aspirin). The incidence rates for diclofenac may be underestimated because of a higher incidence of early withdrawals due to GI adverse events than celecoxib and ibuprofen.

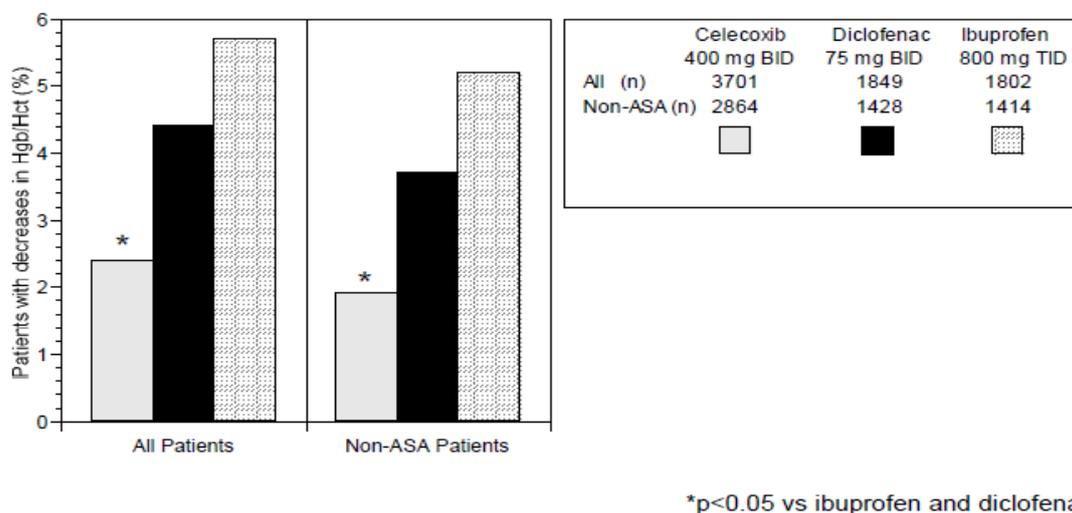
Figure 1: Incidence of symptomatic ulcers and ulcer complications



Celecoxib (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) was also associated with a significantly lower incidence of clinically relevant decreases in haemoglobin (>20 g/L) or haematocrit (≥10 points) than ibuprofen and diclofenac regardless of aspirin use (Figure 2).

The incidence of clinically relevant decreases in haemoglobin and haematocrit in celecoxib patients taking aspirin was lower than in ibuprofen and diclofenac patients taking aspirin.

Figure 2: Incidence of clinically relevant decreases in haemoglobin and/or haematocrit



In the original registration studies, the incidence of serious upper gastrointestinal complications (bleeding, perforation, gastric outlet obstruction) with celecoxib is not significantly different from placebo and is approximately 8-fold less than with non-specific COX inhibitors.

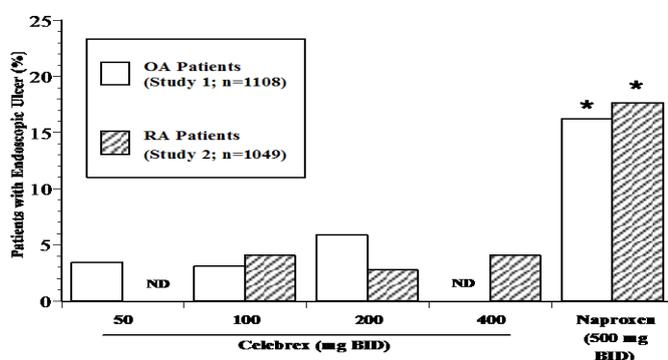
Endoscopic Studies

Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomised 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 BD. In all three studies that included naproxen 500 mg BD, and in the study that included ibuprofen 800 mg TDS, celecoxib was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared celecoxib with diclofenac 75 mg BD; 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.

Figure 3 and Table 5 summarise the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

Figure 3: Incidence of endoscopically observed gastroduodenal ulcers after twelve weeks of treatment



ND = Not Done

* Significantly different from all other treatments; $p < 0.05$.

Celecoxib 100 mg BD, 200 mg once daily, or 200 mg BD are the recommended doses.

These studies were not powered to compare the endoscopic ulcer rates of celecoxib vs. placebo.

Study 1: placebo ulcer rate = 2.3%

Study 2: placebo ulcer rate = 2.0%

Table 5: 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 BD	3.4% (8/233)	---
Celecoxib 100 mg BD	3.1% (7/227)	4.0% (9/223)
Celecoxib 200 mg BD	5.9% (13/221)	2.7% (6/219)
Celecoxib 400 mg BD	---	4.1% (8/197)
Naproxen 500 mg BD	16.2% (34/210)*	17.6% (37/210)*

* $p \leq 0.05$ vs all other treatments

Figure 4 and Table 6 summarise 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.

Figure 4: Cumulative incidence of gastroduodenal ulcers based on 4 serial endoscopies over 12 weeks

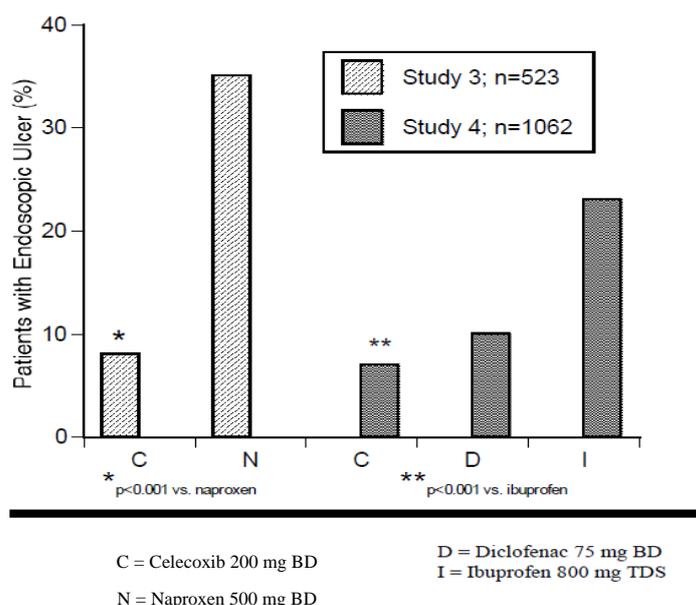


Table 6: Incidence of gastroduodenal ulcers from 3-month serial endoscopy studies in OA and RA patients

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

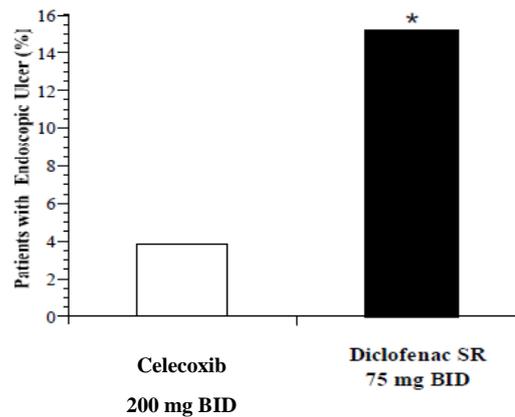
* p≤0.05 Celecoxib vs. naproxen based on interval and cumulative analyses

† p≤0.05 Celecoxib vs. ibuprofen based on interval and cumulative analyses

One randomised 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 Figure 5.

Figure 5:

Prevalence of Endoscopically Observed Gastroduodenal Ulcers after Six Months of Treatment in Patients with Rheumatoid Arthritis



* 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.

Serious clinically significant upper GI bleeding has been observed in patients receiving celecoxib in controlled and open labelled trials, albeit infrequently. Patients most at risk of developing an ulcer complication were the elderly (≥ 75 years), patients in poor health or with cardiovascular disease, aspirin users and patients with a history of a GI ulcer or upper GI bleeding.

Use with Aspirin

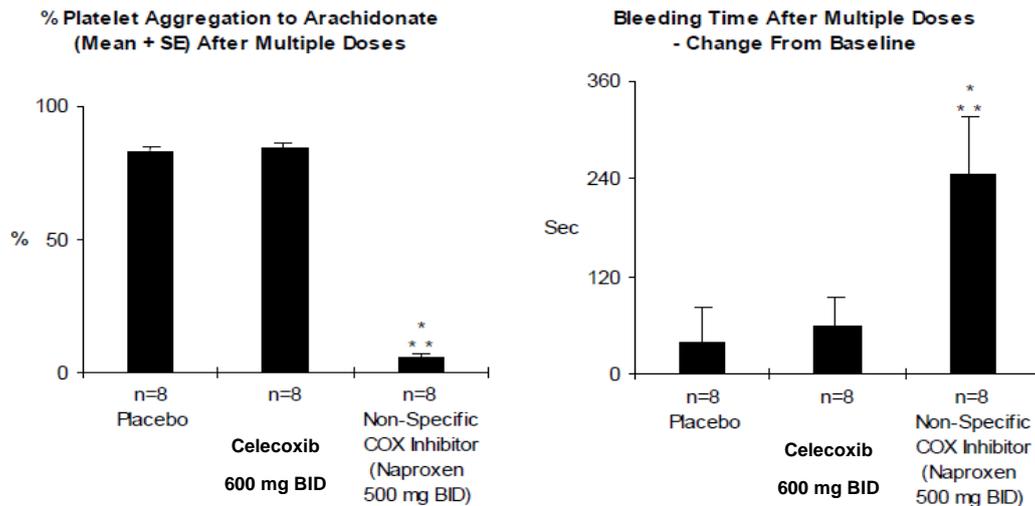
Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin (≤ 325 mg/day). In the celecoxib groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than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

In the Celecoxib Long-term Arthritis Safety Study, approximately 22% of patients were taking aspirin (≤ 325 mg/day). Subjects on concomitant low-dose aspirin experienced 4-fold higher rates of *complicated and symptomatic ulcers* on celecoxib.

Platelet Function

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

Figure 6:



* Significantly different from placebo; $p < 0.05$

** Significantly different from celecoxib; < 0.05

Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

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

Two studies involving patients with sporadic adenomatous polyps were conducted with celecoxib i.e., the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint of 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.

In the APC trial, the hazard ratios compared to placebo for a composite endpoint of cardiovascular death, myocardial infarction, or stroke (adjudicated) were 3.4 (95% CI 1.4-8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1-7.2) with celecoxib 200 mg twice daily (cumulative rates for this composite endpoint over 3 years were 20/671 subjects, 3.0%, and 17/685 subjects, 2.5%, respectively, compared to 6/679 subjects, 0.9%, for placebo). The increases for both celecoxib dose groups versus placebo were mainly driven by myocardial infarction.

In the PreSAP trial, the hazard ratio compared to placebo for this same composite endpoint was 1.2 (95% CI 0.6-2.4) with celecoxib 400 mg once daily (cumulative rates for this composite endpoint over 3 years were 21/933 subjects, 2.3%, compared to 12/628 subjects, 1.9%, for placebo).

When data from the APC and PreSAP trials were considered together, risk for cardiovascular thromboembolic events was greater in celecoxib-treated patients with a history of atherosclerotic cardiovascular disease, than in celecoxib-treated patients without such history.

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

Data from a third long-term study, ADAPT (The Alzheimer's Disease Anti-inflammatory Prevention Trial), did not show a significantly increased cardiovascular risk with celecoxib 200

mg BD compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61 – 2.12) with celecoxib 200 mg twice daily. The incidence of myocardial infarction was 1.1% (8/717 patients) with celecoxib 200 mg twice daily and 1.2% (13/1070 patients) with placebo.

Cardiovascular Safety – Celecoxib Long-term Arthritis Safety Study (CLASS)

Cardiovascular safety outcomes were evaluated in CLASS (see section **5.1 Pharmacodynamic properties - Clinical trials** for description of trial). Kaplan-Meier cumulative rates for investigator reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischaemic attacks and ischaemic cerebrovascular accidents) demonstrated no differences between the celecoxib, diclofenac or ibuprofen treatment groups. The cumulative rates in all patients at nine months for celecoxib, diclofenac and ibuprofen were 1.2%, 1.4% and 1.1%, respectively. The cumulative rates in non-aspirin users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in the non-aspirin users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased risk to a similar degree.

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see section **4.3 Contraindications**).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

When celecoxib is given under fasting conditions, peak plasma concentrations are reached after approximately 2-3 hours. Intersubject variability in the C_{max} and AUC is about 30%. Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional up to 200 mg BD; at higher doses there are less than proportional increases in C_{max} and AUC (see section **5.2 Pharmacokinetic properties - Food Effects**). Absolute bioavailability studies have not been conducted because of celecoxib's low solubility in aqueous media. The relative oral bioavailability of celecoxib capsules compared with a suspension is about 99%. With multiple dosing, steady state conditions are reached on or before day 5.

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%. 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. Celecoxib, at doses up to 200 mg BD can be administered without regard to the timing of meals. When multiple total daily doses of celecoxib as high as 1200 mg were given with food, an improved correlation between the dose and AUC (0-12) was observed.

Coadministration 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.

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the therapeutic dose range. *In-vitro* studies indicate that it binds primarily to albumin, and to a lesser extent, α_1 glycoprotein.

The apparent volume of distribution at steady state is about 400 L in healthy young adults, suggesting extensive tissue distribution.

Metabolism

Celecoxib is extensively metabolised in the liver. *In-vitro* and *in-vivo* studies indicate that metabolism is mainly by cytochrome P450 CYP 2C9 (see section **4.5 Interactions with other medicines and other forms of interactions**). Three metabolites have been identified in human plasma, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate. Pharmacological activity resides in the parent drug. The main metabolites found in human plasma have no detectable COX-1 or COX-2 inhibitory activity.

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP 2C9*3 polymorphism.

Patients who are known or suspected to be poor P450 2C9 metabolisers based on previous history should be administered celecoxib with caution as they may have abnormally high plasma concentrations due to reduced metabolic clearance. Consider starting treatment at a reduced dose (see sections **4.2 Dose and method of administration** and **4.5 Interactions with other medicines and other forms of interactions**).

Excretion

Elimination of celecoxib is mostly by hepatic metabolism with less than 1% of the dose being excreted unchanged in the urine. Following a single oral dose of radiolabelled drug, approximately 57% of the dose was excreted in the faeces and 27% was excreted into the urine. The primary metabolite in both the urine and faeces was the carboxylic acid metabolite (73% of the dose) with low amounts of the glucuronide also appearing in the urine. At steady state the elimination half-life ($t_{1/2}$) was 4-15 hours and the clearance was about 500 mL/min. It appears that the low solubility of the drug prolongs absorption resulting in variable terminal half-life ($t_{1/2}$) determinations.

Special Populations

Hepatic Impairment

A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) 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 half the recommended dose in arthritis patients with moderate hepatic impairment.

Patients with severe hepatic impairment have not been studied. Therefore, the use of celecoxib in patients with severe hepatic impairment (Child-Pugh score ≥ 10) is contraindicated (see sections **4.3 Contraindications** and **4.2 Dose and method of administration**).

Renal Impairment

In elderly volunteers with age related reductions in glomerular filtration rate (GFR) (mean GFR > 65 mL/min/1.73m²) and in patients with chronic stable renal insufficiency (GFR 35 – 60 mL/min/1.73m²) celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance. Severe renal insufficiency would not be expected to alter clearance of celecoxib since the main route of elimination is via hepatic metabolism to inactive metabolites. There are no studies in patients with severe renal impairment.

Elderly (> 65 years)

At steady state, subjects older than 65 years of age had a 40% higher C_{max} and a 50% higher AUC than those of younger subjects. In elderly females, the C_{max} and AUC were higher than those for elderly males predominantly due to the lower body weight of the females. No dosage adjustment in the elderly is generally necessary. However, for elderly patients with a body weight of less than 50kg treatment should be initiated at the lowest recommended dose.

Children

Celecoxib is not approved for use in patients under 18 years of age.

Race

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Celecoxib was not carcinogenic in 2-year studies in rats given oral doses up to 200 mg/kg/day for males and 10 mg/kg/day for females (approximately 2-4 fold the human exposure as measured by the $AUC_{0-24\text{ h}}$ at 400 mg BD, which is twice the recommended maximum daily dose), or in mice given dietary doses up to 25 mg/kg/day for males and 50 mg/kg/day for females (slightly less than human exposure at 400 mg BD).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Lactose monohydrate
- povidone
- colloidal anhydrous silica
- sodium lauryl sulfate
- croscarmellose sodium and
- magnesium stearate

The capsule shells contain

- Gelatin
- titanium dioxide
- sodium lauryl sulfate and
- TekPrint SW-9008 Black Ink (Proprietary ingredient # 2328)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

CELECOXIB APOTEX (celecoxib) 100 mg capsules

Available in blisters of 10, 20, 50 and 60 capsules.

CELECOXIB APOTEX (celecoxib) 200 mg capsules

Available in blisters of 10, 20, 30, 50, 60 and 120 capsules.

The capsules are supplied in PVC/PCTFE(Aclar)/Al blister packs.

Not all pack sizes are being distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

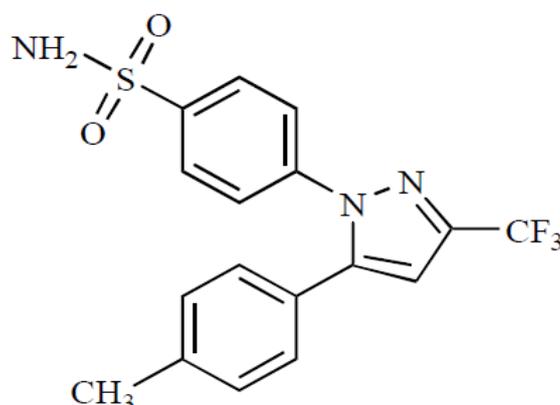
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Celecoxib is a diaryl substituted pyrazole.

Celecoxib is weakly acidic with a pKa in water of 11.1 and is practically insoluble in water, freely soluble to soluble in anhydrous ethanol and soluble in methylene chloride. Celecoxib is chemically unrelated to anti-inflammatory agents of steroidal or non-steroidal nature. Celecoxib does not contain a chiral centre.

Chemical structure



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

Molecular formula: C₁₇H₁₄F₃N₃O₂S

Molecular weight: 381.38

CAS number

169590-42-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

Tel: (02) 8877 8333
Web: www1.apotex.com/au

9 DATE OF FIRST APPROVAL

29 May 2014

10 DATE OF REVISION

20 November 2019

Summary table of changes

Section Changed	Summary of new information
–	Change in trade name