AUSTRALIAN PRODUCT INFORMATION

CELEBREX RELIEF®

(celecoxib) capsule

1 NAME OF THE MEDICINE

Celecoxib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CELEBREX RELIEF 200 mg capsule contains 200 mg of celecoxib as the active ingredient.

Excipients with known effect: lactose, phenylalanine, and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

CELEBREX RELIEF 200 mg capsules: No. 2, light brown opaque cap and white opaque body, hard-shell gelatin capsule filled with white to off-white powder. Axially printed with MYLAN over CE 200 in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

For the short-term treatment of primary dysmenorrhoea in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

CELEBREX RELIEF should not be used for more than 5 days at a time except on medical advice.

As the cardiovascular (CV) risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials).

Adults

Acute Pain from 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.

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.

Method of Administration

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

Dosage Adjustment

CYP2C9 Poor Metabolisers

Patients who are known or suspected to be CYP2C9 poor metabolisers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at a reduced dose (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 5.2 PHARMACOKINETIC PROPERTIES).

Hepatic Impairment

No dosage adjustment is necessary in patients with mild hepatic impairment.

There is no clinical experience in patients with severe hepatic impairment. Therefore, the use of CELEBREX RELIEF (over the counter celecoxib) in patients with moderate and severe hepatic impairment (Child-Pugh score ≥7 is contraindicated (see Section 4.3 CONTRAINDICATIONS and Section 5.2 PHARMACOKINETIC PROPERTIES).

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 4.3 CONTRAINDICATIONS and Section 5.2 PHARMACOKINETIC PROPERTIES).

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 (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric Population

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

4.3 CONTRAINDICATIONS

CELEBREX RELIEF 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 (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors. Severe, rarely fatal, anaphylactoid reactions to NSAIDs have been reported in such patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Anaphylactoid Reactions).

CELEBREX RELIEF should not be used with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

CELEBREX RELIEF is contraindicated in patients with:

- Known hypersensitivity to celecoxib or any of the excipients contained in the CELEBREX RELIEF capsules (see Section 6.1 LIST OF EXCIPIENTS).
- Demonstrated allergic-type reactions to sulfonamides.
- Unstable ischaemic heart disease of thrombus aetiology or documented myocardial infarction or stroke within 3 months.
- Congestive heart failure (NYHA II-IV).
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Severe renal impairment (estimated creatinine clearance <30 mL/min).

- Moderate to severe hepatic impairment (Child-Pugh# score ≥7; Note - this is more restrictive than for prescription celecoxib, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES).

- 3rd trimester of pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

CELEBREX RELIEF 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).

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 initiate CELEBREX RELIEF should be based on an assessment of the individual patient's overall risks and benefits of therapy (see Section 4.3 CONTRAINDICATIONS).

Cardiovascular Thrombotic Events

COX-2 inhibitors, including celecoxib, have been associated with an increased risk of serious cardiovascular thrombotic adverse events, myocardial infarction and stroke, which can be fatal (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 CV thrombotic events. This risk may increase with dose and duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

CELEBREX RELIEF should be used with caution in patients with significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease as well as patients at high risk of cardiovascular disease, including those with significant and multiple risk factors (e.g. diabetes, hypertension, hypercholesterolaemia, cardiac failure and smokers). See Section 4.3 CONTRAINDICATIONS.

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials, Cardiovascular Safety).

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 symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Gastrointestinal Effects

Infrequently, serious gastrointestinal (GI) toxicity such as bleeding, ulceration, and upper and lower GI perforation (including perforations of the stomach or intestine) has been observed in patients treated with CELEBREX RELIEF.

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.

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.

Patients most at risk of developing GI complications with NSAIDs are elderly patients, patients with CV disease, patients using concomitant antiplatelet drugs (such as aspirin) or corticosteroids, patients who consume alcohol or patients with a prior history of GI disease (such as ulceration, GI bleeding or inflammatory conditions). Celecoxib should be used with extreme caution in these patients. Physicians and patients should remain alert for ulceration and GI bleeding even in the absence of 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 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 H_2-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 Section 4.3 CONTRAINDICATIONS and Section 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 drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported very rarely in association with the use of celecoxib. Fixed drug eruption (FDE) which may present as a more severe variant known as generalised bullous fixed drug eruption (GBFDE) has also been reported 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.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

DRESS has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

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 - Use with ACE Inhibitors, Angiotensin Receptor Antagonists, Anti-inflammatory Drugs and Thiazide Diuretics), and the elderly. Discontinuation of NSAID therapy 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. The relative roles of cyclooxygenase-1 (COX-1) and COX-2 in renal physiology are not completely understood. Celecoxib reduces the urinary excretion of PGE_2 and 6-keto-$PGF_{1\alpha}$ (a prostacyclin metabolite) but leaves serum thromboxane B_2 (TXB_2) and urinary excretion of 11-dehydro-TXB_2, a thromboxane metabolite (both COX-1 products) unaffected.

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

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

Use with ACE Inhibitors, Angiotensin Receptor Antagonists, Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), 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 Oral Anticoagulants

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Oral Anticoagulants).

Use with Drugs Metabolised by CYP2D6

Celecoxib has shown to be a moderately potent CYP2D6 inhibitor. For drugs that are metabolised by CYP2D6, a dose reduction during initiation of celecoxib treatment or a dose increase upon termination of celecoxib treatment may be necessary (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Dextromethorphan and Metoprolol).

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 and hepatic failure (some with fatal outcome or requiring 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.

Physician and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. A patient with symptoms and/or signs suggesting liver dysfunction (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms) 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.) CELEBREX RELIEF 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. 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 Clinical Trials, 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, CELEBREX RELIEF should be used with caution in patients with fluid retention, hypertension, heart failure, compromised cardiac function, pre-existing oedema 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

Elderly patients are at higher risk of adverse events, therefore those aged 65 years or over are instructed not to take CELEBREX RELIEF unless advised to do so by a doctor.

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

CELEBREX RELIEF 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 CYP2C9 metabolisers 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. 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).

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

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

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

Antihypertensives including Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Antagonists, Diuretics and Beta-blockers

Inhibition of prostaglandins may diminish the effect of antihypertensives including ACE inhibitors, angiotensin II antagonists (also known as angiotensin receptor blockers or ARBs), diuretics and beta-blockers. This interaction should be given consideration in patients taking celecoxib concomitantly with these drugs.

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, angiotensin II antagonists or diuretics, may result in deterioration of renal function, including possible acute renal failure. Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the clinical need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

Furosemide

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

Aspirin

CELEBREX RELIEF can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX RELIEF may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX RELIEF 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, CELEBREX RELIEF is not a substitute for aspirin for cardiovascular prophylaxis.

Ciclosporin

Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with ciclosporin.

Fluconazole

Concomitant administration of fluconazole at 200 mg once daily (OD) 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). CELEBREX RELIEF should be introduced at the lowest recommended dose in patients receiving fluconazole.

Dextromethorphan and Metoprolol

Concomitant administration of celecoxib resulted in increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates). These increases are due to celecoxib inhibition to the CYP2D6 substrate metabolism via CYP2D6. Therefore, the dose of drugs which are CYP2D6 substrate may need to be reduced when treatment with celecoxib is initiated or increased when treatment with celecoxib is terminated (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use with Drugs Metabolised by CYP2D6).

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 CELEBREX RELIEF 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.

Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g. neutropenia, thrombocytopenia, renal dysfunction). During concomitant use of celecoxib and methotrexate, patients should be monitored for methotrexate toxicity.

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.

Oral Anticoagulants

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran and rivaroxaban). Because increases in prothrombin time (INR) have been reported, anticoagulation/INR should be monitored, particularly in the first few days, after initiating or changing celecoxib therapy in patients taking a warfarin/coumarin-type anticoagulant 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 or similar agents (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Gastrointestinal Effects).

Digoxin

Concomitant use of celecoxib with digoxin has been reported to increase serum concentration and prolong half-life of digoxin. During concomitant use of celecoxib and digoxin, serum digoxin levels should be monitored.

Other Drug Interactions

No drug interaction data are available for celecoxib and the co-administration of the following products: paracetamol, aminoglycosides, bone marrow depressants, butemide, colestyramine, colchicine, gold compounds, indapamide, insulin, nephrotoxic 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 $AUC_{0\text{-}24h}$ 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

Pregnancy Category B3

There is no information on the use of celecoxib in pregnant women. CELEBREX RELIEF 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 CELEBREX RELIEF is contraindicated during the third trimester of pregnancy, and CELEBREX RELIEF 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.

Oligohydramnios and neonatal renal impairment

Use of NSAIDs from about 20 weeks gestation may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary from about 20 weeks, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with NSAIDs if oligohydramnios occurs.

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 $AUC_{0\text{-}24\,h}$ 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), $AUC_{0\text{-}24\,h}$ was similar to that in humans dosed at 400 mg BD. At the threshold dose of 60 mg/kg/day in rabbits, $AUC_{0\text{-}24\,h}$ 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 $AUC_{0\text{-}24\,h}$ 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 ≥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 ≥ 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 disorders					
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%
Musculoskeletal and connective tissue disorders					
Back pain	2.8%	3.6%	2.2%	2.6%	0.9%
General disorders and administration site conditions					
Oedema peripheral	2.1%	1.1%	2.1%	1.0%	3.5%
Injury	2.9%	2.3%	3.0%	2.6%	3.2%
Nervous system disorders					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric disorders					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory, thoracic and mediastinal disorders					
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 and subcutaneous tissue disorders					
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.

Table 2: Adverse events which occurred in 0.1 - 1.9% of patients taking celecoxib (100-200 mg BD or 200 mg once daily) regardless of causality:

Blood and lymphatic system disorders	Anaemia, thrombocythaemia
Cardiac disorders	Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction, arrhythmia, palpitation, tachycardia
Ear and labyrinth disorders	Deafness, ear abnormality, ear ache, tinnitus, vertigo
Eye disorders	Vision blurred, cataract, conjunctivitis, eye pain, glaucoma
Gastrointestinal disorders	Constipation, diverticulitis, dysphagia, eructation, oesophagitis, gastritis, gastroenteritis, gastroesophageal reflux, haemorrhoids, hiatal hernia, melaena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting
General disorders and administration site conditions	Asthenia, chest pain, cyst, oedema generalised, face oedema, fatigue, pyrexia, influenza-like symptoms, pain, peripheral pain, injection site reaction
Hepatobiliary disorders	Hepatic function abnormal, AST increased, ALT increased
Infections and infestations	Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media, cellulitis, cystitis, urinary tract infection
Injury, poisoning and procedural complications	Fracture accidental
Immune system disorders	Hypersensitivity
Investigations	BUN increased, CPK increased, blood alkaline phosphatase increased, non-protein nitrogen increased, blood creatinine increased, weight increased
Metabolism and nutritional disorders	Diabetes mellitus, hypercholesterolaemia, hyperglycaemia, hypokalaemia
Musculoskeletal and connective tissue disorders	Arthralgia, arthrosis, bone disorder, myalgia, neck stiffness, synovitis, tendinitis, leg cramps
Nervous system disorders	Hypertonia, hypoaesthesia, migraine, neuralgia, neuropathy, paraesthesia, dysgeusia
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast neoplasm
Psychiatric disorders	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Reproductive system and breast disorders	Breast fibroadenosis, breast pain, dysmenorrhoea, menstrual disorder, vaginal haemorrhage, vaginitis, prostatic disorder
Respiratory, thoracic and mediastinal disorders	Bronchitis**,** bronchospasm, bronchospasm aggravated, cough, dyspnoea, laryngitis, pneumonia, epistaxis
Renal and urinary system disorders	Albuminuria, dysuria, haematuria, pollakiuria, nephrolithiasis, urinary incontinence
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, hyperhidrosis, urticaria, ecchymosis, dermatitis contact, skin mass
Vascular disorders	Hot flushes

Table 3: Other serious adverse events which occur rarely (<0.1%), regardless of causality

The following serious adverse events have occurred rarely in patients, taking celecoxib.

Cardiac disorders	Syncope, cardiac failure congestive, ventricular fibrillation
Vascular disorders	Thrombophlebitis
Gastrointestinal disorders	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus, oesophageal ulcer, gastric ulcer, duodenal ulcer
Hepatobiliary disorders	Cholelithiasis
Infection and infestation	Peripheral gangrene, meningitis aseptic
Blood and lymphatic disorders	Thrombocytopenia
Nervous system disorders	Ataxia, epilepsy, cerebrovascular accident
Psychiatric disorders	Suicide, confusional state
Renal and urinary disorders	Renal failure acute
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism
Ear and labyrinth disorders	Decreased hearing
General disorders and administration site conditions	Sepsis, sudden death

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 Drug Reactions from Polyp Prevention Trials

The following additional adverse events in Table 4 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). Frequencies of ADRs in Table 4 were determined based on long-term polyp prevention studies and are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%). The adverse events in Table 4 are listed by system organ class and are ranked by frequency in descending order.

Table 4 Adverse reactions occurring in celecoxib patients from long-term studies involving patients with sporadic adenomatous polyps

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

System Organ Class Frequency	Adverse Drug Reaction
Eye disorders	
Uncommon	Vitreous floaters, conjunctival haemorrhage
Ear and labyrinth disorders	
Uncommon	Hypoacusis
Cardiac disorders	
Common	Angina pectoris, myocardial infarction
Uncommon	Angina unstable, aortic valve incompetence, arteriosclerosis coronary artery, sinus bradycardia, ventricular hypertrophy
Vascular disorders	
Very Common	Hypertension*
Uncommon	Deep vein thrombosis, haematoma
Respiratory, thoracic, and mediastinal disorders	
Common	Dyspnoea
Uncommon	Dysphonia
Gastrointestinal disorders	
Very Common	Diarrhoea*
Common	Nausea, gastro-oesophageal reflux disease, diverticulum, vomiting*, dysphagia, irritable bowel syndrome
Uncommon	Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
Hepatobiliary disorders	
Common	Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)*
Skin and subcutaneous tissue disorders	
Uncommon	Dermatitis allergic
Musculoskeletal and connective tissue disorders	
Common	Muscle spasms
Uncommon	Synovial cyst
Renal and urinary disorders	
Common	Nephrolithiasis
Uncommon	Nocturia
Reproductive system and breast disorders	
Common	Vaginal haemorrhage, benign prostatic hyperplasia, prostatitis
Uncommon	Breast tenderness, dysmenorrhoea, ovarian cyst, menopausal symptoms
General disorders and administration site conditions	
Uncommon	Oedema
Investigations	
Common	Blood creatinine increased, prostatic specific antigen increased, weight increased
Uncommon	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, diarrhoea and hepatic enzyme increased are included in Table 4 because these events 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.

Post-Marketing Experience

The following adverse reactions have been identified during post approval use of celecoxib.

Blood and lymphatic system disorders:

Agranulocytosis, aplastic anaemia, pancytopenia, leukopenia.

Hepatobiliary disorders:

Hepatic necrosis, hepatitis, jaundice, hepatic failure, hepatitis fulminant, cholestasis, hepatitis cholestatic, liver transplant, hepatic enzyme increased.

Immune system disorders:

Anaphylactic reaction.

Metabolism and nutrition disorders:

Hypoglycaemia, hyponatraemia.

Musculoskeletal and connective tissue disorders:

Myositis.

Nervous system disorders:

Ageusia, anosmia, intracranial haemorrhage (including fatal intracranial haemorrhage), cerebral haemorrhage.

Psychiatric disorders:

Hallucination.

Renal and urinary disorders:

Tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion.

Respiratory, thoracic and mediastinal disorders:

Pneumonitis.

Reproductive system and breast disorders:

Menstrual disorders, infertility female (female fertility decreased).

Skin and subcutaneous tissue disorders:

Angioedema, photosensitivity reaction, erythema multiforme, dermatitis exfoliative, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis bullous, generalised bullous fixed drug eruption (GBFDE), fixed drug eruption (FDE).

Vascular disorders:

Vasculitis.

A causal association for the following adverse effects has not yet been established however they could not be excluded as a possible class-effect:

Pregnancy, puerperium and perinatal conditions:

Oligohydramnios, neonatal renal impairment.

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.

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 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: M01AH Coxibs

Mechanism of Action

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

Pharmacodynamic effects

Celecoxib is a cyclooxygenase-2 (COX-2) specific inhibitor, a member of a larger class of non-steroidal anti-inflammatory drugs (NSAIDs) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. 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

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 6: Analgesic efficacy of celecoxib for primary dysmenorrhoea

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 ($p<0.05$)

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)

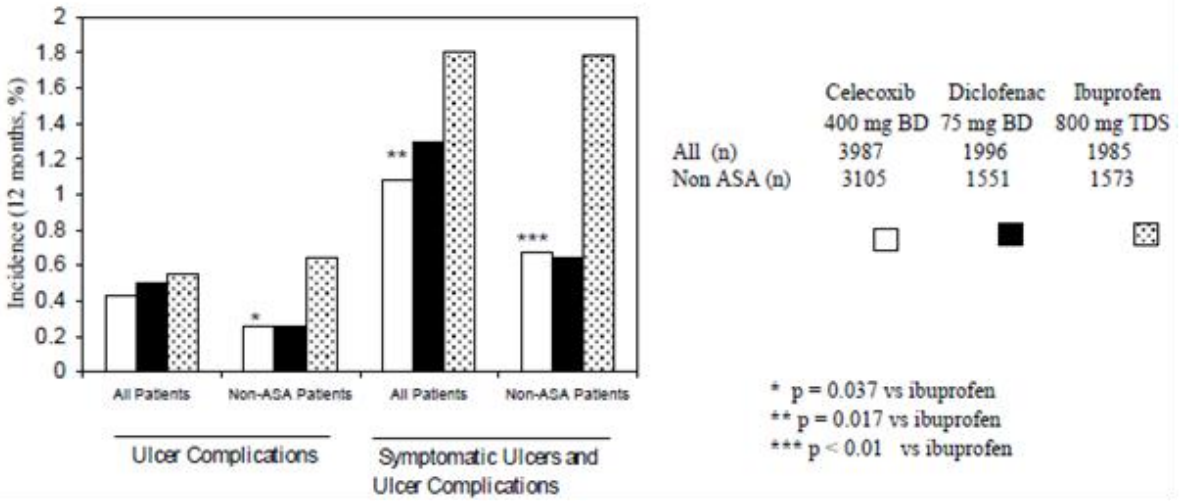
Study Design

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 (CV) 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.

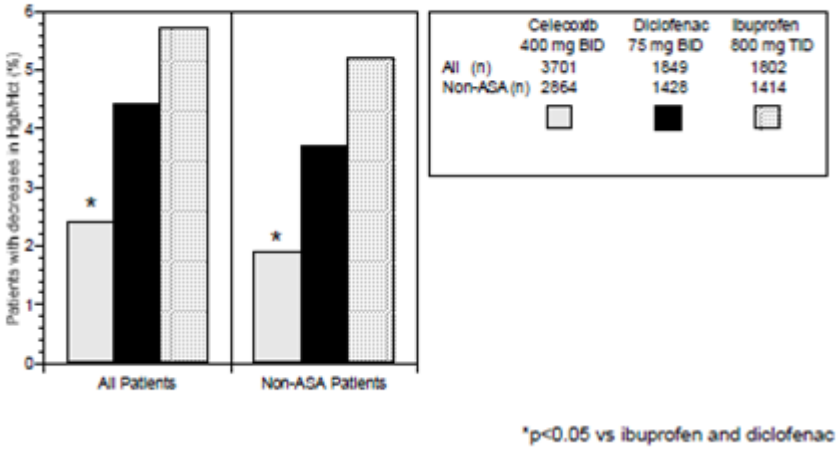
Figure 1: Incidence of symptomatic ulcers and ulcer complications



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



*p<0.05 vs ibuprofen and diclofenac

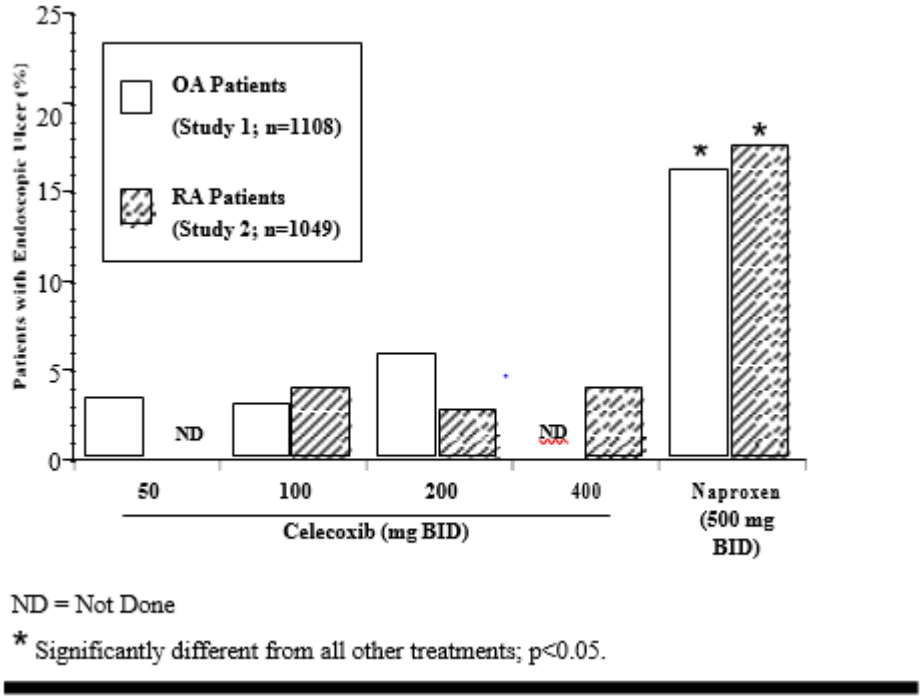
In the original registration studies, the incidence of serious upper gastrointestinal complications (bleeding, perforation, gastric outlet obstruction) with celecoxib is not significantly different from placebo and is approximately 8-fold less than with non-specific COX inhibitors.

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 7 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 7: 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≤ 0.05 vs all other treatments

Figure 4 and Table 8 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

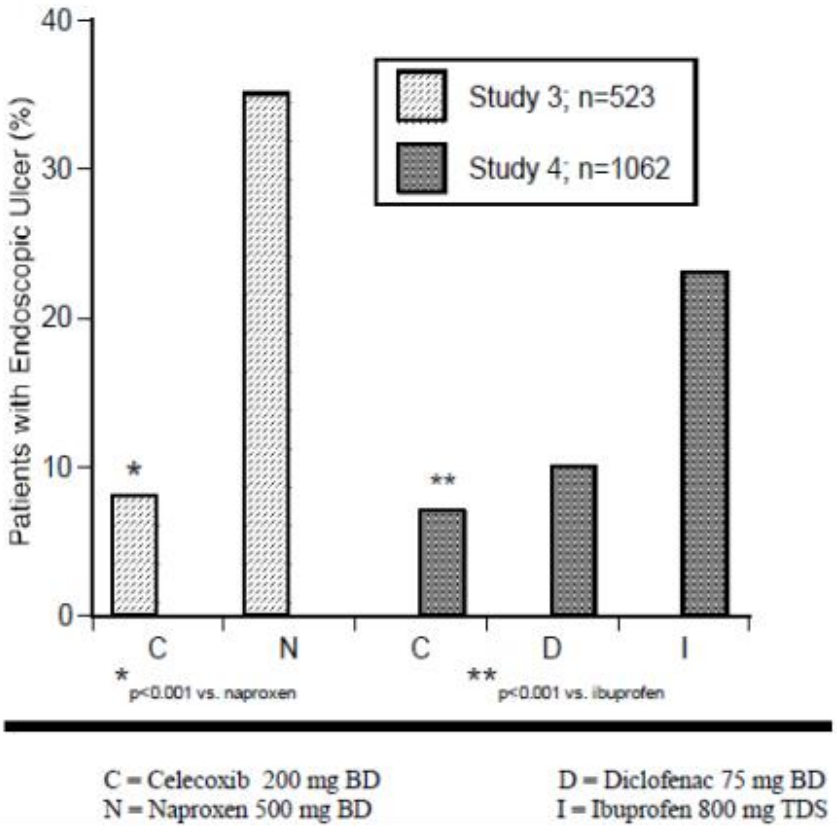


Table 8: Incidence of gastroduodenal ulcers from 3-month serial endoscopy studies in OA and RA patients

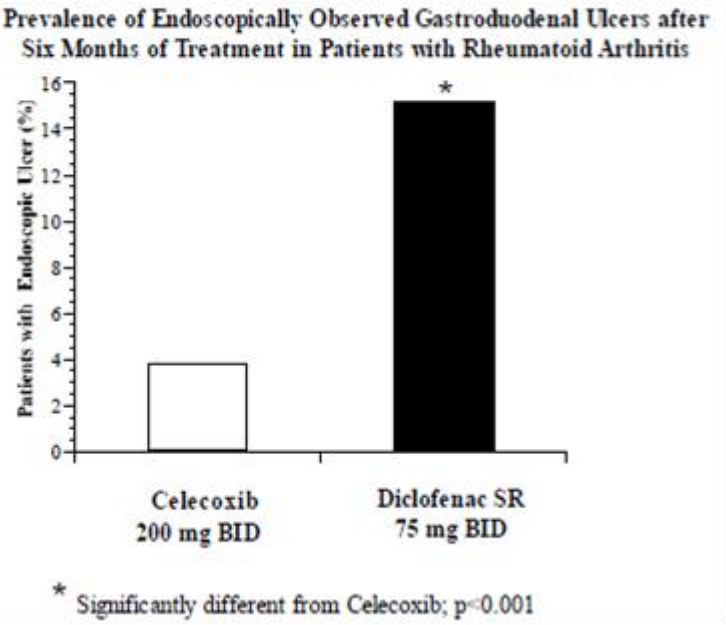
	Week 4	Week 8	Week 12	Final
Study 3 (n=523)				
Celecoxib 200 mg BD	4.0% (10/252)*	2.2% (5/227)*	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BD	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (89/257)
Study 4 (n=1062)				
Celecoxib 200 mg BD	3.9% (13/337)†	2.4% (7/296)†	1.8% (5/274)†	7.0% (25/356)†
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:



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

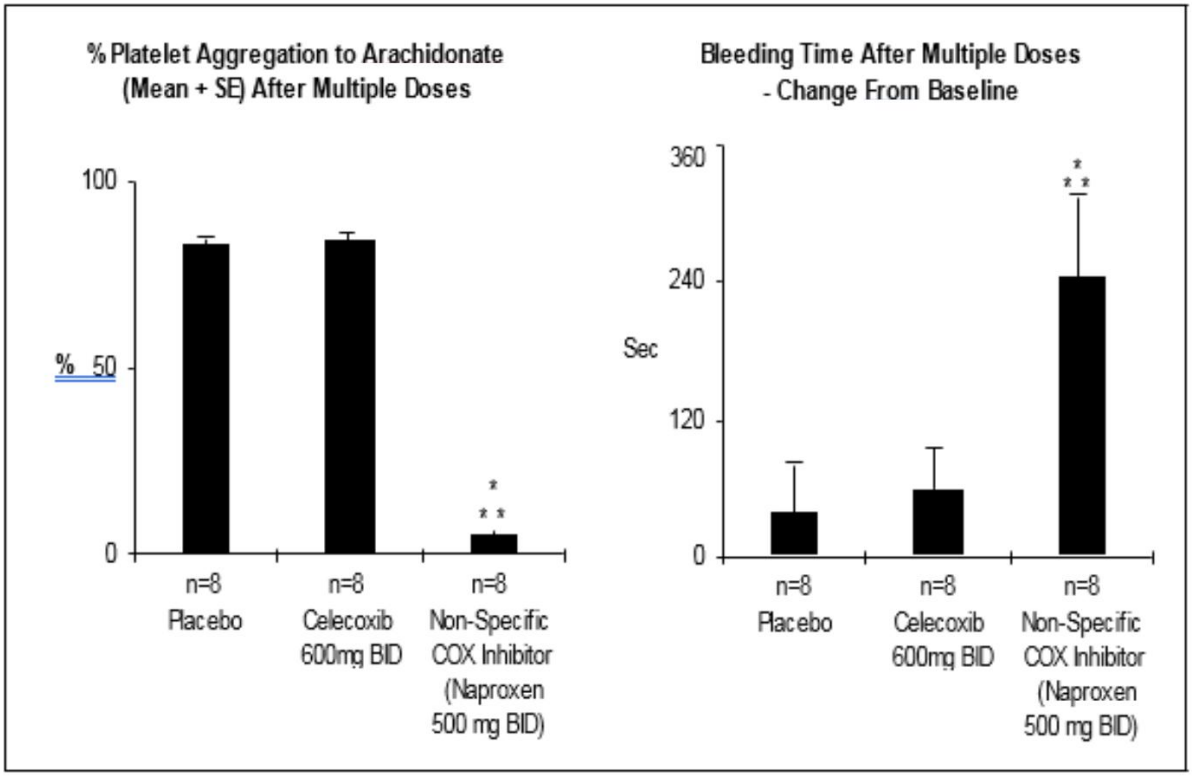
Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin (≤325 mg/day). In the celecoxib groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than 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 (see Figure 6).

Figure 6: Effects of celecoxib on platelet aggregation and bleeding time



* Significantly different from placebo; $p<0.05$

** Significantly different from celecoxib $p<0.05$.

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

Cardiovascular Safety - Prospective Randomised Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION)

Study design

The PRECISION study was a double blind study of CV safety in OA or RA patients with or at high risk for CV disease comparing celecoxib (200-400 mg daily) with naproxen (750- 1000 mg daily) and ibuprofen (1800-2400 mg daily). The primary endpoint, Antiplatelet Trialists Collaboration (APTC), was an independently adjudicated composite of CV death (including haemorrhagic death), non-fatal myocardial infarction or non-fatal stroke. The study power was readjusted from 90% to 80% to accommodate for lower than expected APTC event rate and higher than expected drop off treatment rate. All patients were prescribed open label esomeprazole (20-40 mg) for gastroprotection. Patients who were taking low dose aspirin were permitted to continue therapy.

Other independently adjudicated secondary and tertiary endpoints included CV, gastrointestinal and renal outcomes. Additionally, there was a 4 month sub study focusing on the effects of the three drugs on blood pressure as measured by ambulatory monitoring (ABPM).

Study results

Table 9: Population and treatment dose

Analysis Set	Celecoxib 100-200 mg BD	Ibuprofen 600-800 mg TDS	Naproxen 375-500 mg BD	Total
Randomised (ITT)	8,072	8,040	7,969	24,081
On-Treatment (mITT)	8,030	7,990	7,933	23,953
Average Dose[1] (mg/day)	209±37	2045±246	852±103	NA

1 Average dose dispensed

ITT – Intent to Treat; All randomised subjects

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

Primary endpoint

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

The primary analysis for ITT and mITT are described below in Table 10.

Table 10: Primary analysis of the adjudicated APTC composite endpoint

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib 100 – 200 mg BD	**Ibuprofen 600 - 800 mg TDS**	**Naproxen 375 - 500 mg BD**
N	8,072	8,040	7,969
Subjects with Events	188 (2.3%)	218 (2.7%)	201 (2.5%)
Pairwise Comparison	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**Ibuprofen vs Naproxen**
HR (95% CI)	0.93 (0.76, 1.13)	0.86 (0.70, 1.04)	1.08 (0.89, 1.31)
Modified Intent-To-Treat Analysis (mITT, on treatment through month 42 and 30 days)			
	Celecoxib 100 – 200 mg BD	**Ibuprofen 600 - 800 mg TDS**	**Naproxen 375 - 500 mg BD**
N	8,030	7,990	7,933
Subjects with Events	134 (1.7%)	155 (1.9%)	144 (1.8%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.90 (0.72, 1.14)	0.81 (0.64, 1.02)	1.12 (0.889, 1.40)

Key secondary and tertiary endpoints

The analysis of Major Adverse Cardiovascular Events (MACE)* for mITT and ITT are described below in Table 11.

Table 11: On-treatment adjudicated major adverse CV events

	Celecoxib 100-200 mg BD	Ibuprofen 600-800 mg TDS	Naproxen 375-500 mg BD
Intent-to-treat Analysis (ITT, through month 30)			
N	8072	8040	7969
Subjects with first events (%)	337 (4.2%)	384 (4.8%)	346 (4.3%)

	Celecoxib 100-200 mg BD	**Ibuprofen 600-800 mg TDS**	**Naproxen 375-500 mg BD**
Pairwise Comparison	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**Ibuprofen vs Naproxen**
CV-related death[a]	68 (0.8%) vs 86 (1.1%)	68 (0.8%) vs 80 (1.0%)	80 (1.0%) vs 86 (1.1%)
Fatal or non-fatal MI[b]	78 (1.0%) vs 71 (0.9%)	78 (1.0%) vs 92 (1.1%)	92 (1.1%) vs 71 (0.9%)
Fatal or non-fatal stroke[b]	54 (0.7%) vs 65 (0.8%)	54 (0.7%) vs 53 (0.7%)	53 (0.7%) vs 65 (0.8%)
Revascularisation[a]	174 (2.2%) vs 161 (2.0%)	174 (2.2%) vs 198 (2.5%)	198 (2.5%) vs 161 (2.0%)
Hospitalisation for UA[a]	55 (0.7%) vs 64 (0.8%)	55 (0.7%) vs 65 (0.8%)	65 (0.8%) vs 64 (0.8%)
Hospitalisation for TIA[a]	18 (0.2%) vs 18 (0.2%)	18 (0.2%) vs 27 (0.3%)	27 (0.3%) vs 18 (0.2%)
Pairwise Comparison HR (95%CI)	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**Ibuprofen vs Naproxen**
MACE	0.97 (0.83, 1.12)	0.87 (0.75, 1.01)	1.11 (0.69, 1.29)
CV death[a]	0.78 (0.57, 1. 07)	0.84 (.0.61, 1.16)	0.93 (0.69, 1.26)
Fatal or non-fatal MI[b]	1.09 (0.79, 1.50)	0.84 (0.62, 1.14)	1.29 (0.95, 1.76)
Fatal or non-fatal stroke[b]	0.82 (0.57, 1.18)	1.01 (0.69, 1.47)	0.81 (0.56, 1.17)
Revascularisation[a]	1.07 (0.87, 1.33)	0.87 (0.71, 1.07)	1.23 (1.00, 1.52)
Hospitalisation for UA[a]	0.86 (0.60, 1.23)	0.84 (0.59, 1.21)	1.02 (0.72, 1.44)
Hospitalisation for TIA[a]	0.99 (0.51, 1.90)	0.66 (0.37, 1.20)	1.50 (0.83, 2.73)
Modified Intent to Treat Analysis (mITT, on treatment through month 42 and 30 days)			
N	8030	7990	7933
Subjects with Events, n(%)			
MACE	247 (3.1%)	284 (3.6%)	253 (3.2%)
CV death	35 (0.4%)	51 (0.6%)	49 (0.6%)
Non-fatal MI	58 (0.7%)	76 (1.0%)	53 (0.7%)
Non-fatal stroke	43 (0.5%)	32 (0.4%)	45 (0.6%)
Hospitalisation for UA	46 (0.6%)	49 (0.6%)	44 (0.6%)
Revascularisation	132 (1.6%)	158 (2.0%)	122 (1.5%)
Hospitalisation for TIA	12 (0.1%)	21 (0.3%)	16 (0.2%)
Pairwise Comparison, HR (95%CI)	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**ibuprofen vs Naproxen**
MACE	0.95 (0.80, 1.13)	0.82 (0.69, 0.97)	1.17 (0.98, 1.38)
CV death	0.69 (0.45, 1.07)	0.64 (0.42, 0.99)	1.08 (0.73, 1.60)
Non-fatal MI	1.06 (0.73, 1.54)	0.72 (0.51, 1.01)	1.48 (1.04, 2.11)
Non-fatal stroke	0.93 (0.61, 1.42)	1.26 (0.79, 1.98)	0.74 (0.47, 1.16)
Hospitalisation for UA	1.02 (0.67, 1.54)	0.89 (0.59, 1.33)	1.16 (0.77, 1.74)
Revascularisation	1.06 (0.83, 1.35)	0.78 (0.62, 0.99)	1.35 (1.07, 1.72)
Hospitalisation for TIA	0.73 (0.35, 1.55)	0.54 (0.26, 1.09)	1.38 (0.72, 2.64)

Abbreviations: BD = twice a day; CI = confidence interval; CV - cardiovascular; HR = Hazard ratio; ITT = intent to-treat, MACE - major adverse cardiovascular event; MI = myocardial infarction; mITT = modified intent-to-treat; N = number of subjects in group; TIA = transient ischaemic attack (APTC composite endpoint plus coronary revascularisation, or hospitalisation for unstable angina or transient ischaemic attack); TDS = three times daily; UA = unstable angina.

*MACE = APTC composite endpoint plus coronary revascularisation, or hospitalisation for unstable angina or transient ischaemic attack

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

a MACE component endpoints

b Overlap of component endpoints = MACE composite endpoints that include fatal/non-fatal outcome (tertiary endpoint).

The analysis of gastrointestinal events for ITT and mITT are described below in Table 12.

Table 12: On-treatment adjudicated gastrointestinal endpoints

	Celecoxib 100-200 mg BD	**Ibuprofen 600-800 mg TDS**	**Naproxen 375-500 mg BD**
Intent-to-Treat Analysis (ITT, through month 30)			
N	8072	8040	7969
Subjects with events, n(%)			
CSGIE	55 (0.7%)	72 (0.9%)	56 (0.7%)
IDA of GI Origin	33 (0.4%)	64 (0.8%)	69 (0.9%)
Pairwise Comparison HR (95%CI)	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**Ibuprofen vs Naproxen**
CSGIE	0.97 (0.67, 1.40)	0.76 (0.53, 1.08)	1.27 (0.90, 1,81)
IDA of GI Origin	0.47 (0.31, 0.71)	0.51 (0.33, 0.77)	0.92 (0.65, 1.29)
Modified Intent-to-Treat Analysis (mITT, on treatment through month 42 and 30 days)			
N	8030	7990	7933
Subjects with events, n(%)			
CSGIE	27 (0.3%)	59 (0.7%)	52 (0.7%)
IDA of GI Origin	27 (0.3%)	58 (0.7%)	66 (0.8%)
Pairwise Comparison HR (95%CI)	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**Ibuprofen vs Naproxen**
CSGIE	0.51 (0.32, 0.81)	0.43 (0.27, 0.68)	1.16 (0.80, 1.69)
IDA of GI Origin	0.39 (0.25, 0.62)	0.43 (0.27, 0.68)	0.91 (0.64, 1.29)

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

**IDA (Iron Deficiency Anaemia) = clinically significant iron deficiency anaemia of GI origin or decrease in Hct and/or Hgb (defined as Hct ≥ 10 points and or Hgb of ≥ 2 g/dL from baseline

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

The analysis of clinically significant renal events*, hospitalisation for CHF and hypertension for mITT are described below in Table 13.

Table 13: On-treatment adjudicated renal events, hospitalisation for CHF and hypertension

	Celecoxib 100-200 mg BD	**Ibuprofen 600-800 mg TDS**	**Naproxen 375-500 mg BD**
Intent-to-treat Analysis (ITT, through month 30)			
N	8072	8040	7969
Subjects with first event	118 (1.5%)	166 (2.1%)	139 (7.1%)
Subjects with events, n(%)			
Renal events[a]	57 (0.7%)	92 (1.1%)	71 (0.9%)
Hospitalisation for CHF	45(0.6%)	46 (0.6%)	48 (0.6%)
Hospitalisation for hypertension	24 (0.3%)	40 (0.5%)	34 (0.4%)
Pairwise Comparison HR (95%CI)	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**Ibuprofen vs Naproxen**
Subject with any event	0.83(0.65, 1.07)	0.70 (0.55, 0.89)	1.19(0.95, 1.49)

	Celecoxib 100-200 mg BD	**Ibuprofen 600-800 mg TDS**	**Naproxen 375-500 mg BD**
Renal events[a]	0.79 (0.56, 1.12)	0.61 (0.44, 0.85)	1.29 (0.95, 1.76)
Hospitalisation for CHF	0.92 (0.61, 1.39)	0.98 (0.65, 1.47)	0.95 (0.63, 1.42)
Hospitalisation for hypertension	0.69 (0.41, 1.17)	0.59 (0.36, 0.99)	1.17 (0.74, 1.84)
Modified Intent to Treat Analysis (mITT, on treatment through month 42 and 30 days)			
N	8030	7990	7933
Subjects with events, n(%)			
Renal events	42 (0.5%)	73 (0.9%)	62 (0.8%)
Hospitalisation for CHF	28 (0.3%)	38 (0.5%)	35 (0.4%)
Hospitalisation for hypertension	25 (0.3%)	37 (0.5%)	32 (0.4%)
Any of the above	89 (1.1%)	139 (1.7%)	120 (1.5%)
Pairwise Comparison HR (95%CI)	**Celecoxib vs Naproxen**	**Celecoxib vs Ibuprofen**	**Ibuprofen vs Naproxen**
Renal events	0.66 (0.44, 0.97)	0.54 (0.37, 0.79)	1.21 (0.86, 1.70)
Hospitalisation for CHF	0.77 (0.47, 1.27)	0.70 (0.43, 1.13)	1.12 (0.71, 1.77)
Hospitalisation for hypertension	0.76 (0.45, 1.28)	0.64 (0.39, 1.07)	1.18 (0.74, 1.90)
Any of the above	0.72 (0.55, 0.95)	0.60 (0.46, 0.79)	1.19 (0.93, 1.52)

*N.B: Renal events included a composite of pre-defined rises in creatinine levels (verified serum creatinine of ≥2.0 mg/dL (177 μmol/L) and an increase of ≥0.7 mg/mL (62 μmol/L)) , or hospitalisation for acute renal failure (defined as a doubling in serum creatinine, or confirmation of hyperkalaemia with ≥ 50% elevation in serum creatinine), or the initiation of haemodialysis or peritoneal dialysis.

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

All-Cause Mortality

In the mITT populations celecoxib, naproxen and ibuprofen were associated with 53 (0.7%), 79 (1.0%), and 73 (0.9%) deaths, respectively. In the ITT population the celecoxib, naproxen and ibuprofen were associated with 132 (1.6%), 163 (2.0%) and 142 (1.8%) deaths, respectively. No significant differences were observed in pairwise comparisons between treatments. All-cause mortality was analysed as 1 component of the tertiary composite endpoint although it should be noted that the analysis was not adjusted for multiplicity.

ABPM Substudy

In the PRECISION-ABPM substudy, among the total of 444 analysable patients, at Month 4, celecoxib-treated patients had the smallest change in 24-hour ambulatory systolic blood pressure (SBP) compared to ibuprofen and naproxen: celecoxib produced a slight reduction of 0.3 mmHg while ibuprofen and naproxen increased mean 24-hour SBP by 3.7 and 1.6 mmHg, respectively. These changes resulted in a statistically significant and clinically meaningful difference of -3.9 mmHg (p=0.0009) between celecoxib and ibuprofen; a non-significant difference of -1.8 (p=0.119) mmHg between celecoxib and naproxen, and a non-significant difference of -2.1 mmHg (p=0.0787) between naproxen and ibuprofen.

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 3.0% (20/671) and 2.5% (17/685) for the 400 mg BD and 200 mg BD celecoxib treatment groups, respectively, compared to 0.9% (6/679) for the placebo group. The increases for both celecoxib dose groups versus placebo were mainly driven by myocardial infarction.

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

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 the ADAPT study (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 – 2.15) 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 description of trial in this section). 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 4.2 DOSE AND METHOD OF ADMINISTRATION). 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 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.

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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 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.

Patients with severe hepatic impairment have not been studied. Therefore, the use of over-the-counter celecoxib in patients with moderate and severe hepatic impairment (Child-Pugh score ≥7) is contraindicated (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.3 CONTRAINDICATIONS).

Renal Impairment

In elderly volunteers with age related reductions in glomerular filtration rate (GFR) (mean GFR >65 mL/min/1.73 m^2) and in patients with chronic stable renal insufficiency (GFR 35-60 mL/min/1.73 m^2) 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 old)

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.

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 $AUC_{0\text{-}24\ h}$ 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

CELEBREX RELIEF 200 mg capsules contain lactose monohydrate, sodium lauryl sulfate, povidone, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.

The capsule shell for the 200 mg strength contains gelatin, purified water, titanium dioxide, sodium lauryl sulfate, iron oxide yellow, iron oxide red, iron oxide black and OPACODE monogramming ink S-1-17823 BLACK (ID 12108).

6.2 INCOMPATIBILITIES

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

Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

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 25ºC in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in PVC/PVdC/Al blister packs of 10 capsules.

Australian Register of Therapeutic Goods (ARTG)

AUST R 463627 – CELEBREX RELIEF celecoxib 200 mg capsule blister pack

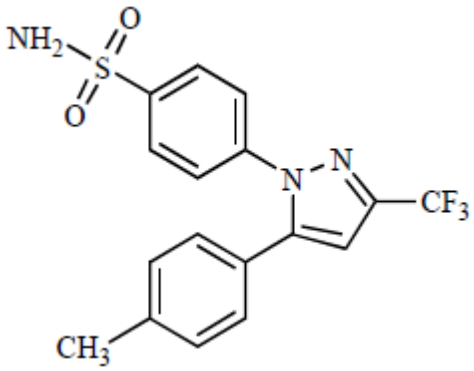
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Celecoxib is weakly acidic with a pKa in water of 11.1 and is practically insoluble in water. 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)-1H-pyrazol-1-yl] benzenesulfonamide

Molecular formula: $C_{17}H_{14}F_3N_3O_2S$ Molecular weight: 381.38

CAS Number

169590-42-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

03/10/2024

10 DATE OF REVISION

13/05/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial update
4.4	Inclusion of warnings to elderly
4.4, 4.8	Addition of adverse effect, generalised bullous fixed drug eruption (GBFDE).

CELEBREX RELIEF_pi\May25/00 (CCDS 04-Nov-2024)