AUSTRALIAN PRODUCT INFORMATION – CELEBREX® (CELECOXIB) CAPSULES

1. NAME OF THE MEDICINE

Celecoxib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CELEBREX 100 mg capsule contains 100 mg celecoxib.

Each CELEBREX 200 mg capsule contains 200 mg celecoxib.

Excipient(s) with known effect

CELEBREX 100 mg and 200 mg capsules contain 149.7 mg and 49.8 mg of lactose monohydrate, respectively.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Capsule, hard.

CELEBREX 100 mg capsule is opaque, white capsules with 2 blue bands marked 7767 and 100.

CELEBREX 200 mg capsule is opaque, white capsules with 2 gold bands marked 7767 and 200.

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 (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).

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

Adults

Osteoarthritis

200 mg taken once daily (OD) or in two divided doses.

Rheumatoid arthritis

200 mg taken in two divided doses.

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

Ankylosing spondylitis

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

Primary dysmenorrhoea

400 mg as a single dose or divided on the first day followed by 200 mg OD 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

Loading dose of 400 mg then 200 mg once or twice daily (BD) as required for up to 5 days.

The effective dose in this patient population is 200 mg BD.

Method of administration

To be taken orally without regard to timing of meals.

Dosage adjustment

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 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.

In arthritis patients with moderate hepatic impairment, CELEBREX should be introduced at half the recommended dose.

There is no clinical experience in patients with severe hepatic impairment. Therefore, the use of CELEBREX in patients with severe hepatic impairment (Child-Pugh score ≥10) 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 is not approved for use in patients under 18 years of age.

4.3 Contraindications

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

Demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other 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 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 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).

CELEBREX is contraindicated in:

- Patients with unstable ischaemic heart disease of thrombus aetiology or documented myocardial infarction or stroke within 3 months.
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Estimated creatinine clearance <30 mL/min.
- Congestive heart failure (NYHA II-IV).
- Severe hepatic impairment (Child-Pugh[#] score ≥10; see section 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties.).

[#] 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 section 4.3 Contraindications).

Cardiovascular thrombotic events

COX-2 inhibitors, including celecoxib, have been associated with an increased risk of serious CV 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 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 CV 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 CV 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 CV symptoms. Patients should be informed about the signs and symptoms of serious CV 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.

CELEBREX exhibited a low incidence of gastroduodenal ulceration and serious clinically significant GI events within clinical trials. The following information for NSAIDs 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 NSAIDs. 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 NSAIDs, 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 CELEBREX 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 CELEBREX 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 CELEBREX alone and 1.08% on CELEBREX 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) orcorticosteroids; patients who consume alcohol; or patients with a prior history of GI disease (such as ulceration, GI bleeding or inflammatory conditions). CELEBREX should be prescribed 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 CELEBREX 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 GI 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 GI side effects or allow the continuation of CELEBREX 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 CELEBREX. In post-marketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX 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 Pre-existing asthma later in this section) 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. 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 CV events. NSAIDs, including celecoxib, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

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 NSAID 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 Use with ACE inhibitors, angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics later in this section), and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Clinical trials with CELEBREX 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 in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX.

No information is available regarding the use of CELEBREX in patients with advanced kidney disease. Therefore, treatment with CELEBREX is not recommended in these patients. If CELEBREX 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), 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 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 CELEBREX (see section 4.8 Adverse effects (undesirable effects)).

In controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX 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 CELEBREX.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CELEBREX 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 CELEBREX. In controlled clinical trials the incidence of anaemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia or blood loss. CELEBREX 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 NSAIDs has been reported in such aspirin-sensitive patients, CELEBREX 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 CELEBREX (see section 4.8 Adverse effects (undesirable effects)). Therefore, CELEBREX 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

Of the total number of patients who received CELEBREX in clinical trials, more than 3300 were 65-74 years of age, while approximately 1300 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 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 CELEBREX 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).

Concomitant administration of celecoxib with inhibitors of CYP 2C9 can lead to increases in plasma concentrations of celecoxib. Therefore, a dose reduction of celecoxib may be necessary when celecoxib is co-administered with CYP 2C9 inhibitors.

Concomitant administration of celecoxib with inducers of CYP 2C9 (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 CYP 2C9 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 CELEBREX 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 (frusemide)

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

Aspirin

CELEBREX can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX 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 CELEBREX were not different from those of the two comparators. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for CV 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 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 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 CELEBREX 200 mg BD as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX 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 CELEBREX 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

CELEBREX 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 CELEBREX and methotrexate, patients should be monitored for methotrexate toxicity.

Ketoconazole

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

Phenytoin

CELEBREX 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 CELEBREX 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 INR. However, in post-marketing experience, bleeding events have been reported, some of them fatal, predominantly in the elderly, in association with increases in INR in patients receiving CELEBREX concurrently with warfarin or similar agents (see section 4.4 Special warnings and precautions for use, Gastrointestinal effects).

Digoxin

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

Other drug interactions

No drug interaction data are available for CELEBREX and the co-administration of the following products: paracetamol, aminoglycosides, bone marrow depressants, butemide, cholestyramine, 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 $AUC_{0\text{-}24\ h}$ 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 – Pregnancy Category B3

There is no information on the use of celecoxib in pregnant women. CELEBREX 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 foetal lambs and to contribute to maintenance of patency. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided, and CELEBREX 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 CELEBREX 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 foetal 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 CV 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 CELEBREX 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 CELEBREX 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 CELEBREX of 200 mg (100 mg BD or 200 mg OD) or more, including more than 400 treated at 800 mg (400 mg BD). Approximately 3,900 patients have received CELEBREX 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 CELEBREX arthritis trials

Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX 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 CELEBREX patients from original CELEBREX arthritis trials

	CELEBREX (100-200 mg BD or 200 mg OD) (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 CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX 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.

Adverse events which occurred in 0.1% - 1.9% of patients taking CELEBREX (100 mg - 200 mg BD or 200 mg OD) 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 illness, 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.

S**kin 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.

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

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

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 drug reactions in Table 2 were identified with 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 2 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 ADRs in Table 2 are listed by system organ class are ranked by frequency in descending order.

Table 2: Adverse reactions occurring in CELEBREX 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
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 2 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 CELEBREX.

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: Hypoglycemia, hyponatraemia.

Musculoskeletal and connective tissue disorders: Myositis.

Nervous system disorders: Ageusia, anosmia, intracranial haemorrhage (including fatal intracranial haemorrhage), cerebral haemorrhage.

Psychiatric: 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.

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 CELEBREX 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 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 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)

CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX 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 CELEBREX 100 mg BD or 200 mg OD 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, CELEBREX doses of 100 mg BD or 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 efficacy of CELEBREX 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)

CELEBREX has demonstrated a significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in approximately 2100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the American College of Rheumatology 20 (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg BD and 200 mg BD were similar in efficacy and both were comparable to naproxen 500 mg BD.

Although CELEBREX 100 mg BD and 200 mg BD provided similar overall efficacy, 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 mg - 200 mg BD.

Ankylosing spondylitis (AS)

CELEBREX has been investigated in 896 patients in placebo and active-controlled (diclofenac, naproxen or ketoprofen) clinical trials of 6 weeks (one trial) and 12 weeks (three trials) duration for the symptomatic treatment of AS. At doses of 100 mg (BD, 200 mg OD, and 400 mg OD, CELEBREX 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 CELEBREX 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	**N=156**	**N=137**	**--**	**N=157**	**--**
Baseline Mean	73.5	70.8	--	71.7	--
Mean Change, Week 12	-9.9	-30.0	--	-36.3	--
p-value versus placebo[c]	--	<0.001	--	<0.001	--
Study 137	**N=76**	**N=80**	**N=90**	**--**	**--**
Baseline Mean	69.5	70.4	65.7	--	--
Mean Change, Week 6	-11.9	-25.7	-22.5	--	--
p-value versus placebo[c]	--	0.0068	0.0512	--	--
Study 243	**--**	**N=126**	**--**	**--**	**N=123**
Baseline Mean	--	66.5	--	--	65.9
Mean Change, Week 12	--	-29.1	--	--	-32.7
[95% Confidence Interval][d]	--	[-33.6 to -24.6]	--	--	[-37.1 to -28.2]
Study 247	**--**	**N=107**	**--**	**--**	**N=115**
Baseline Mean	--	66.3	--	--	67.0
Mean Change, Week 12	--	-25.8	-	--	-28.2
[95% Confidence Interval][d]	--	[-31.1 to -20.6]	--	--	[-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 BD (Study 137) or 200 mg OD (Studies 193, 243, and 247); diclofenac 150 mg TDD was administered as Sustained Release 75 mg BD in Study 243, or 50 mg three times daily (TDS) 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 CELEBREX 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 ($p<0.05$)

Dental surgery

The analgesic efficacy of CELEBREX was demonstrated in five studies of patients with post oral surgery pain, a well validated pain model. In these studies 1130 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 CELEBREX, a greater proportion of the CELEBREX group completed the study without rescue medication.

Four further single dose studies compared CELEBREX 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 CELEBREX 100 mg was 45 and 39 mins; CELEBREX 200 mg 38, 30, 44 and 40 mins; ibuprofen 33 and 28 mins, naproxen sodium 24 and 36 mins.

Post-surgery

The efficacy of CELEBREX 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 CELEBREX 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 mg and 23 mg vs. 68 mg; 5 mg and 13 mg vs. 40 mg; 3 mg 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 4 h and 24 h.

The second study was conducted in 77 patients undergoing laparoscopic surgery. The patients received either placebo (38) or 400 mg/day CELEBREX (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 days vs. 2±2 days), bowel (3±2 days vs. 2±1 days) and physical activities (6±3 days 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 h, 48 h and 72 h = 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 CELEBREX 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 24 h after surgery. All patients in the CELEBREX group, 32 of 37 (86%) in the ketoprofen group (p=0.024, CELEBREX 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 CELEBREX 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 24 h after surgery. The total number of oxycodone doses was 215 (mean 5 [range 2-14]) in the CELEBREX 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 CELEBREX was demonstrated in five studies in patients with musculoskeletal pain, including ankle sprain and low back pain. In these studies over 1822 patients were evaluated.

Four studies in ankle sprain demonstrated CELEBREX 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 CELEBREX treatment was observed to be as effective as diclofenac.

Celecoxib Long-term Arthritis Safety Study (CLASS)

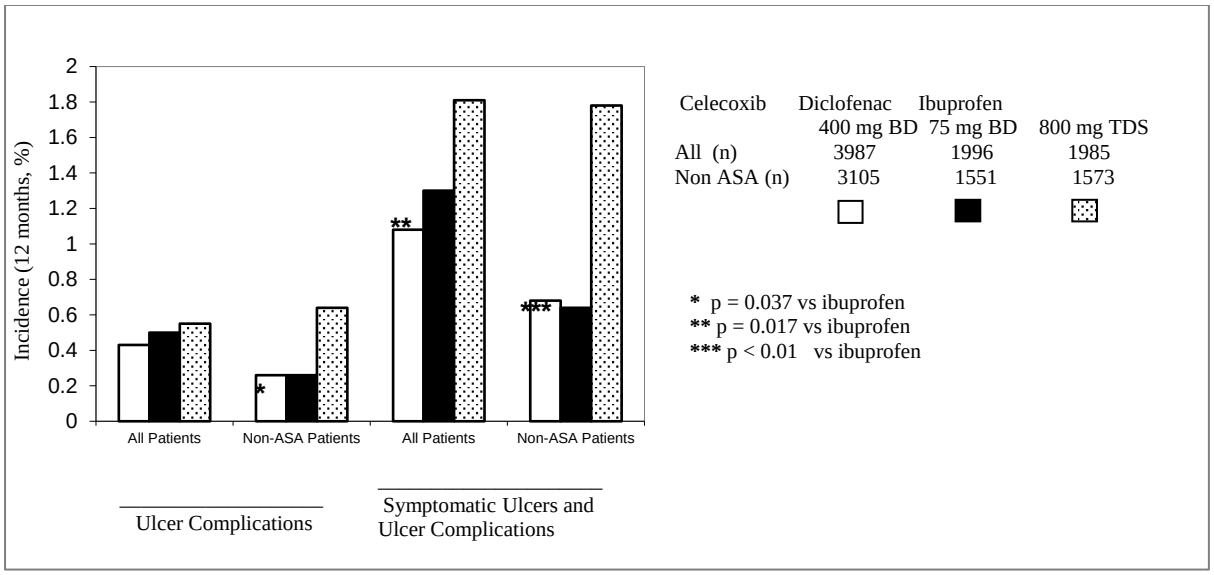
Study design

A prospective 12 month study was conducted in approximately 5800 OA patients and 2200 RA patients. The primary endpoint of this outcome study was the incidence of complicated ulcers (gastrointestinal bleeding, perforation or obstruction) in CELEBREX treated patients compared to each comparator. Patients received CELEBREX 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 CELEBREX 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 CELEBREX vs. those on diclofenac, although the incidence was significantly lower for CELEBREX 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 CELEBREX, diclofenac and ibuprofen (see Use with aspirin later in this section). The incidence rates for diclofenac may be underestimated because of a higher incidence of early withdrawals due to GI adverse events than CELEBREX and ibuprofen.

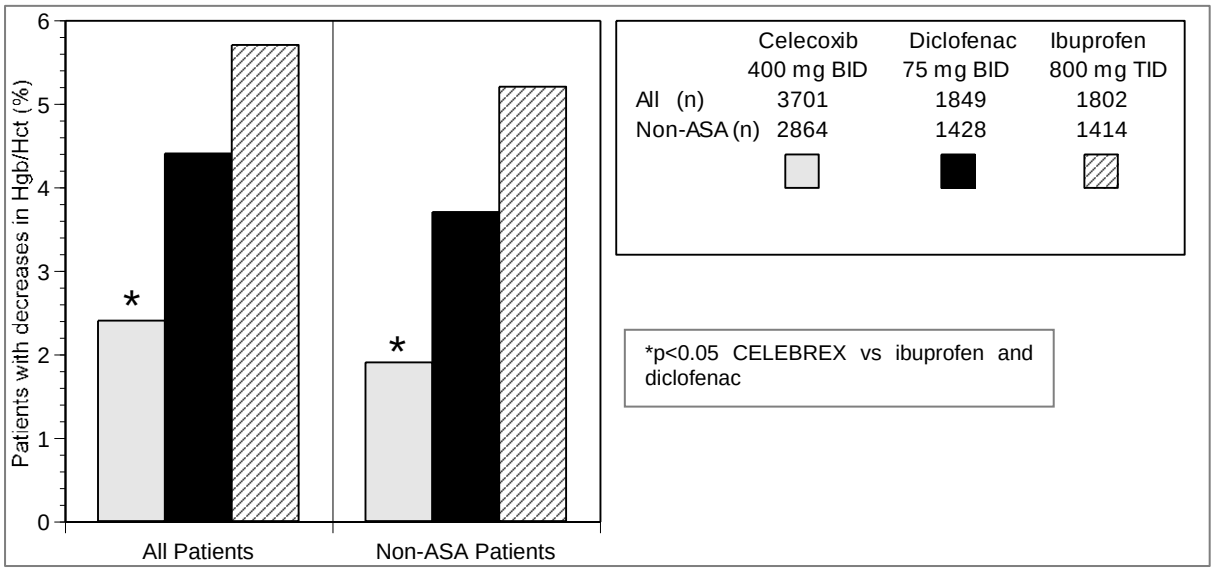
Figure 1: Incidence of symptomatic ulcers and ulcer complications



CELEBREX (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 CELEBREX 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



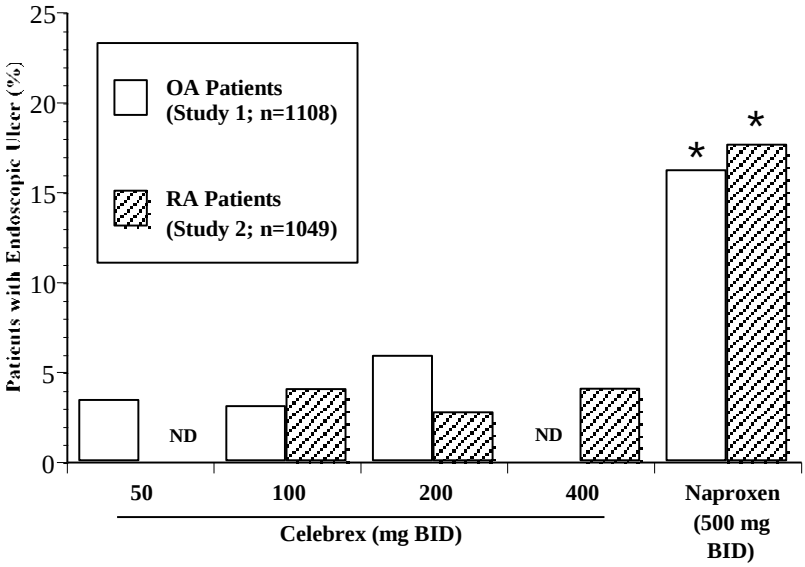
In the original registration studies, the incidence of serious upper gastrointestinal complications (bleeding, perforation, gastric outlet obstruction) with CELEBREX is not significantly different from placebo and is approximately 8-fold less than with non-specific COX inhibitors.

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 1400 patients and 24-week endoscopic ulcer data are available on 184 patients on CELEBREX 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, CELEBREX was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared CELEBREX 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 CELEBREX groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX 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; $p<0.05$.

CELEBREX 100 mg BD, 200 mg OD, or 200 mg BD are the recommended doses.

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

Study 1: placebo ulcer rate = 2.3%
Study 2: placebo ulcer rate = 2.0%

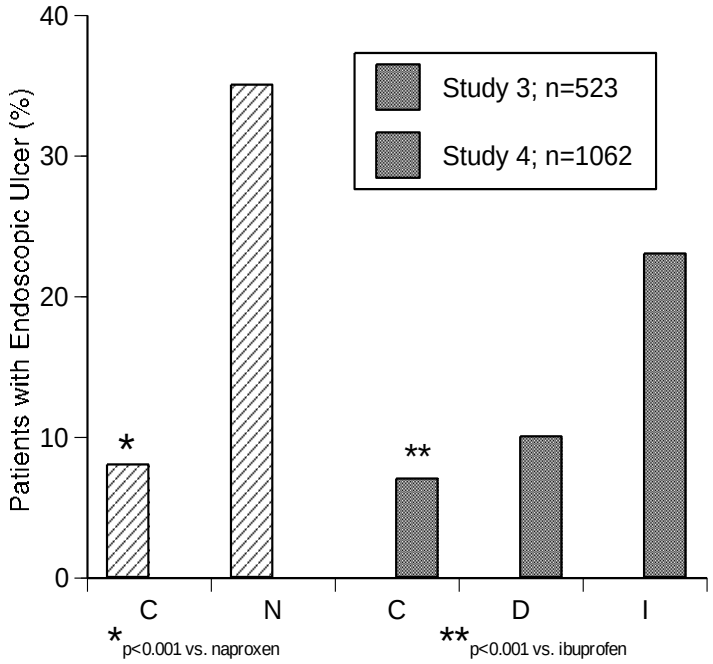
Table 5: Incidence of gastroduodenal ulcers from endoscopic studies in OA and RA patients

	3 Month Studies	
	Study 1 (n = 1108)	**Study 2 (n= 1049)**
Placebo	2.3% (5/217)	2.0% (4/200)
CELEBREX 50 mg BD	3.4% (8/233)	---
CELEBREX 100 mg BD	3.1% (7/227)	4.0% (9/223)
CELEBREX 200 mg BD	5.9% (13/221)	2.7% (6/219)
CELEBREX 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



C = CELEBREX 200 mg BD D = diclofenac 75 mg BD
N = naproxen 500 mg BD I = ibuprofen 800 mg TDS

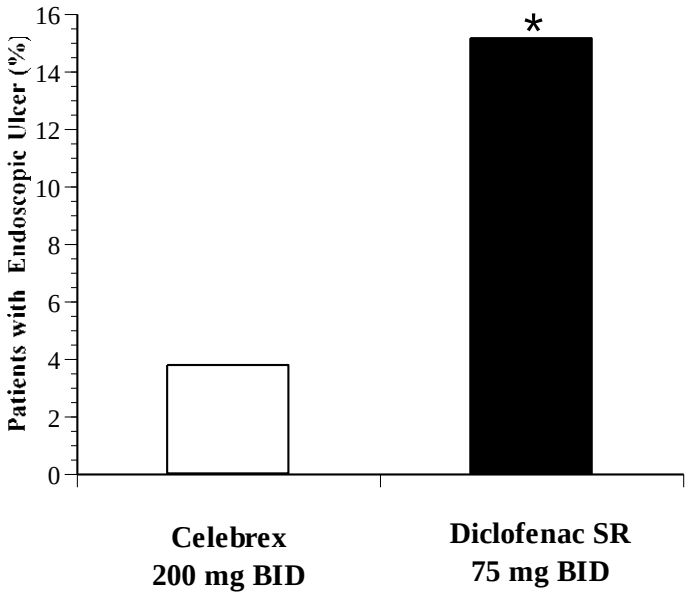
Table 6: Incidence of gastroduodenal ulcers from 3-Month serial endoscopy studies in OA and RA patients

	Week 4	**Week 8**	**Week 12**	**Final**
Study 3 (n=523)				
CELEBREX 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)				
CELEBREX 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 CELEBREX vs. naproxen based on interval and cumulative analyses
† p≤0.05 CELEBREX 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 Celebrex; 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 CELEBREX 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 CV disease, aspirin users and patients with a history of a GI ulcer or upper GI bleeding.

Use with aspirin

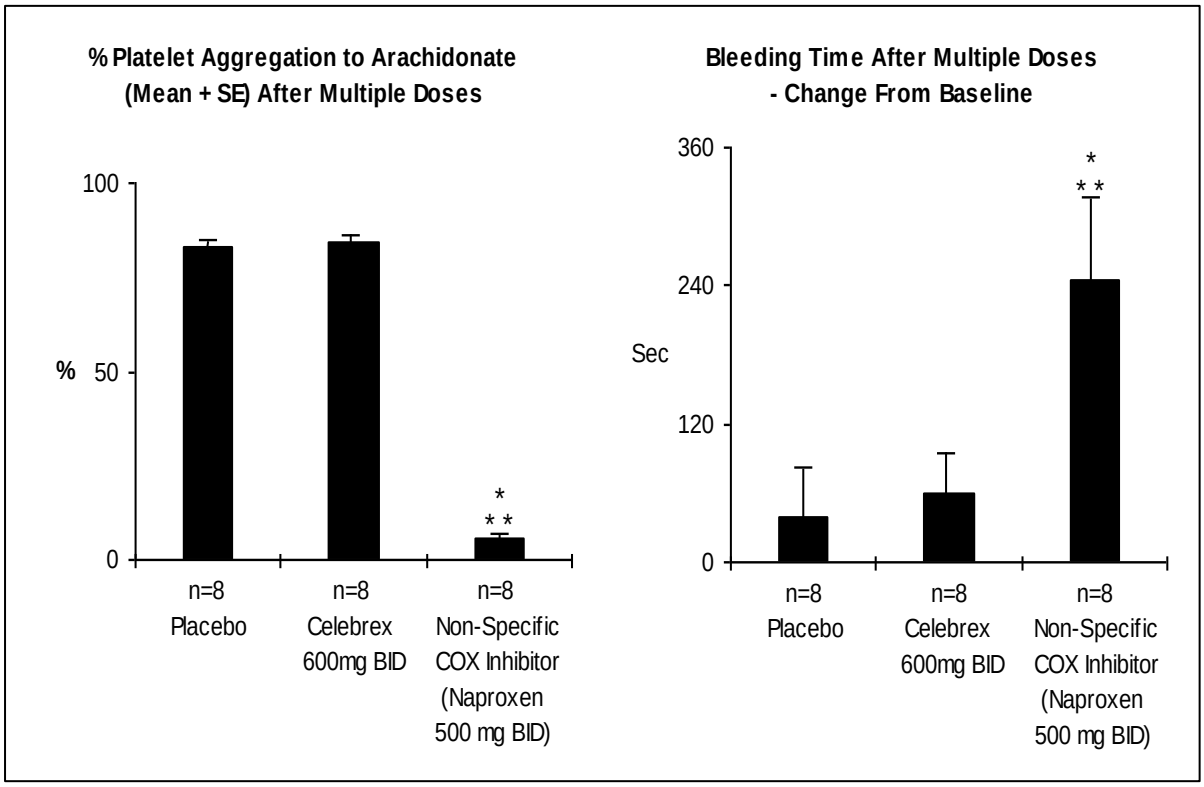
Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin (≤325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than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

Platelet function

In healthy volunteers, CELEBREX, 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 CELEBREX on platelet aggregation and bleeding time



* Significantly different from placebo; $p<0.05$
** Significantly different from CELEBREX $p<0.05$.

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for CV 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 7: Population and treatment dose

Analysis Set	**CELEBREX 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 8.

Table 8: Primary analysis of the adjudicated APTC composite endpoint

Intent-To-Treat Analysis (ITT, through month 30)			
	CELEBREX 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	**CELEBREX vs. naproxen**	**CELEBREX 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)			
	CELEBREX 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	**CELEBREX vs. naproxen**	**CELEBREX 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 9.

Table 9: On-treatment adjudicated major adverse CV events

	CELEBREX 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 (%)	337 (4.2%)	384 (4.8%)	346 (4.3%)
Pairwise Comparison	**CELEBREX vs. naproxen**	**CELEBREX 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)	**CELEBREX vs. naproxen**	**CELEBREX 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 (%)			
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)	**CELEBREX vs. naproxen**	**CELEBREX 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)

	CELEBREX 100 - 200 mg BD	ibuprofen 600 - 800 mg TDS	naproxen 375 - 500 mg BD
Intent to Treat Analysis (ITT, through month 30)			
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 10.

Table 10: On-treatment adjudicated gastrointestinal endpoints

	CELEBREX 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)	**CELEBREX vs. naproxen**	**CELEBREX 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)	**CELEBREX vs. naproxen**	**CELEBREX 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 ≥ 2g/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 11.

Table 11: On-treatment adjudicated renal events, hospitalisation for CHF and hypertension

	CELEBREX 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)	**CELEBREX vs naproxen**	**CELEBREX 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)
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)	**CELEBREX vs. naproxen**	**CELEBREX 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 ≥2.0mg/dL (177μmol/L) and an increase of ≥0.7mg/mL (62μmol/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 analyzable 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 CV death, myocardial infarction, or stroke (adjudicated) with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint.

In the APC trial, the hazard ratios compared to placebo for a composite endpoint of CV death, myocardial infarction, or stroke (adjudicated) were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg BD, and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg BD. 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 OD. Cumulative rate for this composite endpoint over 3 years was 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 CV thromboembolic events was greater in celecoxib-treated patients with a history of atherosclerotic CV 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, did not show a significantly increased CV 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 BD. The incidence of myocardial infarction was 1.1% (8/717 patients) with celecoxib 200 mg BD and 1.2% (13/1070 patients) with placebo.

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

CV safety outcomes were evaluated in CLASS (see description of trial in this section). Kaplan-Meier cumulative rates for investigator-reported serious CV 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 CELEBREX capsules compared with a suspension is about 99%. With multiple dosing, steady state conditions are reached on or before day 5.

Food effects

When CELEBREX 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. CELEBREX, 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 CELEBREX 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 CELEBREX 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. Therefore, CELEBREX 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 CELEBREX in patients with severe hepatic impairment (Child-Pugh score ≥10) 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 100 mg and 200 mg capsules contain lactose monohydrate, sodium lauryl sulfate, povidone, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide and the inks contain: iron oxide yellow CI 77492 (200 mg); indigo carmine CI 73015 (100 mg).

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 25°C.

6.5 Nature and contents of container

PVC/Al or PVC/Aclar/Al blister packs with an outer cardboard carton of 10, 20, 50 and 60 capsules (CELEBREX 100 mg and CELEBREX 200 mg) and 30 and 120 capsules (CELEBREX 200 mg only).

Not all pack sizes may be marketed.

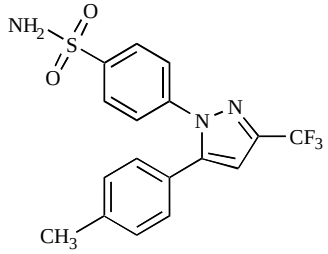
6.6 Special precautions for disposal

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

6.7 Physicochemical properties

Celecoxib is 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



CAS number

169590-42-5.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine.

8. SPONSOR

Viatris Pty Ltd
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Phone: 1800 274 276

9. DATE OF FIRST APPROVAL

25 August 1999.

10. DATE OF REVISION

12 October 2021.

CELEBREX® is a Viatris company trade mark

Summary Table of Changes

Section changed	Summary of new information
8	Sponsorship transfer to Viatris