NEW ZEALAND DATA SHEET

CELOSTEA®

1. Product Name

Celostea, 100 mg, 200 mg, capsule.

2. Qualitative and Quantitative Composition

Each capsule contains 100 mg or 200 mg of celecoxib.

Excipients with known effect: celecoxib, lactose, gelatin and croscarmellose sodium.

Allergen declaration: Contains lactose, sulfites and phenylalanine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Celostea 100mg:
blue opaque cap and white opaque body printed with **MYLAN** over **CE 100** in black ink

Celostea 200mg:
light brown opaque cap and white opaque body printed with **MYLAN** over **CE 200** in black ink

4. Clinical Particulars

4.1 Therapeutic indications

Symptomatic treatment of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

For the management of acute pain and treatment of primary dysmenorrhoea in adults.

The decision to prescribe a selective cyclooxygenase-2 (COX-2) inhibitor should only be made:

- if non-pharmacological interventions and simple analgesic therapies have been tried and found to lack analgesic efficacy or to have unacceptable adverse effects in the individual patient, and
- after assessment of the individual patient's overall risks.

As the cardiovascular risks of the selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. Patients on long-term treatment should be reviewed regularly, such as every three months, with regards to efficacy, risk factors and on-going need for treatment.

4.2 Dose and method of administration

Dose

All patients taking celecoxib should commence therapy at the lowest recommended dose, and be titrated to the lowest dose compatible with effective control of symptoms for the shortest possible period.

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

The following doses can be given without regard to timing of meals (also see section 5.2).

Osteoarthritis

The recommended daily dose is 200 mg taken once daily or in two divided doses. A dose of 200 mg twice daily may be used if needed.

Rheumatoid arthritis

The recommended daily dose is 200 – 400 mg taken in two divided doses.

Ankylosing spondylitis

The recommended daily dose is 200 mg taken once daily or in two divided doses. Some patients may benefit from a total daily dose of 400 mg.

Management of acute pain and treatment of primary dysmenorrhoea

The recommended dose is 400 mg as a single dose on the first day, followed by 200 mg once daily on subsequent days. Patients may be instructed to take an additional dose of 200 mg on any given day, if needed. The maximum recommended dose is 400 mg per day. Celecoxib can be administered up to 2 hours prior to surgery.

Special populations

Elderly (>65 years old)

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.

Children and adolescents

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

Hepatic impairment

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

There is no clinical experience in patients with severe hepatic impairment. Therefore, the use of celecoxib in patients with severe hepatic impairment (Child-Pugh score $\geq$ 10) is contraindicated (see section 4.3, 4.4 and section 5.2).

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 and 4.4).

CYP 2C9 poor metabolisers

Patients who are known, or suspected to be CYP 2C9 poor metabolisers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose (see section 4.5 and section 5.2).

Method of administration

Oral use. Swallow the capsules whole with a glass of fluid.

4.3 Contraindications

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

Demonstrated allergic-type reactions to sulphonamides.

Celecoxib should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs, including other COX-2 specific inhibitors. Severe, rarely fatal, anaphylactoid reactions to non-steroidal anti-inflammatory drugs have been reported in such patients (see section 4.4).

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

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

Celecoxib is contraindicated in:

- Patients with unstable ischaemic heart disease of thrombus aetiology, documented myocardial infarction (MI) or stroke stroke within 3 months.
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients with estimated creatinine clearance <30 mL/min.
- Patients with congestive heart failure (NYHA II-IV).
- Patients with severe hepatic impairment (Child-Pugh[#] score ≥ 10; see section 4.2 and section 5.2)

[#] 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

Cardiovascular effects

COX-2 inhibitors, including celecoxib, have been associated with an increased risk of serious cardiovascular thrombotic adverse events, myocardial infarction and stroke, which can be fatal (see section 5.1).

All NSAIDs, both COX-2 selective and non-selective, may cause an increased risk of serious cardiovascular thrombotic events. This risk may increase with duration of use however may occur with short-term treatment also. The relative increase of this risk appears to be similar in those with or without known cardiovascular disease or cardiovascular risk factors. However, patients with cardiovascular disease or cardiovascular factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline.

Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with celecoxib, it may be assumed that patients at high risk of cardiovascular disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a cardiovascular event. Patients with significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease as well as patients at high risk for cardiovascular disease including those with significant and multiple risk factors for cardiovascular events should only be treated with celecoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.

To minimise the potential risk for an adverse cardiovascular event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible (see section 4.2).

Prescribers should inform the individual patient of the possible increased risks when prescribing celecoxib for patients at high risk of cardiovascular adverse events. Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and symptoms of serious cardiovascular toxicity and the steps to take if they occur. Celecoxib is not a substitute for cardiovascular prophylaxis because of its lack of effect on platelets; therefore, concurrent anti-platelet therapies should not be discontinued. There is no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including celecoxib.

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 celecoxib.

Celecoxib exhibited a low incidence of gastroduodenal ulceration and serious clinically significant GI events within clinical trials (see section 5.1).

Serious GI toxicity, such as peptic ulceration, perforation and bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without warning symptoms, in patients treated with non-steroidal anti-inflammatory drugs. Minor upper GI problems, such as dyspepsia, are common, and may also occur at any time during NSAID therapy. Therefore, physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur.

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.

Patients most at risk of developing GI complications with NSAIDs are elderly patients; patients with cardiovascular disease; patients using concomitant anti-platelet drugs (such as aspirin, even at low doses) or corticosteroids; patients who consume alcohol; or patients with a prior history of GI disease (such as ulceration, GI bleeding or inflammatory conditions). In addition, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with anticoagulants, longer duration of NSAID therapy, smoking and poor general health status. Celostea 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 celecoxib should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a 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. It is unclear how this finding applies to celecoxib. There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of GI side effects or allow the continuation of celecoxib if these adverse reactions appear.

Anaphylactoid reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to celecoxib. In post-marketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving celecoxib. Celecoxib should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see 4.3 and 4.4 - Pre-existing asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Serious skin reactions

Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib. Fixed drug eruption (FDE) which may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE) has also been reported in association with the use of celecoxib. Patients appear to be at highest risk for these events early in the course of therapy; the onset of the event occurring in the majority of the cases within the first month of treatment. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hypertension

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

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 - Oral anticoagulants).

Use with medicines metabolised by CYP2D6

Celecoxib has shown to be a moderately potent CYP2D6 inhibitor. For medicines 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 - Dextromethorphan and metoprolol).

Use with other NSAIDs

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

Hepatic effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy.

Rare cases of severe hepatic reactions, including jaundice, fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with NSAIDs, including celecoxib (see section 4.8).

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

Physician and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. A patient with symptoms and/or signs suggesting liver dysfunction (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms), or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), celecoxib should be discontinued.

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

Renal effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-

inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Such patients should be carefully monitored while receiving treatment with celecoxib. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors (see section 4.4), and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. The relative roles of cyclooxygenase 1 (COX-1) and COX-2 in renal physiology are not completely understood. Celecoxib reduces the urinary excretion of PGE_2 and 6-keto-$PGF_{1\alpha}$ (a prostacyclin metabolite) but leaves serum thromboxane B_2 (TXB_2) and urinary excretion of 11-dehydro-TXB_2, a thromboxane metabolite (both COX-1 products) unaffected.

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

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

Haematological effects

Anaemia is sometimes seen in patients receiving celecoxib. In controlled clinical trials the incidence of anaemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with celecoxib should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia or blood loss. Celecoxib does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see section 5.1).

Pre-existing asthma

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

Fluid retention and oedema

Fluid retention and oedema have been observed in some patients taking celecoxib (see section 4.8). As with all NSAIDs, celecoxib may exacerbate pre-existing hypertension, cardiac failure or oedema, and the treatment of these conditions may be compromised. Therefore, celecoxib 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.

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.

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

Detecting infections

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

4.5 Interaction with other medicines and other forms of interaction

Oral anticoagulants

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban). In patients on concurrent therapy with warfarin or similar agents, serious bleeding events, some of them fatal, predominantly in elderly have been reported. Because increases in prothrombin time (INR) have been reported, anticoagulation/INR should be monitored, in patients taking a warfarin/coumarin-type anticoagulant after initiating treatment with celecoxib or changing the dose. If INR increases, it may be sufficient to reduce the dose of the oral anticoagulant in order to manage the interaction (see section 4.4).

Aspirin

Celecoxib can be used with low dose aspirin. However, concomitant administration of aspirin with celecoxib may result in an increased rate of GI ulceration or other complications, compared to use of celecoxib alone (see section 5.1, Special studies, Upper gastrointestinal complications). Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

Antihypertensives including angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, diuretics and beta-blockers

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

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. These effects are usually reversible. Therefore, the concomitant administration of these medicines 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.

In a clinical study, approximately half of patients who received the ACE inhibitor, lisinopril, in combination with celecoxib were unresponsive to lisinopril at the final clinic visit, compared to under one third of patients who received lisinopril in combination with placebo; and this difference was statistically significant.

Ciclosporin

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

Effects of celecoxib on other drugs

CYP2D6 inhibition

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.

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 – Use with drugs metabolized by CYP2D6).

Digoxin

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

Methotrexate

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

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

Lithium

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

Oral hypoglycaemics

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

Effects of other drugs on celecoxib

CYP2C9 inhibitors

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

CYP2C9 inducers

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

Fluconazole

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see section 5.2). Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.

Ketoconazole

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

Phenytoin

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

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

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

Furosemide

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy category: B3

There is no information on the use of celecoxib in pregnant women. Celecoxib use is not recommended in pregnancy unless it is considered clinically essential (see information on animal studies below).

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 celecoxib during the third trimester of pregnancy should be avoided and celecoxib should not be used during the first and second trimesters of pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. The effects of celecoxib on labour and delivery in pregnant women are not known.

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

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_{0-24h} at 400 mg twice daily, which is twice the recommended maximum daily dose). This effect is attributable to inhibition of prostaglandin production, and is not associated with permanent alteration of reproductive function. Celecoxib was shown to cross the placenta in rats. Teratology studies disclosed an increased incidence of wavy ribs in one study in rats dosed at 100 mg/kg/day, increased incidences of diaphragmatic hernias at 30 and 100 mg/kg/day in another rat study; and increased

incidences of rib and sternebral abnormalities in rabbits at doses of 60 mg/kg/day or greater and cardiovascular abnormalities in rabbits at doses of 150 mg/kg/day or greater. At the no-effect dose in rats (10 mg/kg/day), $AUC_{0\text{-}24h}$ was similar to that in humans dosed at 400 mg twice daily. At the threshold dose of 60 mg/kg/day in rabbits, $AUC_{0\text{-}24h}$ was slightly below that in humans dosed at 400 mg twice daily. 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 $AUC_{0\text{-}24h}$ at 400 mg twice daily).

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.

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 medicine, taking into account the expected benefit of the medicine to the mother.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Of the total number of patients who received celecoxib in clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger subjects.

Adverse events from original celecoxib arthritis trials

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

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

	Celecoxib	Placebo	Naproxen	Diclofenac	Ibuprofen
	(100 - 200 mg twice daily or 200 mg once daily)		500 mg twice daily	75 mg twice daily	800 mg three times daily
	(N=4146)	(N=1864)	(N=1366)	(N=387)	(N=345)
Infections and infestations					
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Psychiatric disorders					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Nerous system disorders					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
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%
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%
Skin and subcutaneous tissue disorders					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%
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, poisoning and procedural complications					
Injury	2.9%	2.3%	3.0%	2.6%	3.2%

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

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

The following adverse events occurred in 0.1% - 1.9% of patients taking celecoxib (100 mg - 200 mg twice daily or 200 mg once daily) regardless of causality.

Blood and lymphatic system disorders

Anemia, thrombocythaemia

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

Neloplasms benign, malignant and unspecified (incl cyst and polyps)

Breast neoplasm

Immune system disorders

Hypersensitivity

Metabolism and nutritional disorders

Diabetes mellitus, hypercholesterolemia, hyperglycaemia, hypokalemia

Psychiatric disorders

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

Nervous system disorders

Hypertonia, hypoaesthesia, migraine, neuralgia, neuropathy, paraesthesia dysgeusia

Eye disorders

Vision blurred, cataract, conjunctivitis, eye pain, glaucoma

Ear and labyrinth disorders

Deafness, ear abnormality, earache, tinnitus, vertigo

Cardiac disorders

Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction, arrhythmia, palpitations, tachycardia

Vascular disorders

Hot flushes

Respiratory, thoracic and mediastinal disorders

Bronchitis, bronchospasm, bronchospasm aggravated, cough, dyspnoea, laryngitis, pneumonia, epistaxis

Gastrointestinal disorders

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

Hepatobiliary disorders

Hepatic function abnormal, AST increased, ALT increased

Skin and subcutaneous tissue disorders

Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, hyperhidrosis, urticarial, ecchymosis, dermatitis contact, skin mass

Musculoskeletal and connective tissue disorders

Arthralgia, arthrosis, bone disorder, myalgia, neck stiffness, synovitis, tendinitis, leg cramps

Renal and urinary system disorders

Albuminuria, dysuria, haematuria, pollakiuria, nephrolithiasis, urinary incontinence

Reproductive system and breast disorders

Breast fibroadenosis, breast pain, dysmenorrhoea, menstrual disorder, vaginal haemorrhage, vaginitis, prostatic disorder

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

Investigations

BUN increased, CPK increased, blood alkaline phosphatase increased, blood urea increased, blood creatinine increased, weight increased

Injury, poisoning and procedural complications

Fracture accidental

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

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

Blood and lymphatic disorders

Thrombocytopenia

Infection and infestation

Peripheral gangrene, meningitis aseptic

Psychiatric disorders

Suicide, confusional state Nervous system disorders

Ataxia, epilepsy, cerebrovascular accident

Ear and labyrinth disorders

Decreased hearing

Cardiac disorders

Syncope, cardiac failure congestive, ventricular fibrillation

Vascular disorders

Thrombophlebitis

Respiratory, thoracic and mediastinal disorders

Pulmonary embolism

Gastrointestinal disorders

Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus, oesophageal ulcer, gastric ulcer, duodenal ulcer

Hepatobiliary disorders

Cholelithiasis

Renal and urinary disorders

Renal failure acute

General disorders and administration site conditions

Sepsis, sudden death

*In a pooled analysis of 20 placebo-controlled studies with duration greater than 2 weeks up to 1 year in patients with OA and RA, the excess rate of myocardial infarction in patients treated with celecoxib 200 or 400 mg daily over placebo was 0.7 events per 1000 patients (Rare) and there was no excess of strokes.

In preliminary data from two studies in patients with colorectal polyps treated with celecoxib 400 mg daily (see section 5.1 - Clinical Trials, Cardiovascular Safety) the excess rate over placebo of myocardial infarction over 3 years was 7 events per 1000 patients (Uncommon). In the same studies, the excess rate for clearly identified ischaemic stroke for the 400 mg daily dose (not including events that were haemorrhagic or of unknown aetiology) was 0.5 event per 1000 over 3 years (Rare). For all strokes, there was no increased event rate with celecoxib compared with placebo.

Adverse events from analgesia and dysmenorrhoea studies

Approximately 1,700 patients were treated with celecoxib in analgesia and dysmenorrhoea studies. All patients in post-oral surgery pain and dysmenorrhoea studies received a single dose of study medication. Doses up to 600 mg/day were studied in primary dysmenorrhoea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhoea studies were similar to those reported in arthritis studies. In approximately 700 patients treated with celecoxib in the post-general and orthopaedic surgery pain studies, the most commonly reported adverse events were nausea, vomiting, headache, dizziness and fever.

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 - Clinical trials, Cardiovascular Safety). 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 and are ranked by frequency in descending order.

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

System Organ Class Frequency	**Adverse Drug Reaction**
Infections and infestations Common Uncommon	Ear infection, fungal infection (primarily non-systemic)

	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 Uncommon	 Angina pectoris, myocardial infarction Angina unstable, aortic valve incompetence, arteriosclerosis coronary artery, sinus bradycardia, ventricular hypertrophy
Vascular disorders Very Common Uncommon	 Hypertension* Deep vein thrombosis, haematoma
Respiratory, thoracic, and mediastinal disorders Common Uncommon	 Dyspnoea Dysphonia
Gastrointestinal disorders Very Common Common Uncommon	 Diarrhoea* Nausea, gastro-oesophageal reflux disease, diverticulum, vomiting*, dysphagia, irritable bowel syndrome Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
Hepatobiliary disorders Common	 Hepatic enzymes increased (includes alanine aminotransferase increased and aspartate aminotransferase increased) *
Skin and subcutaneous tissue disorders Uncommon	 Dermatitis allergic
Musculoskeletal and connective tissue disorders Common Uncommon	 Muscle spasms Synovial cyst
Renal and urinary disorders Common Uncommon	 Nephrolithiasis Nocturia
Reproductive system and breast disorders Common Uncommon	 Vaginal haemorrhage, benign prostatic hyperplasia, prostatitis Breast tenderness, dysmenorrhoea, ovarian cyst, menopausal symptoms
General disorders and administration site conditions Uncommon	 Oedema
Investigations Common	

Uncommon	Blood creatinine increased, prostatic specific antigen increased, weight increased Blood potassium increased, blood sodium increased, blood testosterone decreased, haematocrit decreased, haemoglobin increased
Injury, poisoning and procedural complications Uncommon	Foot fracture, lower limb fracture, epicondylitis, tendon rupture, fracture

* Hypertension, vomiting, 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 events

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 twice daily, and two at 400 mg twice daily.

Post-marketing experience

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

Blood and lymphatic system disorders: Agranulocytosis, aplastic anaemia, pancytopenia, leukopenia.

Immune system disorders: Anaphylactic reaction.

Metabolism and nutrition disorders: Hypoglycemia, hyponatremia.

Psychiatric: Hallucination.

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

Vascular disorders: Vasculitis.

Respiratory, thoracic and mediastinal disorders: Pneumonitis.

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

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, generalized bullous fixed drug eruption (GBFDE), fixed drug eruption (FDE).

Musculoskeletal and connective tissue disorders: Myositis.

Renal and urinary disorders: Tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion.

Reproductive system and breast disorders: Menstrual disorders, infertility female (female fertility decreased).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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

Signs and symptoms

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

Treatment of overdosage

There are no specific antidotes. Patients should be managed by symptomatic and supportive care following an NSAID 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 risk assessment and advice on the management of overdose please contact the National Poisons Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Coxibs, ATC code: M01AH.

Celecoxib is chemically unrelated to anti-inflammatory agents of steroidal or non-steroidal nature. Celecoxib does not contain a chiral centre.

Mechanism of action

Celecoxib is a member of a class of agents which has a mechanism of action that inhibits prostaglandin synthesis primarily by inhibition of COX-2. 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-vivo and *ex-vivo* studies show that celecoxib has a very low affinity for the constitutively expressed COX-1. 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 efficacy and safety

Osteoarthritis (OA)

Celecoxib has demonstrated significant reduction in joint pain compared to placebo. Celecoxib was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with Celecoxib 100 mg twice daily or 200 mg once daily resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, celecoxib doses of 100 mg twice daily or 200 mg twice daily provided significant reduction of pain within 24-48 hours of initiation of dosing.

At doses of 100 mg twice daily or 200 mg twice daily the efficacy of celecoxib was shown to be similar to that of naproxen 500 mg twice daily. Doses of 200 mg twice daily provided no additional benefit above that seen with 100 mg twice daily. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg twice daily or 200mg once daily

Rheumatoid arthritis (RA)

Celecoxib has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. Celecoxib was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. Celecoxib was shown to be superior to placebo in these studies, using the American College of Rheumatology 20 (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures in RA. Celecoxib doses of 100 mg twice daily and 200 mg twice daily were similar in efficacy and both were comparable to naproxen 500 mg twice daily.

Although celecoxib 100 mg twice daily and 200 mg twice daily provided similar overall efficacy, some patients derived additional benefit from the 200 mg twice daily dose. Doses of 400 mg twice daily provided no additional benefit above that seen with 100 mg – 200 mg twice daily.

Ankylosing spondylitis (AS)

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

Table 3: Global pain intensity[a] in Celecoxib ankylosing spondylitis clinical trials

Study	Placebo	Celecoxib 200 mg TDD[b]	Celecoxib 400 mg TDD[b]	Ketoprofen 100 mg twice daily	Naproxen 500 mg twice daily	Diclofenac 150 mg TDD[b]
Study 193	**N=156**	**N=137**	**N=161**	**-**	**N=157**	**-**
Week 12	-9.9	-30.0*	-30.4*	-	-36.3*	-
Study 137	**N=76**	**N=80**	**-**	**N=90**	**-**	**-**
Week 6	-11.9	-25.7*	-	-22.5	-	-

Study 243	**-**	**N=126**	**N=124**	**-**	**-**	**N=123**
Week 12	-	-29.1**	-31.7**	-	-	-32.7
Study 247	**-**	**N=107**	**N=108**	**-**	**-**	**N=115**
Week 12	-	-25.8**	-30.6**	-	-	-28.2

* Statistically significant difference vs. placebo (p <0.01), based on Analysis of Covariance model with the effects of treatment and centre, and baseline value as covariate. Differences between celecoxib 200 mg TDD and celecoxib 400 mg TDD were not statistically significant.

** Differences compared to diclofenac were not statistically significant (p >0.50), based on Analysis of Covariance model (for Study 243, baseline value and age as covariates and treatment, gender and centres as factors; for Study 247, baseline value as a covariate and treatment and centres as factors. Differences between celecoxib 200 mg TDD and celecoxib 400 mg TDD were not statistically significant.

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

[b] TDD = Total daily dose: celecoxib 200 mg TDD was administered as 100 mg twice daily (Study 137) or 200 mg once daily (Studies 193, 243, and 247); celecoxib 400 mg TDD was administered as 200 mg twice daily (Study 243 and 247) or 400 mg once daily (Study 193); diclofenac 150 mg TDD was administered as Sustained Release 75 mg twice daily in Study 243, or 50 mg three times daily in Study 247.

Analgesia, including dysmenorrhoea

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

Special studies

Celecoxib long-term arthritis safety study (CLASS)

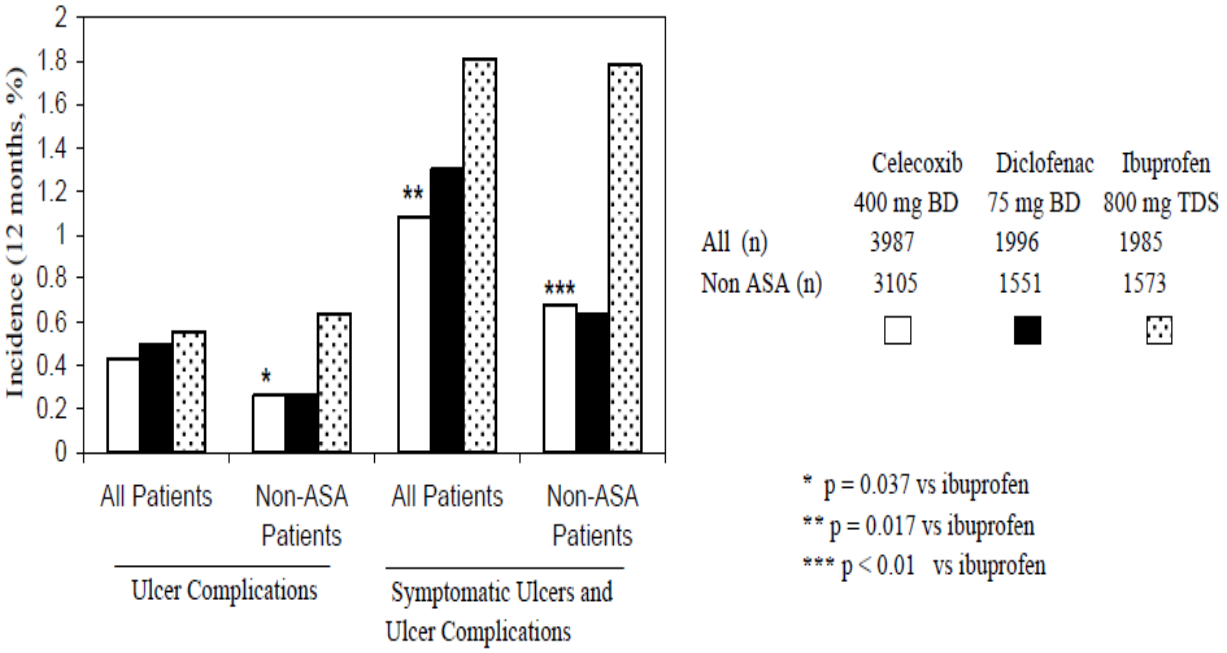
Study design

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

Study Results

No statistically significant differences were demonstrated for the incidence of complicated ulcers among the three treatment groups in all patients. In an additional non-protocol specified analysis, there was no difference in the incidence of complicated and symptomatic ulcers in patients on celecoxib vs. those on diclofenac, although the incidence was significantly lower for celecoxib than for ibuprofen in all patients, and in those patients not taking aspirin (ASA) (Figure 1). Approximately 22% of patients were taking low-dose aspirin. Concomitant low-dose aspirin use increased the risk of complicated and symptomatic ulcers on celecoxib, diclofenac and ibuprofen (see *Section 5.1 - Use with Aspirin*). The incidence rates for diclofenac may be underestimated because of a higher incidence of early withdrawals due to GI adverse events than celecoxib and ibuprofen.

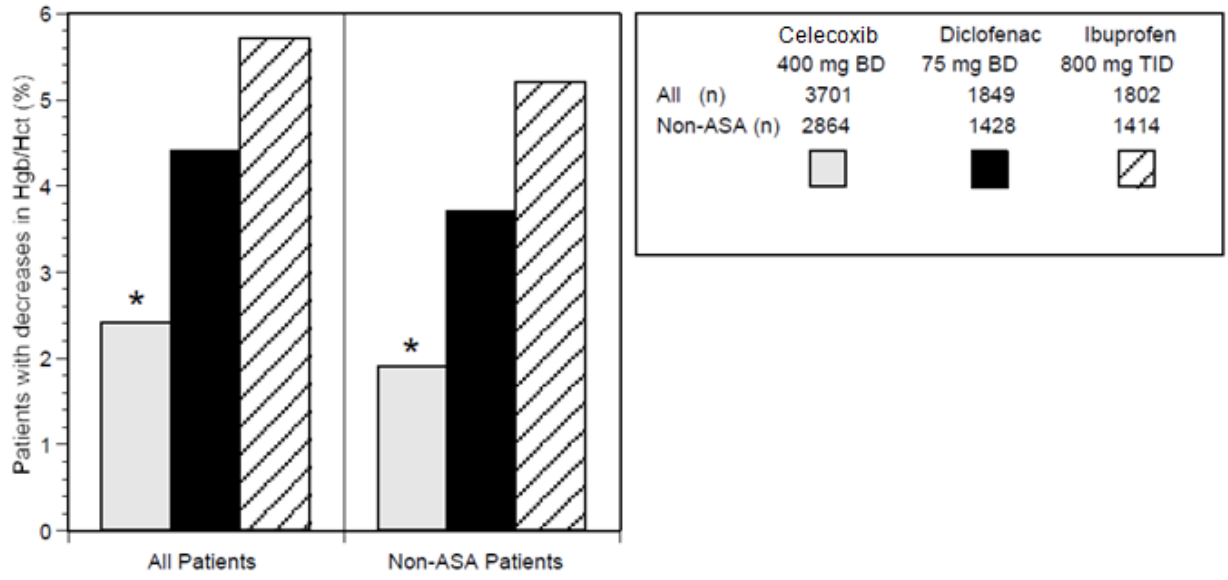
Figure 1: Incidence of symptomatic ulcers and ulcer complications



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

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

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



* p<0.05 celecoxib vs ibuprofen and diclofenac

Upper Gastrointestinal complications

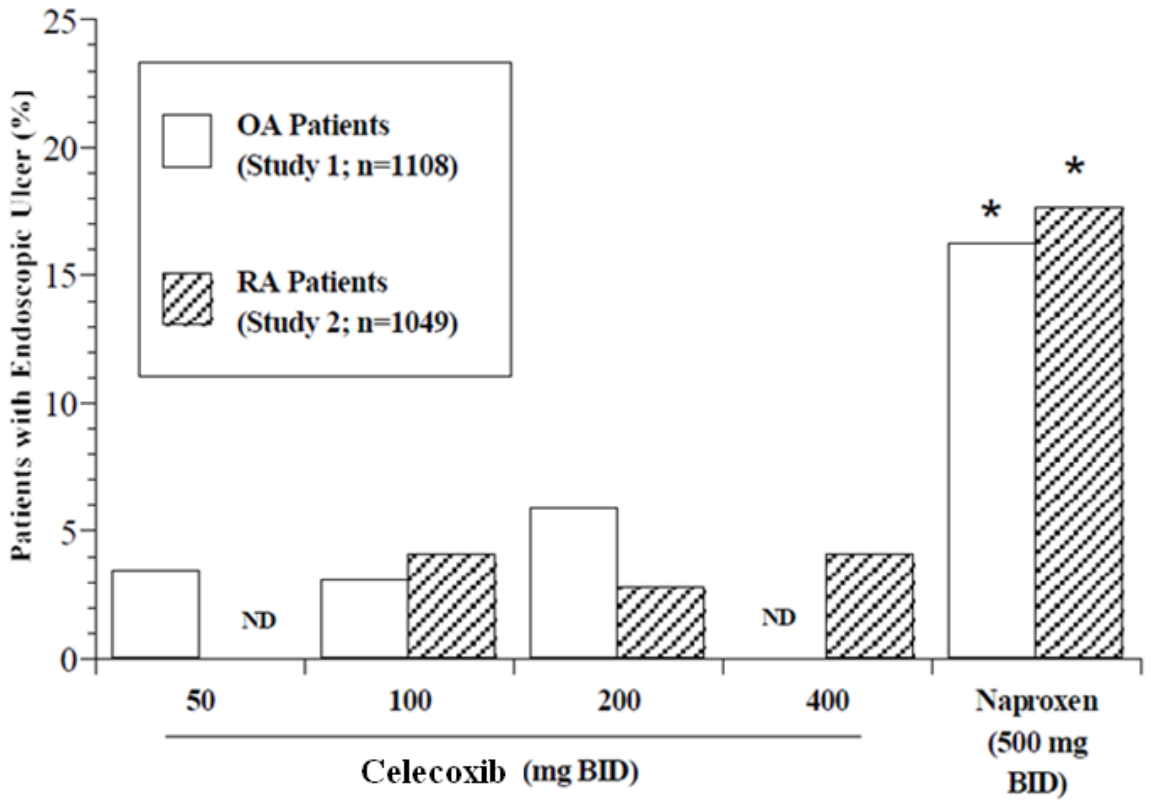
In the original registration studies, the incidence of serious upper gastrointestinal complications (bleeding, perforation, gastric outlet obstruction) with celecoxib was not significantly different from placebo and is approximately 8-fold less than with non-specific COX inhibitors.

Endoscopic studies

Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomised 12-24 week trials using active comparators, two of which also included placebo controls. Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24-week endoscopic ulcer data are available on 184 patients on celecoxib at doses ranging from 50-400 mg twice daily. In all three studies that included naproxen 500 mg twice daily, and in the study that included ibuprofen 800 mg three times daily, celecoxib was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared celecoxib with diclofenac 75 mg twice daily; one study revealed a statistically significantly higher prevalence of endoscopic ulcers in the diclofenac group at the study endpoint (6 months on treatment), and one study revealed no statistically significant difference between cumulative endoscopic ulcer incidence rates in the diclofenac and celecoxib groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of celecoxib over the range studied.

Figure 3 and Table 4 summarise the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

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



ND = Not Done
* Significantly different from all other treatments; p<0.05.

Celecoxib 100 mg twice daily, 200 mg once daily or 200 mg twice daily are the recommended doses.
These studies were not powered to compare the endoscopic ulcer rates of celecoxib vs. placebo.
Study 1: placebo ulcer rate = 2.3%
Study 2: placebo ulcer rate = 2.0%

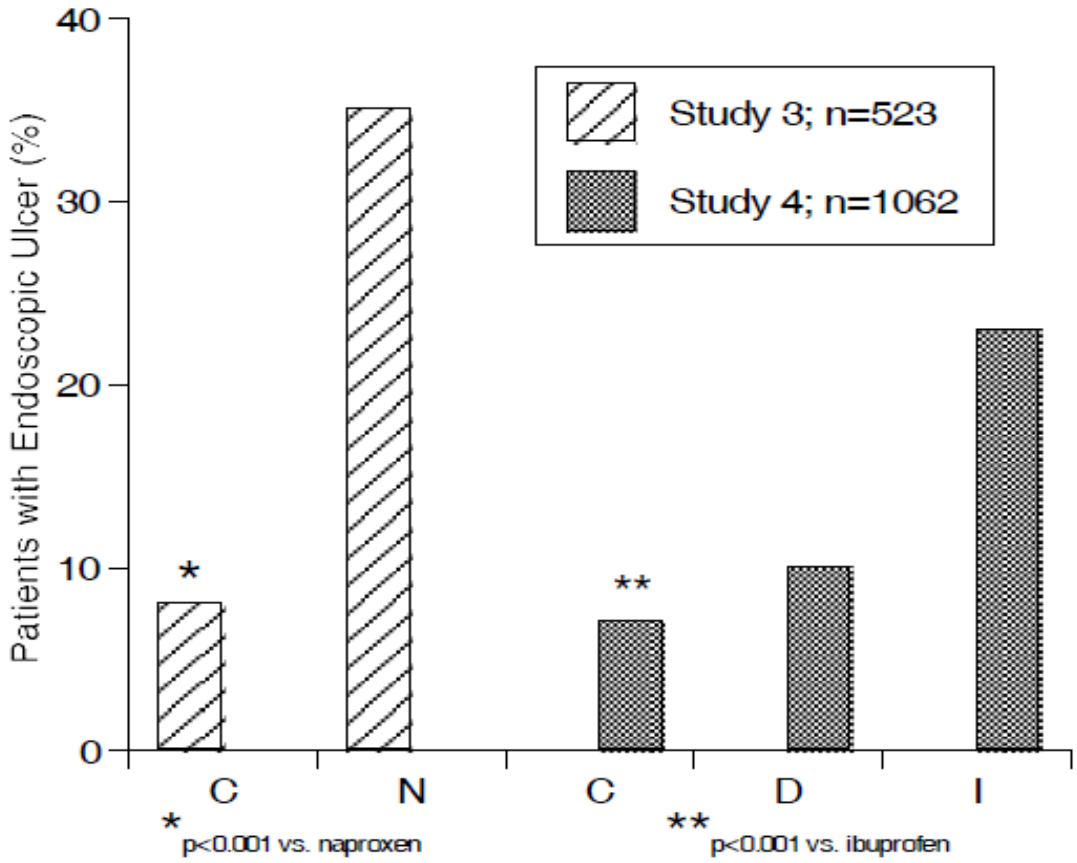
Table 4: Incidence of gastroduodenal ulcers from endoscopic studies in OA and RA patients

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

* p≤ 0.05 vs all other treatments

Figure 4 and Table 5 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 = Celecoxib 200 mg twice daily
N = Naproxen 500 mg twice daily
D = Diclofenac 75 mg twice daily
I = Ibuprofen 800 mg three times daily

Table 5: Incidence of gastroduodenal ulcers from 3-month serial endoscopy studies in OA and RA patients

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

* p≤ 0.05 celecoxib vs. naproxen based on interval and cumulative analyses
† p≤ 0.05 celecoxib vs. ibuprofen based on interval and cumulative analyses

One randomised and double-blinded 6-month study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The results are shown in Figure 5.

Figure 5: Prevalence of endoscopically observed gastroduodenal ulcers after six months of treatment in patients with rheumatoid arthritis

* Significantly different from Celecoxib; p<0.001

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established.

Serious clinically significant upper GI bleeding has been observed in patients receiving celecoxib in controlled and open-labelled trials, albeit infrequently. Among 5,285 patients who received celecoxib in the original arthritis controlled clinical trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 patients (0.04%) experienced significant UGI bleeding. Patients most at risk of developing an ulcer complication were the elderly (≥ 75 years), patients in poor health or with cardiovascular disease, aspirin users and patients with a history of a GI ulcer or upper GI bleeding.

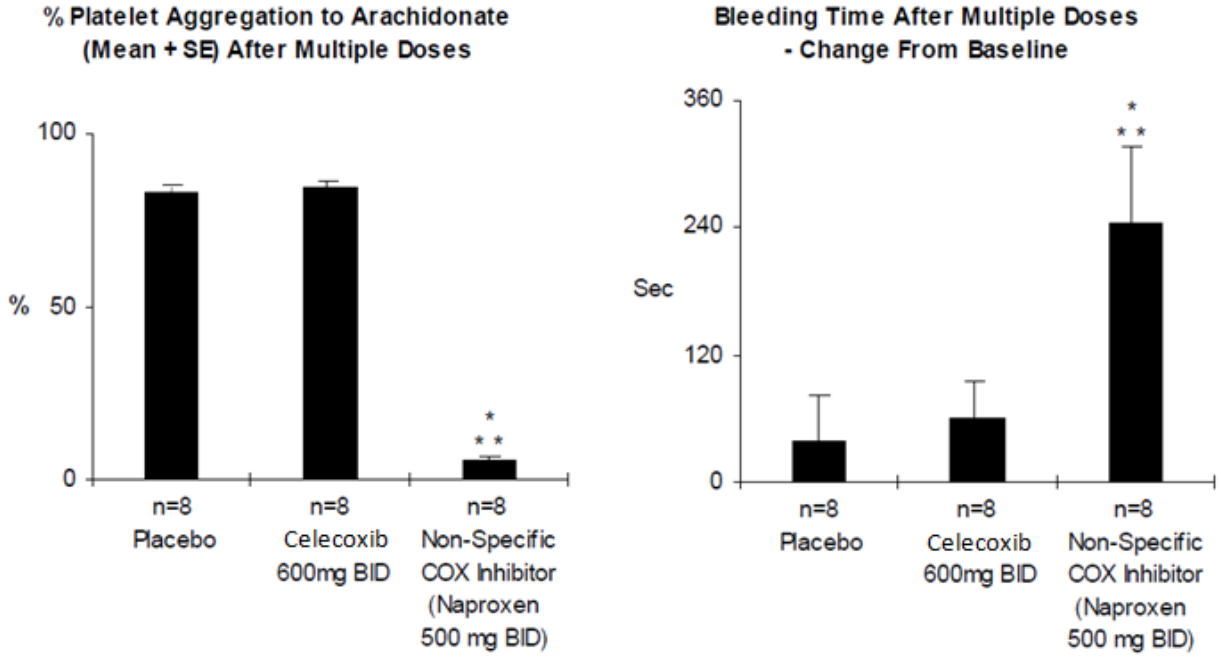
Use with aspirin

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

Platelet function

At total daily doses of 1200 mg (three times the highest recommended therapeutic dose) for up to 7 days duration, celecoxib 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: Effect of high dose celecoxib (600 mg twice daily) on platelet aggregation and bleeding time in healthy individuals



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

Gastrointestinal safety – Meta-analysis from Osteoarthritis and Rheumatoid Arthritis studies

An analysis of 31 randomised controlled clinical studies in osteoarthritis and rheumatoid arthritis, involving 39,605 patients with osteoarthritis (N = 25,903), rheumatoid arthritis (N = 3,232) or patients

with either condition (N = 10,470) compared the incidence of GI adverse events in celecoxib-treated patients to the incidence in patients administered placebo or NSAIDs (including naproxen, diclofenac and ibuprofen). The incidence of clinical ulcers and ulcer bleeds with celecoxib 200 mg – 400 mg total daily dose was 0.2% compared to an incidence of 0.6% with NSAIDs (RR = 0.35; 95% CI 0.22-0.56).

Cardiovascular safety – Prospective randomized 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 was planned with 80% power to evaluate non-inferiority. All patients were prescribed open label esomeprazole (20 – 40 mg) for gastro protection. Patients who were taking low dose aspirin were permitted to continue therapy.

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

Table 6: Population and treatment dose

Analysis Set	**Celecoxib 100-200 mg bid**	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**	**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 7.

Table 7: Primary analysis of the adjudicated APTC composite endpoint

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib 100 - 200 mg bid	**Ibuprofen 600 - 800 mg tid**	**Naproxen 375 - 500 mg bid**
N	8,072	8,040	7,969
Subjects with Events	188 (2.3%)	218 (2.7%)	201 (2.5%)

Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.93 (0.76, 1.13)	0.86 (0.70, 1.04)	1.08 (0.89, 1.31)
Modified Intent-To-Treat Analysis (mITT, on treatment through month 43)			
	Celecoxib 100 - 200 mg bid	**Ibuprofen 600 - 800 mg tid**	**Naproxen 375 - 500 mg bid**
N	8,030	7,990	7,933
Subjects with Events	134 (1.7%)	155 (1.9%)	144 (1.8%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.90 (0.72, 1.14)	0.81 (0.64, 1.02)	1.12 (0.889, 1.40)

Key secondary and tertiary endpoints

The analysis of major adverse cardiovascular events (MACE)* for mITT are described below in Table 8.

Table 8: On-treatment adjudicated major adverse CV events

	Celecoxib 100 - 200 mg bid	**Ibuprofen 60 - 800 mg tid**	**Naproxen 375 - 500 mg bid**
N	8,030	7,990	7,933
Number of Subjects with Events (%)			
MACE	247 (3.1%)	284 (3.6%)	253 (3.2%)
CV death	35 (0.4%)	51 (0.6%)	49 (0.6%)
Nonfatal MI	58 (0.7%)	76 (1.0%)	53 (0.7%)
Nonfatal stroke	43 (0.5%)	32 (0.4%)	45 (0.6%)
Hospitalisation for unstable angina	46 (0.6%)	49 (0.6%)	44 (0.6%)
Revascularisation	132 (1.6%)	158 (2.0%)	122 (1.5%)
Hospitalisation for TIA	12 (0.1%)	21 (0.3%)	16 (0.2%)
Pairwise comparison HR (95%CI)	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
MACE	0.95 (0.80, 1.13)	0.82 (0.69, 0.97)	1.17 (0.98, 1.38)
CV death	0.69 (0.45, 1.07)	0.64 (0.42, 0.99)	1.08 (0.73, 1.60)
Nonfatal MI	1.06 (0.73, 1.54)	0.72 (0.51, 1.01)	1.48 (1.04, 2.11)
Nonfatal stroke	0.93 (0.61, 1.42)	1.26 (0.79, 1.98)	0.74 (0.47, 1.16)
Hospitalisation for unstable angina	1.02 (0.67, 1.54)	0.89 (0.59, 1.33)	1.16 (0.77, 1.74)
Revascularisation	1.06 (0.83, 1.35)	0.78 (0.62, 0.99)	1.35 (1.07, 1.72)
Hospitalisation for TIA	0.73 (0.35, 1.55)	0.54 (0.26, 1.09)	1.38 (0.72, 2.64)

*MACE= APTC composite endpoint plus coronary revascularization, or hospitalization 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

The analysis of gastrointestinal events for mITT are described below in Table 9.

Table 9: On-treatment adjudicated gastrointestinal endpoints

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

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

**IDA (Iron Deficiency Anaemia) = clinically significant iron deficiency anaemia of GI origin or decrease in Hct and/or Hgb (defined as Hct $\geq$ 10 points and or Hgb of $\geq$ 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 10.

Table 10: On-treatment adjudicated renal events, hospitalisation for CHF and hypertension

	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**
N	8,030	7,990	7,933
Subjects with events, n(%)			
Renal events	42 (0.5%)	73 (0.9%)	62 (0.8%)
Hospitalisation for CHF	28 (0.3%)	38 (0.5%)	35 (0.4%)
Hospitalisation for hypertension	25 (0.3%)	37 (0.5%)	32 (0.4%)
Any of the Above	89 (1.1%)	139 (1.7%)	120 (1.5%)
Pairwise comparison, HR (95%CI)	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
Renal events	0.66 (0.44, 0.97)	0.54 (0.37, 0.79)	1.21 (0.86, 1.70)
Hospitalisation for CHF	0.77 (0.47, 1.27)	0.70 (0.43, 1.13)	1.12 (0.71, 1.77)
Hospitalisation for hypertension	0.76 (0.45, 1.28)	0.64 (0.39, 1.07)	1.18 (0.74, 1.90)
Any of the above	0.72 (0.55, 0.95)	0.60 (0.46, 0.79)	1.19 (0.93, 1.52)

*N.B:Renal events included a composite of pre-defined rises in creatinine levels (verified serum creatinine of ≥ 2.0mg/dL (177 µmol/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. Significant differences were observed in the pairwise comparisons between celecoxib and either naproxen HR 0.65 (0.46, 0.92) or celecoxib and ibuprofen HR 0.68 (0.48, 0.97). in the ITT population the celecoxib, naproxen and ibuprofen were associated with 132 (1.6%), 163 (2.0%) and 142 (1.8%) deaths, respectively. No significant differences were observed in pairwise comparisons between treatments.

ABPM substudy

In the PRECISION-ABPM substudy, among the total of 444 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 cardiovascular death, myocardial infarction, or stroke (adjudicated) with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint.

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

In the PreSAP trial, the hazard ratio compared to placebo for this same composite endpoint was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily. Cumulative 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 cardiovascular thromboembolic events was greater in celecoxib-treated patients with a history of atherosclerotic cardiovascular disease, than in celecoxib-treated patients without such history.

Cardiovascular safety – Long-term study of Alzheimer's disease anti-inflammatory prevention trial (ADAPT)

Data from the ADAPT study did not show a significantly increased cardiovascular risk with celecoxib 200 mg twice daily compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61 – 2.12) with celecoxib 200 mg twice daily. The incidence of myocardial infarction was 1.1% (8/717 patients) with celecoxib 200 mg twice daily and 1.2% (13/1070 patients) with placebo.

Cardiovascular safety - Meta-analysis from chronic usage studies

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

In this analysis, the incidence of serious cardiovascular thromboembolic events (CV death, non-fatal myocardial infarction and non-fatal stroke) was similar between celecoxib (N=19,773) and non-selective NSAIDs (N=13,990) treatment (RR=0.84, 95% CI 0.63 - 1.13). This pattern of effect was maintained with or without aspirin use (≤ 325 mg). The incidence of non-fatal myocardial infarction trended higher (RR=1.49, 95% CI 0.82 - 2.70); however that of stroke was significantly lower (RR= 0.31, 95% CI 0.14 - 0.68), and that of cardiovascular death was comparable (RR=0.72, 95% CI 0.37 - 1.39) for celecoxib compared to combined non-selective NSAIDs.

In this analysis, the incidence of serious cardiovascular thromboembolic events (CV death, non-fatal myocardial infarction and non-fatal stroke) was 0.38% for celecoxib (N=7,462) and 0.27% for placebo (N=4,057) treatment (RR=1.14, 95% CI 0.57 - 2.27). This pattern of effect was maintained with or without aspirin use (≤ 325 mg). The incidence of non-fatal myocardial infarction trended higher (RR=1.24, 95% CI 0.27 - 5.76), as did that of cardiovascular death (RR=1.74, 95% CI 0.49-6.17), and that of stroke was similar RR=0.96, 95% CI 0.29 - 3.17) for celecoxib compared to placebo.

Cardiovascular Safety – CLASS trial

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

5.2 Pharmacokinetic properties

Absorption

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

When celecoxib capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%.

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.

Biotransformation

Celecoxib is extensively metabolised in the liver. *In-vitro* and *in-vivo* studies indicate that metabolism is mainly by cytochrome P450 2C9 (see section 4.5). 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. In a pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP 2C9*1/*1, CYP 2C9*1/*3, or CYP 2C9*3/*3, the median C_{max} and AUC_{0-24} of celecoxib on day 7 were approximately 4-fold and 7-fold, respectively, in subjects genotyped as CYP 2C9*3/*3 compared to other genotypes. In three separate single dose studies, involving a total of 5 subjects genotyped as CYP 2C9*3/*3, single-dose AUC_{0-24} increased by approximately 3-fold compared to normal metabolisers. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3-1.0% among different ethnic groups.

Patients who are known or suspected to be poor P450 2C9 metabolisers based on previous history should be administered celecoxib with caution as they may have abnormally high plasma concentrations due to reduced metabolic clearance. Consider starting treatment at half the lowest recommended dose (see section 4.2 and section 4.5).

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.

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.

A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, celecoxib capsules should be introduced at the lowest recommended dose in arthritis patients with moderate hepatic impairment.

Patients with severe hepatic impairment have not been studied. Therefore, the use of celecoxib in patients with severe hepatic impairment (Child-Pugh score $\geq$ 10) is contraindicated.

In elderly volunteers with age-related reductions in glomerular filtration rate (GFR) (mean GFR >65 ml/min/1.73m^2) and in patients with chronic stable renal insufficiency (GFR 35-60 ml/min/1.73m^2) celecoxib pharmacokinetics was comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance. 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. 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.

Elimination

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and faeces. Following a single oral dose of radio-labelled 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 ($t_{½}$) was 4-15 hours and the clearance is about 500 mL/min. It appears that the low solubility of the drug prolongs absorption resulting in variable terminal half-life ($t_{½}$) determinations.

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_{0-24h} at 400 mg twice daily, 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 as measured by the AUC_{0-24h} at 400 mg twice daily).

6. Pharmaceutical Particulars

6.1 List of excipients

Celostea capsule core also contains:

- Sodium lauryl sulfate
- Povidone
- Lactose
- Croscarmellose sodium
- Magnesium stearate
- Colloidal anhydrous silica

Celostea capsule shells (100 mg) also contain:

- Titanium dioxide
- FD&C Blue #2
- Gelatin
- Sodium lauryl sulfate
- Black printing ink (Opacode Black S-1-17823)

Celostea capsule shells (200 mg) also contain:

- Iron oxide black
- Iron oxide red
- Iron oxide yellow
- Titanium dioxide
- Gelatin

- Sodium lauryl sulfate
- Black printing ink (Opacode Black S-1-17823)

6.2 Incompatibilities

No known incompatibilities with other medicines.

6.3 Shelf life

3 years as applicable.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Celostea 100 mg:
blister pack of 10, 20, 30, 50, 60 and 120 capsules; and bottle pack of 100, 120 and 500 capsules

Celostea 200 mg:
blister pack of 10, 20, 30, 50, 60 and 120 capsules; and bottle pack of 100, 120 and 500 capsules

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

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Telephone 0800 168 169

9. Date of First Approval

12 June 2014

10. Date of Revision of the Text

29 August 2025

Section Changed	Summary of New Information
All	Rebranded to Viatris logo, added trademark statement.

2	Updated allergen statement.
4.4	Additional safety information for fixed drug eruption (FDE) and generalised bullous fixed drug eruption (GBFDE).
4.8	Additional safety information for fixed drug eruption (FDE) and generalised bullous fixed drug eruption (GBFDE). Updated ADR reporting website.
4.9	Minor editorial change.
6.1	Removed gluten free statement.
8	Sponsor detail updated to Viatris.

CELOSTEA® is a Viatris company trade mark.