Pfizer Parke Davis

CEBREX™

1. NAME OF THE MEDICINAL PRODUCT

CEBREX™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 200 mg capsule contains 200 mg celecoxib.

Each 400 mg capsule contains 400 mg celecoxib.

3. PHARMACEUTICAL FORM

Hard capsules for oral use

200 mg capsules: Hard gelatin capsules, white opaque cap with gold ink band containing in white “7767”, white opaque body with gold ink band containing in white “200” (containing white to off-white granulation).

400 mg capsules: Hard gelatin capsules, white opaque cap with green ink band containing in white “7767”, white opaque body with green ink band containing in white “400” (containing white to off-white granulation).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA).

Relief of signs and symptoms of ankylosing spondylitis (AS).

Management of acute pain.

Treatment of primary dysmenorrhea.

Management of low back pain.

4.2 Posology and method of administration

Celecoxib capsules, at doses up to 200 mg twice per day, can be taken with or without food.

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.

Symptomatic Treatment of Osteoarthritis (OA): The usual recommended dose of celecoxib is 200 mg administered as a single dose. In some patients, with insufficient relief from symptoms, an increased dose of 200 mg twice daily may increase efficacy. In the absence of an increase in therapeutic benefit after 2 weeks, other therapeutic options should be considered.

Symptomatic Treatment of Rheumatoid Arthritis (RA): The recommended dose of celecoxib is 200 mg twice per day.

Ankylosing Spondylitis (AS): The recommended dose of celecoxib is 200 mg administered as a single dose. Some patients may benefit from a total daily dose of 400 mg.

Management of Acute Pain: The recommended dose of celecoxib is 400 mg initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily or 400 mg once daily as needed.

Treatment of Primary Dysmenorrhea: The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily or 400 mg once daily as needed.

Low Back Pain (LBP): The recommended dose of celecoxib is 200 mg or 400 mg daily, administered as a 200 mg single dose, or as 100 or 200 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.

CYP2C9 Poor Metabolizers: Patients who are known, or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest

recommended dose (see Sections 4.5 Interaction with other medicinal products and other forms of interaction and 5.2 Pharmacokinetic properties - Metabolism).

Elderly: No dosage adjustment is generally necessary. However, for elderly patients weighing lower than 50 kg, it is advisable to initiate therapy at the lowest recommended dose.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). Introduce celecoxib at half the recommended dose in arthritis or pain patients with moderate hepatic impairment (Child-Pugh Class B).

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied (see Section 4.4 Special warnings and precautions for use - Hepatic Effects).

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 4.4 Special warnings and precautions for use - Renal Effects).

Co-administration with Fluconazole: Celecoxib should be introduced at half the recommended dose in patients receiving fluconazole, a CYP2C9 inhibitor. Caution is advised when co-administering celecoxib with other CYP2C9 inhibitors (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Pediatric Patients: Celecoxib has not been studied in subjects under 18 years of age.

4.3 Contraindications

Celecoxib is contraindicated in:

- Patients with known hypersensitivity to celecoxib or any other ingredient of the product.
- Patients with known sulfonamide hypersensitivity.
- Patients who have experienced asthma, urticaria or allergic-type reactions after taking acetylsalicylic acid (ASA [aspirin]) or other non-steroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see Section 4.4 Special warnings and precautions for use).

- Children under 18 years old.

4.4 Special warnings and precautions for use

Cardiovascular Effects

Cardiovascular Thrombotic Events

Celecoxib may cause an increased risk of serious CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs may have a similar risk. 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. To minimize 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. Physicians and patients should remain alert for the development of 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 (see Section 5.1 Pharmacodynamic properties).

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

Celecoxib is not a substitute for aspirin for prophylaxis of CV thromboembolic diseases because of the lack of effect on platelet function. Because celecoxib does not inhibit platelet aggregation, anti-platelet therapies (e.g., aspirin) should not be discontinued.

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 (see Section 5.1 Pharmacodynamic properties – Clinical Studies – ABPM Substudy).

Fluid Retention and Edema

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema

have been observed in some patients taking celecoxib. Therefore, patients with pre-existing congestive heart failure (CHF) or hypertension should be closely monitored. Celecoxib should be used with caution in patients with compromised cardiac function, pre-existing edema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.

Gastrointestinal (GI) Effects

Upper and lower GI perforations, ulcers or bleeds have occurred in patients treated with celecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with CV disease, patients using concomitant glucocorticoids, antiplatelet drugs (such as aspirin), or other NSAIDs, patients using alcohol or patients with a prior history of, or active, GI disease, such as ulceration, GI bleeding or inflammatory conditions. Most spontaneous reports of fatal GI events have been in elderly or debilitated patients.

Renal Effects

NSAIDs including celecoxib may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.

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

Advanced Renal Disease

Renal function should be closely monitored in patients with advanced renal disease who are administered celecoxib (see Section 4.2 Posology and method of administration).

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to celecoxib (see Section 4.3 Contraindications).

Serious Skin Reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis,

Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hepatic Effects

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of celecoxib in patients with severe hepatic impairment is not recommended. Celecoxib should be used with caution when treating patients with moderate hepatic impairment (Child-Pugh Class B), and initiated at half the recommended dose (see Section 4.2 Posology and method of administration).

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

A patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib.

Use with 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, 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 (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

General

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

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

CYP2D6 Inhibition

Celecoxib has shown to be a moderately potent CYP2D6 inhibitor. For drugs that are metabolized 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 Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interaction

General

Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Consider starting treatment at half the lowest recommended dose (see Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties - Metabolism).

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

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

Clinical pharmacokinetics study and *in vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6.

Drug-specific

Interaction of celecoxib with warfarin or similar agents

See Section 4.4 Special warnings and precautions for use - Use with Oral Anticoagulants.

Lithium

In healthy subjects, lithium plasma levels increased approximately 17% in subjects receiving lithium together with celecoxib. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Aspirin

Celecoxib does not interfere with the anti-platelet effect of low-dose aspirin (see Section 4.4 Special warnings and precautions for use - Gastrointestinal (GI) Effects). Because of its lack of platelet effects, celecoxib is not a replacement for aspirin in the prophylactic treatment of CV disease.

Anti-hypertensives including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II antagonists (also known as angiotensin receptor blockers [ARBs]), diuretics and beta-blockers

Inhibition of prostaglandins may diminish the effect of anti-hypertensives including ACEIs and/or ARBs, diuretics and beta-blockers. This interaction should be given consideration in patients taking celecoxib concomitantly with ACEIs and/or ARBs, diuretics and beta-blockers.

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 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.

Results from lisinopril study

In a 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients co-administered with celecoxib 200 mg BID, 48% were considered unresponsive to

lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic blood pressure increased >10% compared to baseline), compared to 27% of patients co-administered with placebo; this difference was statistically significant.

Cyclosporine

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

Fluconazole and ketoconazole

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 CYP2C9 by fluconazole. Celecoxib should be introduced at half the recommended dose in patients receiving the CYP2C9 inhibitor fluconazole (see Section 4.2 Posology and method of administration). Ketoconazole, a CYP3A4 inhibitor, showed no clinically relevant inhibition in the metabolism of celecoxib.

Dextromethorphan and metoprolol

Concomitant administration of celecoxib 200 mg twice daily resulted in a 2.6-fold and a 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib inhibition to the CYP2D6 substrate metabolism via CYP2D6. Therefore, the dose of drugs as 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 - CYP2D6 Inhibition).

Diuretics

Clinical studies have shown that NSAIDs, in some patients, can reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.

Methotrexate

No pharmacokinetic and clinically important interactions have been observed in a clinical study between celecoxib and methotrexate.

Oral contraceptives

In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics

of a prototype combination oral contraceptive (1 mg norethindrone/0.035 mg ethinyl estradiol).

Other drugs

No clinically important interactions have been observed with celecoxib and antacids (aluminum and magnesium), omeprazole, glibenclamide (glyburide), phenytoin, or tolbutamide.

4.6 Fertility, pregnancy and lactation

Fertility

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.

Pregnancy

There are no studies in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3 Preclinical safety data). The relevance of these data for humans is unknown.

Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during the third trimester of pregnancy.

Celecoxib should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from 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.

If used during second or third trimester of pregnancy, NSAIDs may cause fetal 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. Pregnant women on celecoxib should be closely monitored for amniotic fluid volume.

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 in nursing infants from celecoxib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the expected benefit of the drug to the mother.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical Trials Experience

The following adverse drug reactions (ADRs) in Table 1 were identified with incidence rates greater than 0.01% in celecoxib group and greater than those reported in placebo group, during 12 placebo- and/or active-controlled clinical trials of treatment duration up to 12 weeks at daily doses from 100 mg up to 800 mg in adults.

The frequencies on the ADRs in Table 1 are updated based on a more recent pooling of 89 randomized, controlled clinical trials data representing clinical exposure in 38,102 patients taking celecoxib. ADR frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%). The ADRs in Table 1 are listed by system organ class and ranked by frequency in descending order.

Table 1. Adverse Drug Reactions (ADRs) in 12 Placebo- and/or Active-controlled Clinical Trials and ADR Frequency from 89 Pain and Inflammation Randomized, Controlled Clinical Trials with Daily Doses of 25 mg to 800 mg, in Adult Populations

System Organ Class Frequency	Adverse Drug Reaction
Infections and infestations	
Common	Bronchitis, sinusitis, upper respiratory tract infection, urinary tract infection
Uncommon	Pharyngitis, rhinitis
Blood and lymphatic system disorders	
Uncommon	Anaemia
Rare	Thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity
Psychiatric disorders	
Common	Insomnia
Uncommon	Anxiety
Rare	Confusional state
Nervous system disorders	
Common	Dizziness
Uncommon	Hypertonia, somnolence
Eye disorders	
Uncommon	Vision blurred
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Palpitations
Rare	Cardiac failure congestive, arrhythmia, tachycardia
Vascular disorders	
Common	Hypertension (including aggravated hypertension)
Rare	Flushing
Respiratory, thoracic and mediastinal	

System Organ Class Frequency	Adverse Drug Reaction
disorders	
Common	Cough
Gastrointestinal disorders	
Common	Vomiting, abdominal pain, diarrhoea, dyspepsia, flatulence
Uncommon	Gastric ulcer, tooth disorder
Rare	Duodenal ulcer, oesophageal ulcer
Very rare	Intestinal perforation, pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)
Skin and subcutaneous tissue disorders	
Common	Pruritus (includes pruritus generalized), rash
Uncommon	Urticaria, ecchymosis
Rare	Angioedema, alopecia
Very rare	Dermatitis bullous
General disorders and administration site conditions	
Common	Oedema peripheral
Uncommon	Face oedema, influenza like illness
Injury, poisoning and procedural conditions	
Uncommon	Injury

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 - Cardiovascular Safety - Long-Term Studies Involving Patients with Sporadic Adenomatous Polyps).

Frequencies of ADRs in Table 2 were determined based on these long-term polyp prevention studies and 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 ranked by frequency in descending order.

Table 2. Adverse Reactions from Polyp Prevention Studies of Duration up to 3 Years and Daily Doses of 400 mg to 800 mg

System Organ Class Frequency	**Adverse Drug Reaction**
Infections and infestations	
Common	Ear infection, fungal infection**
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	Conjunctival hemorrhage, vitreous floaters
Ear and labyrinth disorders	
Uncommon	Hypoacusis
Cardiac disorders	
Common	Myocardial infarction, angina pectoris
Uncommon	Angina unstable, aortic valve incompetence, arteriosclerosis coronary artery, sinus bradycardia, ventricular hypertrophy
Vascular disorders	
Very Common	Hypertension*
Uncommon	Deep vein thrombosis, haematoma

System Organ Class Frequency	Adverse Drug Reaction
Respiratory, thoracic, and mediastinal disorders	
Common	Dyspnoea
Uncommon	Dysphonia
Gastrointestinal disorders	
Very Common	Diarrhoea*
Common	Vomiting*, dysphagia, irritable bowel syndrome, gastrooesophageal reflux disease, nausea, diverticulum
Uncommon	Hemorrhoidal 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, prostatitis, benign prostatic hyperplasia
Uncommon	Ovarian cyst, menopausal symptoms, breast tenderness, dysmenorrhoea
General disorders and administration	

System Organ Class Frequency	Adverse Drug Reaction
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, fracture, epicondylitis, tendon rupture

* 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 reactions from studies of 12-week duration.

** Fungal infections were primarily non-systemic.

Post-marketing Experience

Adverse reactions identified from post-marketing experience are provided below. Even though these were identified as reactions from post-marketing reports, trial data was consulted to estimate frequency. As above, frequencies are based on a pooling of trials representing exposure in 38,102 patients. Frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%), not known (cannot be estimated from the available data).

Immune system disorders: Very rare: anaphylactic reaction

Psychiatric disorders: Rare: hallucination

Nervous system disorders: Very rare: cerebral haemorrhage, meningitis aseptic, ageusia, anosmia

Eye disorders: Uncommon: conjunctivitis

Vascular disorders: Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders: Rare: pulmonary embolism, pneumonitis

Gastrointestinal disorders: Rare: gastrointestinal haemorrhage

Hepato-biliary disorders: Rare: hepatitis; Very rare: hepatic failure, hepatitis fulminant, hepatic necrosis (see Section 4.4 Special warnings and precautions for use - Hepatic Effects), cholestasis, hepatitis cholestatic, jaundice

Skin and subcutaneous tissue disorders: Rare: photosensitivity reaction; Very rare: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative

Renal and urinary disorders: Rare: renal failure acute (see Section 4.4 Special warnings and precautions for use - Renal Effects), hyponatraemia; Very rare: tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion

Reproductive system and breast disorders: Rare: menstrual disorder; Not known: infertility female (female fertility decreased) (see Section 4.6 Fertility, pregnancy and lactation)†

General disorders and administration site conditions: Uncommon: chest pain

† Women intending to become pregnant are excluded from all trials, thus consultation of the trial database for the frequency of this event was not reasonable.

4.9 Overdose

Clinical experience of overdose is limited. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered to healthy subjects without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided. Dialysis is unlikely to be an efficient method of drug removal because of high protein binding of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: M01AH Coxibs

The mechanism of action of celecoxib is via inhibition of prostaglandin synthesis primarily by inhibition of COX-2. At therapeutic concentrations in humans celecoxib does not inhibit cyclooxygenase-1 (COX-1). COX-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, in particular prostaglandin E2, causing inflammation, edema and pain. Celecoxib acts as an anti-inflammatory, analgesic, and antipyretic agent in animal models by blocking the production

of inflammatory prostanoids via COX-2 inhibition. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

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 synthesized by activation of COX-1 thereby not interfering with normal COX-1 related physiological processes in tissues, particularly the stomach, intestine, and platelets.

Clinical Studies

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 4200 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 to 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 200 mg 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 2100 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 to 200 mg twice daily.

Analgesia, including Primary Dysmenorrhea

In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, celecoxib relieved pain that was rated by patients as moderate to severe. Single doses of celecoxib provided pain relief within 60 minutes (see Section 4.2 Posology and method of administration).

Ankylosing Spondylitis (AS)

Celecoxib was evaluated in AS patients in two placebo- and active-controlled (naproxen or ketoprofen) clinical trials of 6 and 12 weeks duration. Celecoxib at doses of 100 mg twice daily, 200 mg once daily and 400 mg once daily was shown to be statistically superior to placebo in these studies for all three co-primary efficacy measures assessing global pain intensity (Visual Analogue Scale), global disease activity (Visual Analogue Scale), and functional impairment (Bath Ankylosing Spondylitis Functional Index). In the 12-week study, there was no difference in the extent of improvement between the 200 mg and 400 mg celecoxib doses in a comparison of mean change from baseline, but there was a greater percentage of patients who responded to celecoxib 400 mg, 53%, than to celecoxib 200 mg, 44%, using the Assessment in Ankylosing Spondylitis response criteria (ASAS 20). The ASAS 20 defines response as improvement from baseline of at least 20% and an absolute improvement of at least 10 mm, on a 0 to 100 mm scale, in at least three of the four following domains: patient global, pain, Bath Ankylosing Spondylitis Functional Index, and inflammation. The responder analysis also demonstrated no change in the responder rates beyond 6 weeks.

Low Back Pain (LBP)

Celecoxib was used to treat patients who had pre-existing non-neuropathic LBP of duration $\geq$12 weeks. In the table shown below, efficacy results in 5 clinical trials are presented using the Patient's Assessment of Pain Intensity (100 mm visual analog scale) from baseline to end of treatment:

Patient's Assessment of Pain Intensity in LBP Clinical Trials

Study ID (Duration) Treatment (TDD)	**N**	**Baseline Pain Intensity[c]**	**Change in Pain Intensity[c]**	**P-Value for Treatment Difference[c]**
Study 244 (12 Weeks)[a]				
Placebo	177	76.6	-30.1	--
Celecoxib 200 mg	183	73.6	-35.9	0.0503
Study 245 (12 Weeks)[a]				
Placebo	191	75.7	-26.2	--
Celecoxib 200 mg	183	72.8	-32.2	0.0427
Study 1165 (6 Weeks)[b]				
Celecoxib 400 mg	402	65.5	-34.6	0.008
Tramadol 200 mg	389	66.1	-30.4	--
Study 1338 (6 Weeks)[b]				
Celecoxib 400 mg	386	65.9	-34.8	0.595
Tramadol 200 mg	385	66.6	-34.4	--
Study 1174 (4 Weeks)				
Placebo	410	65.1	-26.2	--
Celecoxib 400 mg	410	65.0	-31.7	<0.001
Loxoprofen 180 mg	407	65.6	-29.3	Not Evaluated

N = Number of patients providing data at baseline and end of treatment. TDD = Total daily dose.

[a] Patient's Assessment of Pain Intensity a co-primary efficacy measure in these studies, along with Patient's Global Assessment of Low Back Pain (treatment differences significantly favored celecoxib over placebo in Studies 244 and 245) and the Roland-Morris Disability Questionnaire (treatment difference significantly favored celecoxib over placebo in Study 244).

[b] The primary efficacy measure in these studies was the percentage of patients who experienced at least 30% improvement on the Numerical Rating Scale (NRS) Pain Assessment, for which results in both studies showed statistical superiority for celecoxib over tramadol.

[C] Based on least-squares means from Analysis of Covariance models, with changes in pain intensity calculated by subtracting baseline value from end-of-treatment value; p-values were calculated based on least-squares mean differences between treatment groups.

Further Information from Clinical Studies

Endoscopic Studies

Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in 5 controlled randomized 12 to 24 week trials using active comparators, 2 of which also included placebo controls. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of celecoxib over the range studied.

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

Table 3. 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)*

*$p \leq 0.05$ vs. all other treatments.

Table 4 summarizes data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

Table 4. Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in Osteoarthritis and Rheumatoid Arthritis 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)				

	Week 4	Week 8	Week 12	Final
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)
* $p \leq 0.05$ celecoxib vs. naproxen based on interval and cumulative analyses † $p \leq 0.05$ celecoxib vs. ibuprofen based on interval and cumulative analyses				

One randomized and double-blind 6-month study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The incidence of endoscopic ulcers in patients taking celecoxib 200 mg twice daily was 4% vs. 15% for patients taking diclofenac SR 75 mg twice daily ($p<0.001$).

In 4 of the 5 endoscopic studies, approximately 11% of patients (440/4,000) were taking aspirin ($\leq$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.

The correlation between findings of endoscopic studies and the relative incidence of clinically significant serious upper GI events has not been established. Serious clinically significant upper GI bleeding has been observed in patients receiving celecoxib in controlled and open-labeled trials, albeit infrequently (see Section 4.4 Special warnings and precautions for use - Gastrointestinal (GI) Effects).

Gastrointestinal Safety Meta-Analysis from Osteoarthritis and Rheumatoid Arthritis Studies

An analysis of 31 randomized controlled clinical studies in OA and RA, involving 39,605 patients with OA (N=25,903), RA (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 to

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).

The Celecoxib Long-Term Arthritis Safety Study (CLASS) including Use with Aspirin

In a prospective long-term safety outcome study conducted post-marketing in approximately 5,800 OA patients and 2,200 RA patients, patients received celecoxib 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg three times daily, or diclofenac 75 mg twice daily (common therapeutic doses). Median exposures for celecoxib (n=3,987) and diclofenac (n=1,996) were 9 months while ibuprofen (n=1,985) was 6 months. The Kaplan-Meier cumulative rates at 9 months are provided for all analyses. The primary endpoint of this outcome study was the incidence of ***complicated ulcers*** (gastrointestinal bleeding, perforation, or obstruction). Patients were allowed to take concomitant low-dose (≤325 mg/day) aspirin (ASA) for CV prophylaxis (ASA subgroups: celecoxib, n=882; diclofenac, n=445; ibuprofen, n=412). Differences in the incidence of *complicated ulcers* between celecoxib and the combined group of ibuprofen and diclofenac were not statistically significant. Those patients on celecoxib and concomitant low-dose ASA experienced 4-fold higher rates of *complicated ulcers* compared to those not on ASA (see Section 4.4 Special warnings and precautions for use - Gastrointestinal (GI) Effects). The results for celecoxib are displayed in Table 5.

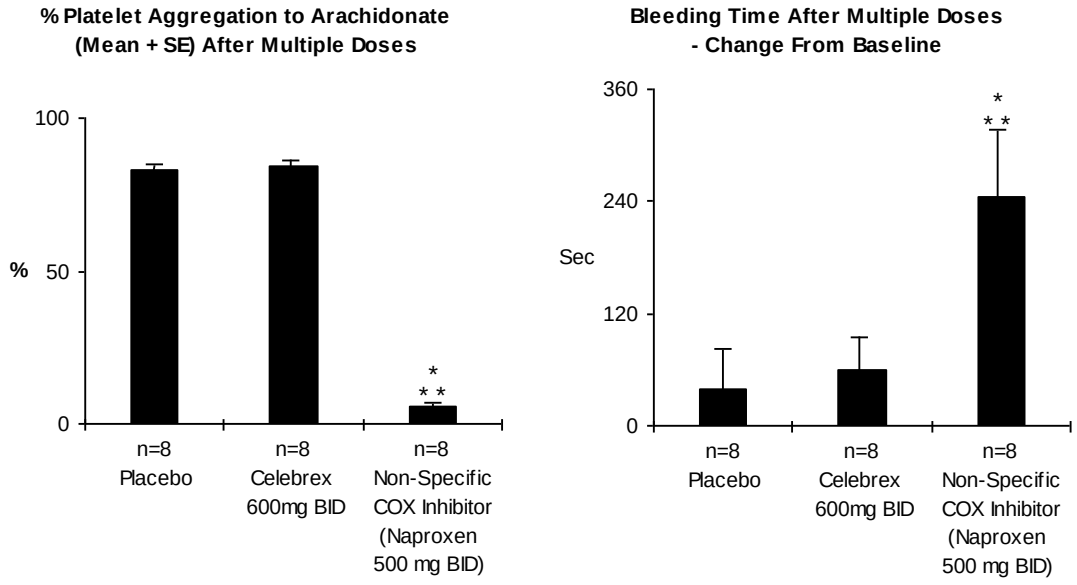
Table 5. Effects of Co-administration of Low-dose Aspirin on Complicated Ulcer Rates with Celecoxib 400 mg Twice Daily (Kaplan-Meier Rates at 9 months [%])

	Non-Aspirin Users N=3105	**Aspirin Users N=882**
Complicated Ulcers	0.32	1.12

Platelet Function

In healthy volunteers, celecoxib at therapeutic doses and at multiple doses of 600 mg twice daily (three times the highest recommended dose) had no effect on platelet aggregation and bleeding time compared to placebo. Active controls (non-specific COX inhibitors) all significantly reduced platelet aggregation and prolonged bleeding time (see Figure 1).

Figure 1. 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.

Celecoxib versus Omeprazole and Diclofenac for At-Risk Osteoarthritis and Rheumatoid Arthritis Patients (CONDOR) Trial

In this prospective, 24-week study in patients with age ≥60 years or history of gastroduodenal ulcers (users of low-dose aspirin excluded), the percentage of patients with clinically significant GI events (composite primary endpoint) was lower in patients treated with celecoxib 200 mg twice daily compared to patients treated with diclofenac SR 75 mg twice daily plus omeprazole 20 mg once daily. This difference was driven by clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of defined or presumed GI origin. Results for the individual components of this composite endpoint were as follows:

Predefined Composite GI Endpoint	Celecoxib 200 mg Twice Daily (N = 2238)	Diclofenac SR 75 mg Twice Daily + Omeprazole 20 mg Once Daily (N = 2246)
Components	**N (%) of Patients**	
Gastroduodenal hemorrhage	3 (0.1)	3 (0.1)
Large bowel hemorrhage	1 (<0.1)	1 (<0.1)
Acute GI hemorrhage of unknown origin	1 (<0.1)	0 (0.0)
Clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of defined GI origin	5 (0.2)	24 (1.1)
Clinically significant decreases in hemoglobin (≥2 g/dL) and/or hematocrit (≥10%) of presumed occult GI origin	10 (0.4)	53 (2.3)
Total*	**20 (0.9)**	**81 (3.6)**

For the following components of the predefined composite GI endpoint, there were no events in either treatment group: gastric outlet obstruction; gastroduodenal, small bowel, or large bowel perforation; small bowel hemorrhage. All events comprising the composite GI endpoint were adjudicated by an independent, expert panel blinded to randomized treatment assignments.

* In a time-to event analysis using life-table techniques, p<0.0001 for the comparison between the celecoxib treatment group and the diclofenac plus omeprazole treatment group for this endpoint.

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 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 400 mg twice daily and 200 mg twice daily celecoxib treatment groups, respectively, compared to 0.9% (6/679) for 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 placebo group.

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 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 0.61-2.15) with celecoxib 200 mg twice daily.

Cardiovascular Safety - Meta-Analysis from Chronic Usage Studies

A meta-analysis of safety data (adjudicated, investigator-reported serious adverse events) from 39 completed celecoxib clinical studies of up to 65 weeks duration has been conducted, representing 41,077 patients [23,030 (56.1%) patients exposed to celecoxib 200 mg to 800 mg total daily dose (TDD); 13,990 (34.1%) patients exposed to non-selective NSAIDs, and 4,057 (9.9%) patients exposed to placebo].

In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was similar between celecoxib (N=19,773; 0.96 events/100 patient-years) and non-selective NSAIDs (N=13,990; 1.12 events/100 patient-years) treatment (RR=0.90, 95% CI 0.60 - 1.33). This pattern of effect was maintained with or without ASA use ($\leq$325 mg). The adjudicated event rate of non-fatal myocardial infarction trended higher (RR=1.76, 95% CI 0.93-3.35); however that of non-fatal stroke trended lower (RR=0.51, 95% CI 0.23-1.10), and that of CV death was comparable (RR=0.57, 95% CI 0.28-1.14) for celecoxib compared to combined non-selective NSAIDs.

In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was 1.42/100 patient-years for celecoxib (N=7,462) and 1.20/100 patient-years for placebo (N=4,057) treatment (RR=1.11, 95% CI 0.47-2.67). This pattern of effect was maintained with or without ASA use ($\leq$325 mg). The incidence of non-fatal myocardial infarction trended higher (RR=1.56, 95% CI 0.21-11.90), as did that of CV death (RR=1.26, 95% CI 0.33-4.77), and that of non-fatal stroke was similar (RR=0.80, 95% CI 0.19-3.31) for celecoxib compared to placebo.

Cardiovascular Safety

CV safety outcomes were evaluated in the CLASS trial (see above for description of trial). Kaplan-Meier cumulative rates for investigator-reported serious CV thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischemic attacks, and ischemic 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.

Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION)

Design

The PRECISION study was a double-blind study of cardiovascular safety in OA or RA patients with or at high risk for cardiovascular 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 cardiovascular death (including hemorrhagic 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 cardiovascular, gastrointestinal and renal outcomes. Additionally, there was a 4-month substudy focusing on the effects of the three drugs on blood pressure as measured by ambulatory monitoring (ABPM).

Results

Table 6. Population and Treatment Dose

Analysis Set	Celecoxib 100-200 mg bid	Ibuprofen 600-800 mg tid	Naproxen 375-500 mg bid	Total
Randomized (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	2,045±246	852±103	NA

[1] Average dose dispensed

ITT – Intent to Treat; All randomized subjects

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

bid – Twice a day

tid – Thrice a day

NA –Not Applicable

Primary Endpoint

- Celecoxib, as compared with either naproxen or ibuprofen, met all four prespecified non-inferiority requirements ($p<0.001$ for non-inferiority in both comparisons). Non-inferiority is established when the hazard ratio (HR) $\leq$1.12 in both ITT and mITT analyses, and upper 95% CI $\leq$1.33 for ITT analysis and $\leq$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 600-800 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%)
Hospitalization for unstable angina	46 (0.6%)	49 (0.6%)	44 (0.6%)
Revascularization	132 (1.6%)	158 (2.0%)	122 (1.5%)
Hospitalization 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)
Hospitalization for unstable angina	1.02 (0.67, 1.54)	0.89 (0.59, 1.33)	1.16 (0.77, 1.74)
Revascularization	1.06 (0.83, 1.35)	0.78 (0.62, 0.99)	1.35 (1.07, 1.72)
Hospitalization 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 hemorrhage; gastric outlet obstruction; gastroduodenal, small bowel or large bowel perforation; large bowel hemorrhage; small bowel hemorrhage; Acute GI hemorrhage of unknown origin, including presumed small bowel hemorrhage; symptomatic gastric or duodenal ulcer

**IDA (Iron Deficiency Anemia) = clinically significant iron deficiency anemia of GI origin or decrease in Hct (Hematocrit) and/or Hgb (Hemoglobin) (defined as Hct $\geq$10 points and or Hgb of $\geq$2 g/dL from baseline

In the ITT population for the CSGIE endpoint there were no significant differences, in the

pairwise comparisons between treatment regimens (data not shown). For the endpoint of iron deficiency anemia 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*, hospitalization for CHF and hypertension for mITT are described below in Table 10.

Table 10. On-treatment Adjudicated Renal Events, Hospitalization 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%)
Hospitalization for CHF	28 (0.3%)	38 (0.5%)	35 (0.4%)
Hospitalization 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)
Hospitalization for CHF	0.77 (0.47, 1.27)	0.70 (0.43, 1.13)	1.12 (0.71, 1.77)
Hospitalization 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 predefined rises in creatinine levels (verified serum creatinine of ≥2.0 mg/dL (177 μmol/L) and an increase of ≥0.7 mg/mL (62 μmol/L)), or hospitalization for acute renal failure (defined as a doubling in serum creatinine, or confirmation of hyperkalemia with ≥50% elevation in serum creatinine), or the initiation of hemodialysis 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 hospitalization for congestive heart failure, and a significantly lower incidence of hospitalization 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.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of celecoxib has been evaluated in approximately 1500 individuals. When given under fasting conditions celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Oral bioavailability from capsules is about 99% relative to administration in suspension (optimally available oral dosage form). 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.

Distribution

Plasma protein binding, which is concentration independent, is about 97% at therapeutic plasma concentrations and celecoxib is not preferentially bound to erythrocytes in the blood.

Metabolism

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been identified in human plasma: a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*3 polymorphism.

In a pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP2C9*1/*1, CYP2C9*1/*3, or CYP2C9*3/*3, the median C_{max} and AUC_{0-24} of celecoxib on day 7 were approximately 4-fold and 7-fold, respectively, in subjects genotyped as CYP2C9*3/*3 compared to other genotypes. In three separate single dose studies, involving a total of 5 subjects genotyped as CYP2C9*3/*3, single-dose AUC_{0-24} increased by approximately 3-fold compared to normal metabolizers. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3%-1.0% among different ethnic groups.

Patients who are known, or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose (see Sections 4.2 Posology and method of administration and 4.5 Interaction with other medicinal products and other forms of interaction).

Excretion

Elimination of celecoxib is mostly by hepatic metabolism with less than 1% of the dose excreted unchanged in urine. After multiple dosing, elimination half-life is 8 to 12 hours and the rate of clearance is about 500 mL/min. With multiple dosing steady-state plasma concentrations are reached before Day 5. The intersubject variability on the main pharmacokinetic parameters (AUC, C_{max}, elimination half-life) is about 30%. The mean steady-state volume of distribution is about 500 L/70 kg in young healthy adults indicating

wide distribution of celecoxib into the tissues. Preclinical studies indicate that the drug crosses the blood/brain barrier.

Food Effects

Dosing with food (high fat meal) delays absorption of celecoxib resulting in a T_{max} of about 4 hours and increases bioavailability by about 20% (see Section 4.2 Posology and method of administration).

Special Populations

Elderly

In the population >65 years, there is a one and a half to two-fold increase in mean C_{max} and AUC for celecoxib. This is a predominantly weight-related rather than age-related change, celecoxib levels being higher in lower weight individuals and consequently higher in the elderly population who are generally of lower mean weight than the younger population. Therefore, elderly females tend to have higher drug plasma concentrations than elderly males. No dosage adjustment is generally necessary. However, for elderly patients with a lower than average body weight (<50 kg), initiate therapy at the lowest recommended dose.

Race

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

Hepatic impairment

Plasma concentrations of celecoxib in patients with mild hepatic impairment (Child-Pugh Class A) are not significantly different from those of age and sex matched controls. In patients with moderate hepatic impairment (Child-Pugh Class B) celecoxib plasma concentrations are about twice those of matched controls (see Section 4.2 Posology and method of administration).

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 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. 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.

Renal effects

The relative roles of COX-1 and COX-2 in renal physiology are not completely understood. Celecoxib reduces the urinary excretion of PGE_2 and 6-keto-$PGF_{1\propto}$ (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. Specific studies have shown celecoxib produces no decreases in GFR in the elderly or those with chronic renal insufficiency. These studies have also shown transient reductions in fractional excretion of sodium. In studies in patients with arthritis, a comparable incidence of peripheral edema has been observed to that seen with non-specific COX-inhibitors (which also possess COX-2 inhibitory activity). This was most evident in patients receiving concomitant diuretic therapy. However, increased incidences of hypertension and cardiac failure have not been observed and the peripheral edema has been mild and self-limiting.

5.3 Preclinical safety data

Non-clinical safety data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, mutagenicity or carcinogenicity.

Celecoxib at oral doses $\geq$150 mg/kg/day (approximately 2-fold human exposure at 200 mg twice daily as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses $\geq$30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg twice daily) throughout organogenesis. These effects are expected following inhibition of prostaglandin synthesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses, and reduced embryo/fetal survival.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules (200 mg and 400 mg) contain lactose monohydrate, sodium lauryl sulfate, polyvidone, croscarmellose sodium, and magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf-life

Please see details on carton.

6.4 Special precautions for storage

Store at or below 30°C.

7. MARKETING AUTHORIZATION HOLDER

Pfizer Parke Davis (Thailand) Limited

Warnings (based on the Ministry of Public Health Announcement)

1. Is contraindicated in patients who are hypersensitive to this drug, in pregnant and lactating women.
2. Is contraindicated in patients who have coronary artery surgery in the immediately post-operative period.
3. Is contraindicated in patients with cardiovascular or cerebrovascular diseases.
4. If there is erythema multiforme or flu-like symptom after use, stop using this drug and consult the physician immediately.
5. Is contraindicated in patients who have ever been hypersensitive to this drug and patients with history of sulfonamide hypersensitivity.
6. If the following symptoms occur during using this drug e.g., fever, erythema multiforme, vesicle, skin lesions and other lesions appear in the mucous membranes (such as in the mouth cavity, throat, nasal cavity, sexual organs) and conjunctivitis, stop using this drug and consult the physician immediately as this may be Stevens-Johnson syndrome.
7. Is contraindicated in patients who have had myocardial infarction or congestive heart failure (NYHA II-IV).
8. Is contraindicated in patients who have had coronary heart disease (stenosed or occluded) or paresis, paralysis due to cerebrovascular accident.
9. Use with caution in patients with risk factors for developing coronary heart disease, e.g., hypertension, hyperlipidemia, diabetes, smoking, elderly, etc.

10. Use with caution in patients with hepatic and renal disorders.

คำเตือน (ตามประกาศกระทรวงสาธารณสุข)

1. ห้ามใช้ในผู้ที่แพ้ยานี้ สตรีมีครรภ์และสตรีระยะให้นมบุตร
2. ห้ามใช้ในผู้ที่ได้รับการผ่าตัดหลอดเลือดหัวใจในระยะหลังผ่าตัดใหม่ๆ (immediately postoperative period)
3. ห้ามใช้ยานี้ในผู้ป่วยโรคเกี่ยวกับหลอดเลือดหัวใจ หรือหลอดเลือดสมอง
4. หากใช้ยานี้แล้วมีอาการผื่นแดง หรือมีอาการคล้ายเป็นหวัด ให้หยุดยาและรีบปรึกษาแพทย์ทันที
5. ห้ามใช้ในผู้ที่เคยแพ้ยานี้และผู้ที่มีประวัติแพ้ยาในกลุ่ม sulfonamide
6. เมื่อใช้ยานี้หากมีอาการดังต่อไปนี้ เช่น ไข้ ผื่นแดง ตุ่มน้ำพอง มีการหลุดลอกของผิวหนัง และบริเวณเยื่อบุต่างๆ เช่น ในช่องปาก ลำคอ จมูก อวัยวะสืบพันธุ์ และเยื่อบุตาอักเสบ ให้หยุดยาและปรึกษาแพทย์เพราะอาจเป็น Stevens-Johnson syndrome
7. ห้ามใช้ยานี้ในผู้ป่วยภาวะกล้ามเนื้อหัวใจตาย หรือผู้ป่วยที่มีภาวะหัวใจล้มเหลวเลือดคั่ง (congestive heart failure NYHA II-IV)
8. ห้ามใช้ยานี้ในผู้ป่วยที่เคยเป็นโรคหลอดเลือดหัวใจตีบตัน หรือเคยมีภาวะอัมพฤกษ์ อัมพาตอันเกิดจากโรคหลอดเลือดสมอง
9. ระมัดระวังการใช้ยานี้ในผู้ที่มีปัจจัยเสี่ยงต่อการเกิดโรคหลอดเลือดหัวใจ เช่น ความดันโลหิตสูง ระดับไขมันในเลือดสูง โรคเบาหวาน ผู้สูบบุหรี่ ผู้สูงอายุ เป็นต้น
10. ระมัดระวังการใช้ยานี้ในผู้ป่วยที่มีความผิดปกติของตับและไต