Celebrex®
Celecoxib
CDS
AfME Markets using same as LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

WARNING

Cardiovascular events: NSAIDs are associated with an increased risk of adverse cardiovascular thrombotic events, including fatal MI and stroke. Risk may be increased with duration cf use or pre-existing cardiovascular risk factors or disease. Carefully evaluate individual cardiovascular risk profiles prior to prescribing. Use caution with fluid retention. Avoid use in heart failure. Concurrent administration of ibuprofen, and potentially other nonselective NSAIDs, may interfere with aspirin's cardioprotective effect. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of cardiovascular events; alternate therapies should be considered for patients at high risk.

Gastrointestinal events: NSAIDs may increase risk of gastrointestinal irritation, inflammation, ulceration, bleeding, and perforation. These events can be fatal and may occur at any time during therapy and without warning. Use caution with a history of GI disease (bleeding or ulcers), concurrent therapy with aspirin, anticoagulants and/or corticosteroids, smoking, use of ethanol, the elderly or debilitated patients. Use the lowest effective dose for the shortest duration of time, consistent with individual patient goals, to reduce risk of GI adverse events; alternate therapies should be considered for patients at high risk. When used concomitantly with aspirin, a substantial increase in the risk of gastrointestinal complications (eg, ulcer) occurs; concomitant gastroprotective therapy (eg, proton pump inhibitors) is recommended

Coronary artery bypass graft surgery: Use is contraindicated for treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. Risk of MI and stroke may be increased with use following CABG surgery.

1. NAME OF THE MEDICINAL PRODUCT

CELEBREX

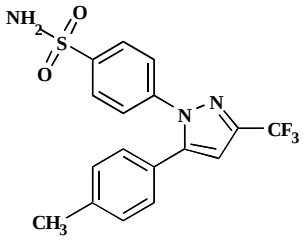
2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg capsule contains 100 mg celecoxib.

Each 200 mg capsule contains 200 mg celecoxib.

Each 400 mg capsule contains 400 mg celecoxib.

For the full list of excipients, see section 6.1.



3. PHARMACEUTICAL FORM

Hard capsules for oral use.

100 mg Capsules: Opaque, white capsules with two blue bands marked 7767 and 100.

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200 mg Capsules: Opaque, white capsules with two gold bands marked 7767 and 200.

400 mg Capsules: Opaque, white capsules with two green bands marked 7767 and 400

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of osteoarthritis and rheumatoid arthritis

Relief of signs and symptoms of juvenile idiopathic arthritis in patients 2 years and older with body weight equal to or above 10 kg.
Relief of signs and symptoms of ankylosing spondylitis
Management of acute pain
Treatment ***of primary*** *dysmenorrheal*

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 risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.

Adults

Symptomatic Treatment of **Osteoarthritis**: The recommended dose of celecoxib is 200 mg administered as a single dose or as 100 mg twice per day.
Symptomatic Treatment of **Rheumatoid Arthritis**: The recommended dose of celecoxib is 100 or 200 mg twice per day.
Ankylosing Spondylitis (AS): The recommended dose of celecoxib is 200 mg administered as a single dose or as 100 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.
Management of Acute Pain: The recommended dose 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, as needed.
Treatment of Primary Dysmenorrhea: The recommended

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- Patients with congestive heart failure (NYHA II-IV);

- Patients with established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease;

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dose 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, as needed.

Elderly

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

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Peadiatric population

Juvenile Idiopathic Arthritis:

Pediatric Patients (2 years and older)	Dose
≥10 kg to ≤25 kg	50 mg capsule twice daily
>25 kg	100 mg capsule twice daily

Celecoxib has been studied in juvenile idiopathic arthritis patients 2 to 17 years of age. Safety and efficacy of celecoxib in children have not been studied beyond 6 months duration or in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. (See Section 05.1)

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 04.5 and **Error! Reference source not found.**5.2)

Hepatic Impairment

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

The daily recommended dose of CELEBREX capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by 50%. The use of CELEBREX in patients with severe hepatic impairment is not recommended .

Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. (See Section 04.4; *Hepatic Effects*.)

Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment.

No information is available from controlled clinical studies regarding the use of CELEBREX in patients with advanced renal disease. Therefore, treatment with CELEBREX is not recommended in these patients with advanced renal disease. If CELEBREX therapy must be initiated, close monitoring of the patients renal function is advisable. (See Section 04.4; *Renal Effects*.)

Coadministration with Fluconazole

Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole, a CYP2C9 inhibitor. Caution is advised when coadministering celecoxib with other CYP2C9 inhibitors. (See Section 04.5)

Method of Administration

For patients who have difficulty swallowing capsules, the contents of a celecoxib capsule can be added to applesauce, rice gruel, yogurt or mashed banana. To do so, the entire capsule contents must be carefully emptied onto a level teaspoon of cool or room temperature applesauce, rice gruel, yogurt or mashed banana and should be ingested immediately with water. The sprinkled capsule contents on applesauce, rice gruel or yogurt are stable for up to 6 hours under

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refrigerated conditions (2-8° C/ 35-45° F). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions and should be ingested immediately.

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 (aspirin) or nonsteroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
- Patients with congestive heart failure (NYHA II-IV);
- Patients with established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease;
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. (See Section ~~04.4~~).

4.4 Special warnings and precautions for use

Cardiovascular Effects

Cardiovascular Thrombotic Events: Celecoxib may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with dose, duration of use, and baseline cardiovascular risk factors. Patients with known cardiovascular disease may be at greater risk. To minimize 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. Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur. (See Section ~~05.1~~.)

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. (See Section ~~04.3~~.)

Celecoxib is not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of the lack of effect on platelet function. Because celecoxib does not inhibit platelet aggregation, antiplatelet therapies (e.g., acetylsalicylic acid) 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 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.

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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 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 gastrointestinal (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 cardiovascular disease, patients using concomitant aspirin, or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions. Most spontaneous reports of fatal gastrointestinal 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 04.2.)

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to celecoxib. (See Section 04.3.)

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 the lowest recommended dose. (See Section 04.2.)

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

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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 Warfarin or Similar Agents

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, anticoagulant activity should be monitored after initiating treatment with celecoxib or changing the dose.

Systemic Onset Juvenile Idiopathic Arthritis

NSAIDs including celecoxib should be used only with caution in patients with systemic onset JIA, due to the risk of disseminated intravascular coagulation. Patients receiving celecoxib who have systemic onset JIA should be monitored for the development of abnormal coagulation tests.

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.

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 0~~4.2~~ and **Error! Reference source not found.**~~5.2~~)

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 0~~4.4~~).

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.

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Aspirin: Celecoxib does not interfere with the anti-platelet effect of low-dose aspirin (see Section **0~~4.4~~**). Because of its lack of platelet effects, celecoxib is not a substitute for aspirin in the prophylactic treatment of cardiovascular disease.

ACE-inhibitors and Angiotensin II antagonists: Inhibition of prostaglandins may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors and/or angiotensin II antagonists. This interaction should be given consideration in patients taking celecoxib

concomitantly with ACE-inhibitors and/or angiotensin II antagonists. However, a clinical study with lisinopril showed no significant pharmacodynamic interaction with respect to blood pressure.

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

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 CYPP450 2C9 by fluconazole. Celecoxib should be introduced at the lowest recommended dose in patients receiving the CYP2C9 inhibitor fluconazole (see Section 04.2). Ketoconazole, a CYP3A4 inhibitor, showed no clinically relevant inhibition in the metabolism of celecoxib.

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.

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, methotrexate, glibenclamide (glyburide), phenytoin, or tolbutamide.

Co-administration of NSAIDs and ciclosporin or tacrolimus have been suggested to increase the nephrotoxic effect of ciclosporin and tacrolimus. Renal function should be monitored when celecoxib and any of these drugs are combined.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category C

Celecoxib has shown to have reproductive toxicity in rats (See Section 05.3) when given in doses 6 times the human dose. There are no adequate and well controlled studies in pregnant women. Celecoxib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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.

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.

Breastfeeding

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.

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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.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking celecoxib should refrain from driving or operating machinery.

4.8 4.8 **Undesirable effects**

Clinical Trials

1) The following adverse reactions in **Error! Reference source not found.**~~Table 1~~ were reported at incidence rates greater than 0.01% *and* greater than those reported for placebo during 12 placebo- and/or active-controlled clinical trials of duration up to 12 weeks at daily doses from 100 mg up to 800 mg in adults. Adverse reactions are listed by system organ class and ranked by frequency. Frequencies are based on a more recent pooling of trials representing exposure in more than 38,000 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%).

Infections and infestations	
Common[17]	Bronchitis, sinusitis, upper respiratory tract infection, urinary tract infection
Uncommon	Pharyngitis, rhinitis
Uncommon	Anemia
Rare	Thrombocytopenia
Immune system disorders	
Uncommon[17]	Allergy aggravated (hypersensitivity)
Common[17]	Insomnia
Uncommon	Anxiety

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Rare	Confusion (confusional state)
Nervous system disorders	
Common[17]	Dizziness
Uncommon	Hypertonia, somnolence
Eye disorders	
Uncommon	Blurred vision
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Palpitation
Rare	Congestive heart failure, arrhythmia, tachycardia
Vascular disorders	
Common	Hypertension (including aggravated hypertension)
Rare	Flushing
Common[17]	Coughing (cough)
Gastrointestinal disorders	
Common[17]	Vomiting, abdominal pain, diarrhea, dyspepsia, flatulence
Uncommon	Gastric ulcer, tooth disorder
Rare	Duodenal ulcer, esophageal ulceration (esophageal ulcer)
Very rare	Intestinal perforation, pancreatitis
Hepatobiliary disorders	
Uncommon	Elevation of hepatic enzymes (hepatic enzyme increased, includes alanine aminotransferase increased and aspartate aminotransferase increased)
Common[17]	Pruritus (includes pruritus generalized), rash
Uncommon	Urticaria, ecchymosis
Rare	Angioedema, alopecia
Very rare	Bullous eruption (dermatitis bullous)
General disorders and administration site conditions	
Common[17]	Peripheral edema
Uncommon	Face edema, flu-like symptoms (influenza-like illness)
Injury, poisoning and procedural conditions	
Uncommon[17]	Accidental injury (injury)

Pediatric Population

Generally, the **adverse reactions** observed in the pivotal pediatric study (

see Section 0~~5.1~~; Juvenile Idiopathic **Arthritis** [JIA]) were similar to those observed in adult arthritis studies (see **Error! Reference source not found.**~~Table 1~~). Additionally, the following adverse reactions are not listed in Table 1 and were attributed by the investigator in the pivotal pediatric study as possibly related to treatment with celecoxib: headache (11.3%, very common), exacerbation of hematuria (0.6%, uncommon) and asthma [1 patient who had controlled asthma at baseline] (0.6%, uncommon). Compared with naproxen, celecoxib at doses of 3 and 6 mg/kg twice

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daily had no observable deleterious effect on growth and development during the course of the 12-week double-blind study.

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2) The following additional adverse reactions* in **Error! Reference source not found.**~~Table 2~~ were reported at incidence rates greater than placebo in long-term polyp prevention studies of duration up to 3 years at daily doses from 400 mg up to 800 mg (see Section 0~~5.1~~; *Cardiovascular Safety – Long-Term Studies Involving Patients With Sporadic Adenomatous Polyps*). Adverse reactions are listed by system organ class and ranked by frequency. Frequencies are defined as: very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%).

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

**Fungal infections were primarily non-systemic.

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 more than 38,000 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%).

Immune system disorders: Very rare: anaphylaxis (anaphylactic reaction)

Psychiatric disorders: Rare: hallucinations

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

Eye disorders: Uncommon: conjunctivitis

Vascular disorders: Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders: Rare: pulmonary embolism

Gastrointestinal *disorders*: Rare: gastrointestinal hemorrhage

Hepato-biliary disorders: Rare: hepatitis; Very rare: liver failure, fulminant hepatitis, liver necrosis (See Section 0~~4.4~~), cholestasis, cholestatic hepatitis, jaundice

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

Renal and urinary disorders: Rare: acute renal failure (See Section 0~~4.4~~), hyponatremia; Very rare: interstitial nephritis, nephrotic syndrome, minimal change disease

Reproductive system and breast disorders: Rare: menstrual disorder; Not known†: female fertility decreased (See Section 0~~4.6~~)

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

ihave 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.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Pharmacotherapeutic group: Coxibs, ATC code: M01AH

Mechanism of action

The mechanism of action of celecoxib is via inhibition of prostaglandin synthesis primarily by inhibition of cyclooxygenase 2 (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.

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In *vivo* and *ex vivo* studies show that celecoxib has a very low affinity for the constitutively expressed cyclooxygenase 1 enzyme (COX-1). 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.

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Clinical Studies

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.

Food Effects

Dosing with food (high fat meal) delays absorption of celecoxib resulting in a Tmax of about 4 hours and increases bioavailability by about 20%. (See Section 04.2).

In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in C_{max}, T_{max} or $T_{1/2}$ after administration of capsule contents on applesauce.

Biotransformation

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 i.e., 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 Cmax 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 04.2 and 04.5)

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Elimination

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 8-12 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, Cmax, elimination half-life) is about 30%. The mean steady state volume of distribution is about 500 L/70kg in young healthy adults indicating wide distribution of celecoxib into the tissues. Preclinical studies indicate that the drug crosses the blood/brain barrier.

Special Populations

Elderly

In the population >65 years there is a one and a half to two-fold increase in mean Cmax 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.

Children

The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 juvenile idiopathic arthritis (JIA) patients 2 years to 17 years of age weighing ≥10 kg with oligoarticular, oligoarticular extended, or polyarticular rheumatoid factor positive or negative) course JIA and in patients with systemic onset JIA (with currently inactive systemic features). Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient.

Twice-daily administration of 50 mg capsules to JIA patients weighing ≥10 to ≤25 kg and twice daily administration of 100 mg capsules to JIA patients weighing >25 kg should achieve plasma concentrations similar to those observed in the clinical trial that demonstrated the non-inferiority of celecoxib to naproxen 7.5 mg/kg twice daily (see Section 04.2). Celecoxib has not been studied in JIA patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks.

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

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this finding is unknown and therefore treatment should be initiated at the lowest recommended dose.

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. For dosing in patients with hepatic impairment 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>65mL/min/1.73m^2) and in patients with chronic stable renal insufficiency (GFR 35-60mL/min/1.73m^2) celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance. Severe renal insufficiency would not be expected to alter clearance of celecoxib since the main route of elimination is via hepatic metabolism to inactive metabolites.

Renal Effects: At the present time the relative roles of COX-1 and COX-2 in renal physiology is 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

Commented [TU131]: INSERT:5.2 Pharmacokinetic properties

Preclinical safety data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, mutagenicity or carcinogenicity. Conventional embryo-fetal toxicity studies resulted in dose dependent occurrences of diaphragmatic hernia in rat fetuses and cardiovascular malformations in rabbit fetuses. In both species, these effects were observed at systemic exposure levels 5-6 times those seen at the highest recommended clinical dose (400 mg daily).

In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses, and reduced embryo/fetal survival. These effects, which were seen at oral dosages of approximately 6-fold human systemic exposure, are expected following inhibition of prostaglandin synthesis.

Animal Toxicology

An increase in the incidence of background findings of spermatocele with or without secondary changes such as epididymal hypospermia as well as minimal to slight dilation of the seminiferous tubules was seen in the juvenile rat. These reproductive findings while apparently treatment-related did not increase in incidence or severity with dose and may indicate an exacerbation of a spontaneous condition. Similar reproductive

findings were not observed in studies of juvenile or adult dogs or in adult rats treated with celecoxib. The clinical significance of this observation is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose monohydrate, sodium lauryl sulphate, polyvidone, croscarmellose sodium, and magnesium stearate.

Capsule shells
Gelatin, titanium dioxide; ink contains ferric oxide E172 (200 mg capsule) or indigotine E132 (100 mg capsule).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Keep out of the sight and reach of children.
Do not use Celebrex after the expiry date which is stated on the carton / Blister / Bottle / Vial label after EXP:. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.4 Special precautions for storage

Store below 30ºC. The sprinkled capsule contents on applesauce, rice gruel or yogurt are stable for up to 6 hours under refrigerated conditions (2-8° C/ 35-45° F). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions.

6.5 Nature and contents of container

100 mg capsules
Blister pack containing 20 capsules

200 mg capsules
Blister pack containing 10, 20
Blister pack containing 10

400 mg capsules
Blister pack containing 10 capsules

6.6 Special precautions for disposal

Not relevant.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER

Pfizer Saudi Limited for Celebrex 100 and 200 mg Capsules

Pfizer Inc. – USA for Celebrex 400 mg Capsules

MANUFACTURED BY

Pfizer Pharmaceutical LLC, Vega Baja, PR – USA

8. PRESCRIPTION STATUS

Not relevant.

9. DATE OF REVISION OF THE TEXT

- Reference Market November 2013
- SFDA 2015

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Commented [TU136]: REPLACE WITH:8. MARKETING AUTHORISATION NUMBER(S)

Commented [TU137]: REPLACE WITH:9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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To report any side effect(s):

- ***Saudi Arabia:***

- ***Other GCC States:***

- Please contact the relevant competent authority**.**

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers

Union of Arabic Pharmacists