FRONT

TN4643

CELMAC

Celecoxib Capsules

COMPOSITION

CELMAC 200 (Celecoxib Capsules 200 mg)

Each hard gelatin capsule contains:

Celecoxib USP	200 mg
Tartrazine (E 102), Sunset Yellow FCF (E 110)	
Excipients	q.s.
Contains lactose	

CELMAC 400 (Celecoxib Capsules 400 mg)

Each hard gelatin capsule contains:

Celecoxib USP	400 mg
Tartrazine (E 102), Sunset Yellow FCF (E 110)	
Excipients	q.s.
Contains lactose	

DOSAGE FORM:

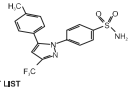
Hard Gelatin Capsule

Category of Distribution: POM

DESCRIPTION:

It is chemically 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

Its empirical formula is $C_{17}H_{14}N_3O_2S$ with a molecular weight of 381.4. Celecoxib has the following structure:



EXCIPIENT LIST

CELMAC 200 (Celecoxib Capsules 200 mg)

Lactose Monohydrate, Sodium Lauryl Sulphate, Croscarmellose

Sodium, Povidone, Purified Water, Magnesium Stearate and E.H.G. Capsule size "1"Violet / White.

CELMAC 400 (Celecoxib Capsules 400 mg)

Lactose Monohydrate, Sodium Lauryl Sulphate, Croscarmellose

Sodium, Povidone, Purified Water, Magnesium Stearate and E.H.G. Capsule size "00" Yellow/White.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:

CELECOXIB is indicated:

1) For relief of the signs and symptoms of osteoarthritis,

2) For relief of the signs and symptoms of rheumatoid arthritis in adults.

3) For the management of acute pain in adults.

4) For the treatment of primary dysmenorrhea.

NOTORIOUS EFFECT OF EXCIPIENTS

Lactose Monohydrate: Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase. This results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence. Therefore, lactose intolerant people should not take this medicine.

Sodium Lauryl Sulphate: It is widely used in cosmetics and oral and topical pharmaceutical formulations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop.

DOSAGE AND METHOD OF ADMINISTRATION

For osteoarthritis and rheumatoid arthritis, the lowest dose of celecoxib should be sought for each patient. These doses can be given without regard to timing of meals.

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200 mg per day administered as a single dose or as 100 mg twice per day.

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100 to 200 mg twice per day.

Management of Acute Pain and 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 as needed.

Familial adenomatous polyposis (FAP): Usual medical care for FAP patients should be continued while on celecoxib. To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg twice per day to be taken with food.

Special Populations

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Hepatic insufficiency:

The daily recommended dose of Celecoxib capsules in patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced by approximately 50%.

Geriatric:

At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib Cmax and AUC are higher than those for elderly males, but these increases are predominantly due to lower body weight in elderly females. Dose adjustment in the elderly is not generally necessary. However, for patients of less than 50 kg in body weight, initiate therapy at the lowest recommended dose.

Race:

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

Renal Insufficiency:

In a one of the published cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Patients with severe renal insufficiency have not been studied. Similar to other NSAIDs, CELECOXIB is not recommended in patients with severe renal insufficiency.

CONTRAINDICATIONS

Celecoxib is contraindicated in patients with known hypersensitivity to celecoxib.

Celecoxib should not be given to patients who have demonstrated allergic-type reactions to sulfonamides.

Celecoxib should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients

SPECIAL WARNINGS & PRECAUTIONS FOR USE

Gastrointestinal (GI) Effects–Risk of GI Ulceration, Bleeding, and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and

perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

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

Advanced Renal Disease

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

Pregnancy

In late pregnancy celecoxib should be avoided because it may cause premature closure of the ductus arteriosus,

Familial Adenomatous Polyposis (FAP): Treatment with celecoxib in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of celecoxib. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

Precautions:

General: Celecoxib cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy taperedslowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of Celecoxib in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed non-infectious, painful conditions.

Hepatic Effects: Borderline elevations of one or more liver

associated enzymes may occur in up to15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including Celecoxib.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver testhas occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with Celecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), celecoxib should be discontinued.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have acompensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs.

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

Caution is also recommended in patients with pre-existing kidney disease.

Hematological Effects: Anemia is sometimes seen in patients receiving celecoxib.Patients on long-term treatment with celecoxib should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. Celecoxib does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages.

Fluid Retention, Edema, and Hypertension: Fluid retention and edema have been observed in some patients taking celecoxib. As with other NSAIDs, celecoxib should be used with caution in patients with fluid retention, hypertension, or heart failure.

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

Laboratory Tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This laboratory abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

General: Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver.

Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P4502D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect ofAngiotensin Converting Enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking Celecoxib concomitantly with ACE-inhibitors.

Furosemide: Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic

effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Aspirin: Celecoxib can be used with low-dose aspirin, However, concomitant administration ofaspirin with Celecoxib increases the rate of GI ulceration or other complications, compared to use of celecoxib alone.

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

Fluconazole: Concomitant administration of fluconazole at 200 mg QD resulted in a two-fold increasein celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism viaP450 2C9 by fluconazole. Celecoxib should be introduced atthe lowest recommended dose in patients receiving fluconazole.

Lithium: Patients on lithium treatment should be closelymonitored when celecoxib is introduced or withdrawn.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, celecoxib did not have a significant effect on the pharmacokinetics of methotrexate.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days, aftorinitiating or changing celecoxib therapy in patients receiving warfarin or similar agents, since thesepatients are at an increased risk of bleeding complications. In post-marketing experience, serious bleeding events,some of which were fatal, have been reported, predominantly in the elderly, in association withincreases in prothrombin time in patients receiving Celecoxib concurrently with warfarin.

PREGNANCY AND LACTATION

Pregnancy

Teratogenic effects: Pregnancy Category C.

There are no studies in pregnant women. Celecoxib should be used duringpregnancy only if the potential benefit justifies the potential risk to the fetus.

No studies have been conducted to evaluate the effect ofcelecoxib on the closure of the ductus arteriosus in humans. Therefore, use of celecoxib during thethird trimester of pregnancy should be avoided.

Nursing mothers:

Celecoxib is excreted in the milk of lactating rats at concentrations similar to thosein plasma. Limited data from one subject indicate that celecoxib is also excreted in human milk.

Because many drugs are excreted in human milk and because of the potential for serious adversereactions in nursing infants from celecoxib, a decision should be made whether to discontinuenursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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.

UNDESIRABLE EFFECTS

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

Adverse events from CELECOXIB premarketing controlled arthritis trials:

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

Table 6
Adverse Event Occurring in ≥2% of Patients Premarketing Controlled Arthritis Trials

	Celecoxib (100-200 mg BID or 200 mg QD) (n=4146)	Placebo (n=1864)
Gastrointestinal		
Abdominal pain	4.1%	2.8%
Diarrhea	5..6%	3.8%
Dyspepsia	8.6%	6.2%
Flatulence	2.2%	1.0%
Nausea	3.5%	4.2%
Body as a whole		
Back Pain	2.8%	3.6%
Peripheral edema	2.1%	1.1%
	2.9%	2.3%
Central and peripheral nervous system		
Dizziness	2.0%	1.7%
Headache	15.8%	20.2%
Psychiatric		
Insomnia	2.3%	2.3%
Respiratory		
Pharyngitis	2.3%	1.1%
Rhinitis	2.0%	1.3%
Sinusitis	5.0%	4.3%
Upper resoratory tract infection	8.1%	6.7%
Skin		
Rash	2.2%	2.1%

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

The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.

Celecoxib

(100-200 mg BID or 200 mg QD)

Gastrointestinal: Constipation, diverticulitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, hiatal hernia, melena, dry mouth, stomatitis, tenesmus, tooth disorder,vomiting

Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction

General: Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, facedema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

Resistance mechanism disorders: Herpes simplex, herpes zoster, infection bacterial, infection fungal,infection soft tissue, infection viral, monilasis, moniliasis genital, otitis media

Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia,neuropathy, paresthesia, vertigo

Female reproductive: Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder,vaginal hemorrhage, vaginitis

Male reproductive: Prostatic disorder

Hearing and vestibular: Deafness, ear abnormality, earache, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary system: Hepatic function abnormal, SGOT increased, SGPT increased

Metabolic and nutritional: BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia,hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weightincrease

Musculoskeletal: Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis,tendinitis

Platelets (bleeding or clotting): Ecchymosis, epistaxis, thrombocythemia

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

Hemic: Anemia

Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis,pneumonia

Skin and appendages: Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rasherythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria

Application site disorders: Cellulitis, dermatitis contact, injection site reaction, skin nodule

Special senses: Taste perversion

Urinary system: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus, urinaryincontinence, urinary tract infection

Vision: Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Other serious adverse reactions which occur rarely (estimated <0.1%), regardless of causality: Thefollowing serious adverse events have occurred rarely in patients taking celecoxib. Cases reported onlyin the post-marketing experience are indicated in italics.

Cardiovascular: Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism,cerebrovascular accident, peripheral gangrene, thrombophlebitis, vasculitis

Gastrointestinal: Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis withbleeding, esophageal perforation, pancreatitis, ileus

Liver and biliary system: Cholelithiasis, hepatitis, jaundice, liver failure

Hemic and lymphatic: Thrombocytopenia, agranulocytosis, aplastic anemia, pancytopenia,leukopenia

Metabolic: Hypoglycemia, hyponatremia

Nervous system: Aseptic meningitis, ataxia, suicide, fatal intracranial hemorrhage.

Renal: Acute renal failure, interstitial nephritis

Skin: Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermalnecrolysis

General: Sepsis, sudden death, anaphylactoid reaction, angioedema

OVERDOSAGE

No overdoses of celecoxib were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity. Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare.

Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. No information is available regarding the removal of celecoxib by hemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic drugs, NSAIDs, Coxibs, ATC code: M01AH01.

Mechanism of Action:

Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans. Celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, celecoxib reduced the incidence and multiplicity of tumors.

Pharmacokinetics:

Absorption

Peak plasma levels of celecoxib occur approximately 3 hrs. after an oral dose. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200 mg BID; at higher doses there are less than proportional increases in Cmax and AUC (see Food Effects). Absolute bioavailability studies have not been conducted. With multiple dosing, steady state conditions are reached on or before day 5.

The pharmacokinetic parameters of celecoxib in a group of healthy subjects are shown in

Table 1
Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Subjects[1]

Means (% CV) PK Parameter Values					
C_{max}, ng/mL	T_{max}, hr	Effective $t_{1/2}$, hr	V_z/F, L	CL/F, L/hr	
750 (38)	2.8 (37)	11.2 (31)	429 (34)	27.7 (28)	

[1]Subjects under fasting conditions (n=36, 19-52 yrs.)

Food Effects

When Celecoxib capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in Cmax and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Co-administration of celecoxib with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC. Celecoxib, at doses up to 200 mg BID can be administered without regard to timing of meals. Higher doses (400 mg BID) should be administered with food to improve absorption.

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. In vitro studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α1-acid glycoprotein.

The apparent volume of distribution at steady state (Vss/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors. Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Excretion

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min

PRECLINICAL SAFETY DATA

Date	: 24-08-2022
Artist	: SPC
Product	: CELMAC CAPS
Actual Size	: 560 x 210 mm
Ref artwork	: ----
Colour	: ■ BLACK
Country	: Tanzania

Pharma Code : 100000 Standard

Direction for Travel

Front

Celecoxib was not carcinogenic in rats given oral doses up to 200 mg/kg for males and 10 mg/kg for females (approximately 2- to 4-fold the human exposure as measured by the AUC0-24 at 200 mg BID) or in mice given oral doses up to 25 mg/kg for males and 50 mg/kg for females (approximately equal to human exposure as measured by the AUC0-24 at 200 mg BID) for two years.

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow.

Celecoxib did not impair male and female fertility in rats at oral doses up to 600 mg/kg/day (approximately 11-fold human exposure at 200 mg BID based on the AUC0-24).

PHARMACEUTICAL PARTICULARS:
INCOMPATIBILITY
Not applicable.

Special Precautions for Storage: Keep out of reach of children.

STORAGE CONDITION
Store below 30 C. Protect from light

NATURE AND CONTENTS OF CONTAINER
Blister pack of 10 capsules

VERSION No. 01

LAST REVISION DATE:

May18, 2021

ajanta pharma limited
Ajanta House, Charkop
Kandivli (W), Mumbai – 400 067
India.

Celecoxib Capsules

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others.It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet,please tell your doctor or pharmacist

Distribution Category: Prescription Only Medicine or POM

In this leaflet:

1. What Celecoxib Capsules are and what they are used for
Celecoxib belongs to a group of medicines called nonsteroidal anti-inflammatory drugs (NSAID), and specifically a sub-group known as cyclooxygenase-2 (COX-2) inhibitors. Your body makes prostaglandins that may cause pain and inflammation. In conditions such as rheumatoid arthritis and osteoarthritis your body makes more of these. Celecoxib acts by reducing the production of prostaglandins, thereby reducing the pain and inflammation.

Celecoxib is used in adults for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

Celecoxib is used in menstrual cramps and other types of short-term pain

You should expect your medicine to start working within hours of taking the first dose, but you may not experience a full effect for several days.

2. Before you take Celecoxib Capsules
You have been prescribed Celecoxib by your doctor. The following information will help you get the best results with Celecoxib. If you have any further questions, please ask your doctor or pharmacist.

Do not take this medicine and tell your doctor if:

- if you are allergic to celecoxib or any of the other ingredients of this medicine
- if you have had an allergic reaction to a group of medicines called "sulfonamides" (e.g. some antibiotics used to treat infections)
- if you currently have an ulcer in your stomach or intestines, or bleeding in your stomach or intestines
  if as a result of taking acetylsalicylic acid or any other anti-inflammatory and pain relieving medicine (NSAID) you have had asthma, nose polyps, severe nose congestion, or an allergic reaction such as an itchy skin rash, swelling of the face, lips, tongue or throat, breathing difficulties or wheezing
- if you are pregnant. If you can become pregnant during ongoing treatment you should discuss methods of contraception with your doctor
- if you are breast-feeding
- if you have severe liver disease
- if you have severe kidney disease
- if you have an inflammatory disease of the intestines such as ulcerative colitis or Crohn's disease
- if you have heart failure, established ischaemic heart disease, or cerebrovascular disease, e.g. you have been diagnosed with a heart attack, stroke, or transient ischaemic attack (temporary reduction of blood flow to the brain; also known as "mini-stroke"), angina, or blockages of blood vessels to the heart or brain
- if you have or have had problems with your blood circulation (peripheral arterial disease) or if you have had surgery on the arteries of your legs

Warnings and Precautions
Talk to your doctor or pharmacist before using Celecoxib Capsules if:

- If you have previously had an ulcer or bleeding in your stomach or intestines. (Do not take Celecoxib if you currently have an ulcer or bleeding in your stomach or intestine)
- If you are taking acetylsalicylic acid (even at low dose for heart protective purposes)
- if you are taking antiplatelet therapies
- if you use medicines to reduce blood clotting (e.g. warfarin/warfarin like anticoagulants or novel oral anti-clotting medicines, e.g. apixaban)
- If you use medicines called corticosteroids (e.g. prednisone)
- if you are using Celecoxib at the same time as other non-acetylsalicylic NSAIDs such as ibuprofen or diclofenac. The use of these medicines together should be avoided
- if you smoke, have diabetes, raised blood pressure or raised cholesterol
- if your heart, liver or kidneys are not working well your doctor may want to keep a regular check on you
- if you have fluid retention (such as swollen ankles and feet)
- if you are dehydrated, for instance due to sickness, diarrhoea or the use of diuretics (used to treat excess fluid in the body)
- if you have had a serious allergic reaction or a serious skin reaction to any medicines
- if you feel ill due to an infection or think you have an infection, as Celecoxib may mask a fever or other signs of infection and inflammation
- if you are over 65 years of age your doctor will want to monitor you regularly
- the consumption of alcohol and NSAIDs may increase the risk of gastrointestinal problems.
- As with other NSAIDs (e.g., ibuprofen or diclofenac) this medicine may lead to an increase in blood pressure, and so your doctor may ask to monitor your blood pressure on a regular basis.
- Some cases of severe liver reactions, including severe liver inflammation, liver damage, liver failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib.
- Of the cases that reported time to onset, most severe liver reactions occurred within one month of start of treatment.
- Celecoxib may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems to become pregnant

Other medicines and Celmac Capsules.
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines,
Dextromethorphan (used to treat coughs)

- ACE inhibitors, angiotensin II antagonists, beta blockers and diuretics (used for high blood pressure and heart failure)
- Fluconazole and rifampicin (used to treat fungal and bacterial infections)
- Warfarin or other warfarin like medicines ("blood-thinning" agents that reduce blood clotting) including newer medicines like apixaban
- Lithium (used to treat some types of depression)
- Other medicines to treat depression, sleep disorders, high blood pressure or an irregular heartbeat
- Neuroleptics (used to treat some mental disorders)
- Methotrexate (used to treat rheumatoid arthritis, psoriasis and leukaemia)
- Carbamazepine (used to treat epilepsy/seizures and some forms of pain or depression)
- Barbiturates (used to treat epilepsy/seizures and some sleep disorders)
- Cyclosporine and tacrolimus (used for immune system suppression e.g, after transplants)

Celecoxib can be taken with low dose acetylsalicylic acid (75 mg or less daily). Ask your doctor for advice before taking both medicines together.

Taking Celmac Capsules with food and drink
Do not drink alcohol while taking **Celmac Capsules.** This is because it may make you feel dizzy or sleepy.

Pregnancy and breast-feeding
Celecoxib must not be used by women who are pregnant or can become pregnant (i.e. women of child bearing potential who are not using adequate contraception) during ongoing treatment. If you become pregnant during treatment with Celecoxib you should discontinue the treatment and contact your doctor for alternative treatment.

Driving and using machines
You should be aware of how you react to Celecoxib before you drive or operate machinery. If you feel dizzy or drowsy after taking Celecoxib, do not drive or operate machinery until these effects wear off.

Important information about some of the ingredients ofCelmac Capsules

Lactose Monohydrate: Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase. This results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence. Therefore, lactose intolerant people should not take this medicine.

Sodium Lauryl Sulphate: It is widely used in cosmetics and oral and topical pharmaceutical formulations. It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. Repeated, prolonged exposure to dilute solutions may cause drying and cracking of the skin; contact dermatitis may develop.'

3. How to take Celmac Capsules
Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. If you think or feel that the effect of Celecoxib is too strong or too weak, talk to your doctor or pharmacist.

Your doctor will tell you what dose you should take. As the risk of side effects associated with heart problems may increase with dose and duration of use, it is important that you use the lowest dose that controls your pain and you should not take Celecoxib for longer than necessary to control symptoms.

Method of administration
Celecoxib is for oral use. The capsules can be taken at any time of the day, with or without food.

However, try to take each dose of Celecoxib at the same time each day.

If you have difficulty swallowing capsules: The entire capsule contents can be sprinkled onto a level teaspoon of semi-solid food (such as cool or room temperature applesauce, rice gruel, yogurt or mashed banana) and swallowed immediately with a drink approximately 240 ml of water.

To open the capsule, hold upright to contain the granules at the bottom then gently squeeze the top and twist to remove, taking care not to spill the contents. Do not chew or crush the granules.

Contact your doctor within two weeks of starting treatment if you do not experience any benefit.

The recommended dose is
For osteoarthritis the recommended dose is 200 mg each day, increased by your doctor to a maximum of 400 mg, if needed.

The dose is usually:

■ One 200 mg capsule once a day;
For rheumatoid arthritis the recommended dose is 200 mg each day, increased by your doctor to a maximum of 400 mg, if needed.

■ One 200 mg capsule once a day;
For ankylosing spondylitis, the recommended dose is 200 mg each day, increased by your doctor to a maximum of 400 mg, if needed,

The dose is usually:

■ One 200 mg capsule once a day;

For Acute Pain and Treatment of Primary Dysmenorrhea (menstrual cramps): 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 as needed.

Kidney or liver problems: make sure your doctor knows if you have liver or kidney problems as you may need a lower dose.
The elderly, especially those with a weight less than 50 kg: If you are over 65 years of age and especially if you weigh less than 50 kg, your doctor may want to monitor you more closely.

You should not take more than 400 mg per day.

Use in children
Celecoxib is for adults only; it is not for use in children.

If you take more Celecoxib than you should
You should not take more capsules than your doctor tells you to. If you take too many capsules contact your doctor, pharmacist or hospital and take your medicine with you.

If you forget to take Celecoxib
If you forget to take a capsule, take it as soon as you remember. Do not take a double dose to make up for a forgotten dose.

If you stop taking Celecoxib
Suddenly stopping your treatment with Celecoxib may lead to your symptoms getting worse. Do not stop taking Celecoxib unless your doctor tells you to. Your doctor may tell you to reduce the dose over a few days before stopping completely.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects listed below were observed in arthritis patients who took Celecoxib, Side effects marked with an asterisk (*) are listed below at the higher frequencies that occurred in patients who took Celecoxib to prevent colon polyps. Patients in these studies took Celecoxib at high doses and for a long duration.

If any of the following happen, stop taking Celecoxib and tell your doctor immediately:

If you have:
An allergic reaction such as skin rash, swelling of the face, wheezing or difficulty breathing

Heart problems such as pain in the chest

Severe stomach pain or any sign of bleeding in the stomach or intestines, such as passing black or bloodstained stools, or vomiting blood

A skin reaction such as rash, blistering or peeling of the skin
Liver failure (symptoms may include nausea (feeling sick), diarrhoea, jaundice (your skin or the whites of your eyes look yellow)).

Very common: may affect more than 1 in 10 people

• High blood pressure, including worsening of existing high blood pressure *

Common: may affect up to 1 in 10 people

• Heart attack*
• Fluid build-up with swollen ankles, legs and/or hands
• Urinary infections
• Shortness of breath*, sinusitis (sinus inflammation, sinus infection, blocked or painful sinuses), blocked or runny nose, sore throat, coughs, colds, flu-like symptoms
• Dizziness, difficulty sleeping
• Vomiting*, stomach ache, diarrhoea, indigestion, wind
• Rash, itching
• Muscle stiffness
• Difficulty swallowing*
• Headache
• Nausea (feeling sick)
• Painful joints
• Worsening of existing allergies
• Accidental injury

Uncommon: may affect up to 1 in 100 people

• Stroke*
• Heart failure, palpitations (awareness of heart beat), fast heart rate
• Abnormalities in liver-related blood tests
• Abnormalities in kidney-related blood tests
• Anaemia (changes in red blood cells that can cause fatigue and breathlessness)
• Anxiety, depression, tiredness, drowsiness, tingling sensations (pins and needles)
• High levels of potassium in blood test results (can cause nausea (feeling sick), fatigue, muscle weakness or palpitations)
• Impaired or blurred vision, ringing in the ears, mouth pain and sores, difficulty hearing*
• Constipation, burping, stomach inflammation (indigestion, stomach ache or vomiting), worsening of inflammation of the stomach or intestine
• Leg cramps
• Raised itchy rash (hives)
• Eye inflammation
• Difficulty breathing
•Skin discolouration (bruising)
•Chest pain (generalised pain not related to the heart)
•Face swelling

Rare: may affect up to 1 in 1,000 people

•Ulcers (bleeding) in the stomach, gullet or intestines; or rupture of the intestine (can cause stomach ache, fever, nausea, vomiting, intestinal blockage), dark or black stools, inflammation of the pancreas (can lead to stomach pain), inflammation of the gullet (oesophagus)

• Low levels of sodium in the blood (a condition known as hyponatraemia)

• Reduced number of white blood cells (which help to protect the body from infection) or blood platelets (increased chance of bleeding or bruising)

•Difficulty coordinating muscular movements
• Feeling confused, changes in the way things taste
• Increased sensitivity to light
• Loss of hair
• Hallucinations
• Bleeding in the eye
• Acute reaction that may lead to lung inflammation
• Irregular heartbeat
• Flushing
• Blood clot in the blood vessels in the lungs, Symptoms may include sudden breathlessness, sharp pains when you breathe or collapse
• Bleeding of the stomach or intestines (can lead to bloody stools or vomiting), inflammation of the intestine or colon
• Severe liver inflammation (hepatitis), Symptoms may include nausea (feeling sick), diarrhoea, jaundice (yellow discolouration of the skin or eyes), dark urine, pale stools, bleeding easily, itching or chills
• Acute kidney failure
• Menstrual disturbances
• Swelling of the face, lips, mouth, tongue or throat, or difficulty swallowing

Very rare: may affect up to 1 in 10,000 people

• Serious allergic reactions (including potentially fatal anaphylactic shock)
• Serious skin conditions such as Stevens–Johnson syndrome, exfoliative dermatitis and toxic epidermal necrolysis (can cause rash, blistering or peeling of the skin) and acute generalised exanthematous pustulosis (symptoms include the skin becoming red with swollen areas covered in numerous small pustules)
• A delayed allergic reaction with possible symptoms such as rash, swelling of the face, fever, swollen glands, and abnormal test results (e.g., liver, blood cell (eosinophilia, a type of raised white blood cell count))
•Bleeding within the brain causing death
• Meningitis (inflammation of the membrane around the brain and spinal cord)
• Liver failure, liver damage and severe liver inflammation (fulminant hepatitis) (sometimes fatal or requiring liver transplant). Symptoms may include nausea (feeling sick), diarrhoea, jaundice (yellow discolouration of the skin or eyes), dark urine, pale stools, bleeding easily, itching or chills
• Liver problems (such as cholestasis and cholestatic hepatitis, which may be accompanied by symptoms such as discoloured stools, nausea and yellowing of the skin or eyes)
• Inflammation of the kidneys and other kidney problems (such as nephrotic syndrome and minimal change disease, which may be accompanied by symptoms such as water retention (oedema), foamy urine, fatigue and a loss of appetite)
• Worsening of epilepsy (possible more frequent and/or severe seizures)
•Blockage of an artery or vein in the eye leading to partial or complete loss of vision
• Inflamed blood vessels (can cause fever, aches, purple blotches on the skin)
• A reduction in the number of red and white blood cells and platelets (may cause tiredness,
easy bruising, frequent nose bleeds and increased risk of infections)
• Muscle pain and weakness
• Impaired sense of smell
•Loss of taste

Not known: frequency cannot be estimated from the available data

• Decreased fertility in females, which is usually reversible on discontinuation of the medicinen

In clinical studies not associated with arthritis or other arthritic conditions, where Celecoxib was taken at doses of 400 mg per day for up to 3 years, the following additional side effects have been observed:

Common: may affect up to 1 in 10 people

• Heart problems: angina (chest pain)
• Stomach problems: Irritable bowel syndrome (can include stomach ache, diarrhoea, indigestion, wind)
• Kidney stones (which may lead to stomach or back pain, blood in urine), difficulty passing urine
• Weight gain

Uncommon: may affect up to 1 in 100 people

• Deep vein thrombosis (blood dot usually in the leg, which may cause pain, swelling or redness of the calf or breathing problems)
• Stomach problems: stomach infection (which can cause irritation and ulcers of the stomach and intestines)
• Lower limb fracture
• Shingles, skin infection, eczema (dry itchy rash), pneumonia (chest infection (possible cough, fever, difficulty breathing))
Floaters in the eye causing blurred or impaired vision, vertigo due to inner ear troubles, sore, inflamed or bleeding gums, mouth sores
• Excessive urination at night, bleeding from piles/ haemorrhoids, frequent bowel movements
• Fatty lumps in skin or elsewhere, ganglion cyst (harmless swellings on or around joints and tendons in the hand or foot), difficulty speaking, abnormal or very heavy bleeding from the vagina, breast pain
• High levels of sodium in blood test results

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Celmac Capsules

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.
- Do not store Celecoxib above 30°C
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information
What Celmac Capsules contains:
The active ingredient is

CELMAC 200 (Celecoxib Capsules 200 mg)
Each hard gelatin capsule contains:
Celecoxib USP .....200 mg
Empty hard gelatin capsule contains approved colours
Excipients.....q.s.

CELMAC 400 (Celecoxib Capsules 400 mg)
Each hard gelatin capsule contains:
Celecoxib USP .....400 mg
Empty hard gelatin capsule contains approved colours
Excipients.....q.s.
List of Excipients:

CELMAC 200 (Celecoxib Capsules 200 mg)
Lactose Monohydrate, Sodium Lauryl Sulphate, Croscarmellose Sodium, Povidone, Purified Water, Magnesium Stearate and E.H.G. Capsule size "1" Violet / White.

CELMAC 400 (Celecoxib Capsules 400 mg)
Lactose Monohydrate, Sodium Lauryl Sulphate, Croscarmellose Sodium, Povidone, Purified Water, Magnesium Stearate and E.H.G. Capsule size "00" Yellow/White.

What CELMAC CAPSULES looks like and contents of the pack

CELMAC 200 (Celecoxib Capsules 200 mg)
Violet (Cap)/White (Body) Hard gelatin capsules of Size "1", containing white to off white coloured powder.

CELMAC 400 (Celecoxib Capsules 400 mg)
Dark yellow (cap)/ white (Body) hard gelatin capsules of size "00", containing white to off white coloured powder.

10 capsules in Alu-Alu blister pack, 3 such blisters in a printed carton along with Pack Insert.
For any information about this medicinal product, please contact Manufacturing Authorization Holder.

DATE OF PUBLICATION OR REVISION

May18, 2021

Manufacturing Authorization Holder	Manufacturer
Ajanta Pharma Limited Ajanta House, Charkop Kandivli (West) Mumbai – 400 067, India. Tel : +91-22-6606 1000 Fax : (0091) 22-66061200/ 300 Email : info@ajantapharma.com	Ajanta Pharma Limited B-4,5-6, MIDC Industrial Area Paithan, Aurangabad, 431148 Dist: Aurangabad Maharashtra, India. e-mail : info@ajantapharma.com