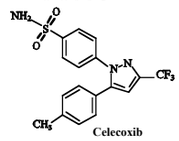
Celbex®
(CELECOXIB)
100mg & 200mg Capsules

سیلبیکس

Celbex® PLUS
(CELECOXIB)
400mg Capsules

سیلبیکس پلس

DESCRIPTION
CELBEXX (Celecoxib) belongs to a new class of arthritis/analgesic medication called "COXIBS". It is used in the treatment of rheumatoid arthritis, osteoarthritis, acute pain condition and in the adjunctive treatment of adenomatous colorectal polyps. Celecoxib (CELBEXX) is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The molecular formula for celecoxib is $C_{17}H_{14}F_3N_3O_2S$ and the structural formula is:



Celecoxib

QUALITATIVE AND QUANTITATIVE COMPOSITION
CELBEXX (Celecoxib) is available for oral administration as:

1. CELBEXX (Celecoxib) Capsules 100mg
   Each capsule contains:
   Celecoxib...100mg

2. CELBEXX (Celecoxib) Capsules 200mg
   Each capsule contains:
   Celecoxib...200mg

3. CELBEXX PLUS (Celecoxib) Capsules 400mg
   Each capsule contains:
   Celecoxib...400mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities. 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.

Pharmacokinetics
Absorption
Peak plasma levels of celecoxib occur approximately 3 hours after an oral dose. Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional up to 200mg b.i.d.; at higher doses there are less than proportional increases in C_{max} and AUC. With multiple dosing, steady state conditions are reached on or before day 5.

Effect of Food and Antacid
When celecoxib was 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 200mg, there is less than a proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. 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 C_{max} and 10% in AUC.
Celecoxib, at doses up to 200mg b.i.d. can be administered without regard to timing of meals. Higher doses (400mg b.i.d.) should be administered with food to improve absorption.

Distribution
In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400L, 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.

Excretion
Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. 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. The effective half-life is approximately 11 hours under fasting conditions. The apparent plasma clearance (CL/F) is about 500mL/min.

Special Populations
Geriatric: At steady state, elderly subjects (over 65 years old) had a 40% higher C_{ss} and a 50% higher AUC compared to the young subjects. In elderly females, celecoxib C_{ss} 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 50kg in body weight, initiate therapy at the lowest recommended dose.

Pediatric: Celecoxib has not been investigated in JRA pediatric patients below 2 years of age, in patients with body weight less than 10kg or beyond 24 weeks.

Hepatic Impairment: Steady state celecoxib AUC is increased about 40% and 180% in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment respectively, as compared to healthy control subjects. Therefore, the daily-recommended dose of celecoxib should be reduced by approximately 50% in patients with moderate (Child-Pugh Class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Renal Impairment: Studies indicate that celecoxib AUC was approximately 40% lower in patients with chronic renal insufficiency (GFR 35-60mL/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.

THERAPEUTIC INDICATIONS
CELBEXX (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 symptomatic relief in the treatment of ankylosing spondylitis.
4. For relief of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients 2 years and older.
5. For the management of acute pain in adults especially in post operative pain.
6. For the treatment of primary dysmenorrhea.
7. To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery).

DOSAGE AND ADMINISTRATION
For osteoarthritis and rheumatoid arthritis, the lowest dose of CELBEXX (Celecoxib) should be sought for each patient. These doses can be given without regard to timing of meals. CELBEXX (Celecoxib) can be taken with or without food.

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis the recommended oral dose is 200mg per day administered as a single dose or as 100mg twice daily. If necessary a dose of 200mg twice daily may be used. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis the recommended oral dose is 100mg to 200mg twice daily. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Ankylosing spondylitis: The recommended daily dose is 200mg taken once daily or in two divided doses. Dose can be increased to 400mg once daily or in two divided doses in patients with insufficient relief of symptoms. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Juvenile rheumatoid arthritis: For the relief of the signs and symptoms of JRA the recommended oral dose for pediatric patients (age 2 yearsand older) is based on weight. For patients >10kg to <25kg the recommended dose is 50mg twice daily. For patients >25kg the recommended dose is 100mg twice daily. For patients who have difficulty swallowing capsules, the contents of a CELBEXX (Celecoxib) capsule can be added to apple sauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature apple sauce and ingested immediately with water. The sprinkled capsule contents on apple sauce are stable for up to 6 hours under refrigerated conditions (2°C-8°C).

Management of acute pain and treatment of primary dysmenorrhea: The recommended dose of CELBEXX (Celecoxib) is 400mg initially, followed by an additional 200mg dose if needed on the first day. On subsequent days, the recommended dose is 200mg twice daily as needed or 400mg once daily.

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

Elderly patients (>65 years): As in younger adults, 200mg per day should be used initially. The dose may, if needed, later be increased to 200mg twice daily. Particular caution should be exercised in elderly with a body weight less than 50kg.

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

Poor Metabolizers of CYP2C9 Substrates: Consideration should be given to starting treatment at half the lowest recommended dose in these patients. Consideration should also be given to using alternative management in JRA patients who are poor metabolizers.

ADVERSE REACTIONS
The following adverse drug reactions have been reported during therapy of celecoxib:

Most common
Gastrointestinal: Abdominal pain, diarrhea, dyspepsia, flatulence, nausea. *Central and peripheral nervous system:* Dizziness, headache, hypertonia. *Respiratory:* Pharyngitis, rhinitis, sinusitis, upper respiratory tract infection. *Others:* Back pain, insomnia, rash.

Less common
Gastrointestinal: Constipation, dysphagia, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, hemorrhoids, melena, dry mouth, stomatitis, vomiting.
Cardiovascular: Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction, palpitation, tachycardia.
Respiratory: Bronchitis, bronchospasm, bronchospasm aggravated, coughing, dyspnea, laryngitis, pneumonia.
Central, peripheral nervous system: Leg cramps, hypertonia, hypoesthesia, migraine, neuralgia, neuropathy, paresthesia, vertigo.
Psychiatric: Anorexia, anxiety, appetite increased, depression, nervousness, somnolence, tiredness.
Reproductive: Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhea, menstrual disorder, vaginal hemorrhage, vaginitis, prostatic disorder.
Liver and biliary system: Hepatic function abnormal, SGOT increased, SGPT increased.
Musculoskeletal: Arthralgia, bone disorder, myalgia, neck stiffness, tendonitis.
Metabolic and nutritional: BUN increased, CPK increased, diabetes mellitus, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increase, creatinine increased, alkaline phosphatase increased, weight increase.
General: Allergy aggravated, allergic reaction, asthenia, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain, anemia, ear abnormality, earache, photosensitivity reaction, pruritus, dermatitis, taste perversion, otitis media, blurred vision, eye pain, glaucoma, urinary tract infection.

Very rare:
Congestive heart failure, pulmonary embolism, vasculitis cerebrovascular accident, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, hepatitis, thrombocytopenia, agranulocytosis, aplastic anemia, pancytopenia, leukopenia, hypoglycemia, hyponatremia, aseptic meningitis, ataxia, acute renal failure, interstitial nephritis, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylactoid reaction, angioedema.

CONTRAINDICATIONS
Celecoxib is contraindicated in:

- Patients with known hypersensitivity to celecoxib.
- Patients who have demonstrated allergic-type reactions to sulfonamides.
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking acetyl salicylic acid (ASA) or other NSAIDs including other COX-2 specific inhibitors. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- Patients with renal impairment associated with creatinine clearance of <30mL/min.
- Patients with severe hepatic impairment (Child-Pugh Class C).
- Patients who have previously had a myocardial infarction or stroke.
- Patients for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Patients with active peptic ulceration or gastrointestinal bleeding and inflammatory bowel disease.
- Patients with established ischemic heart disease (congestive heart failure), peripheral arterial disease and/or cerebrovascular disease.

WARNINGS

Cardiovascular Thrombotic Events:
Chronic use of celecoxib may cause an increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known cardiovascular disease or risk factors for 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.

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 tapered slowly if a decision is made to discontinue corticosteroids.

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. With longer duration of use of NSAIDs, there is a trend for 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. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms.
NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.

Congestive Heart Failure and Edema:
Fluid retention and edema have been observed in some patients taking celecoxib. Therefore, celecoxib should be used with caution in patients with fluid retention, hypertension or heart failure.

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. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. 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.

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

Renal Effects:
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.
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.

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.

Serious Skin Reactions:
Patients appear to be at highest risk for serious skin reactions early in the course of therapy. The onset of these events occurring in the majority of the cases within the first month of treatment. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Famalial 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.

Anaphylactic Reactions:
As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to 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.

Skin Reactions
Celecoxib is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Inflammation
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 noninfectious, painful conditions.

Concomitant NSAID Use
The concomitant use of celecoxib with any dose of a non-aspirin NSAID should be avoided due to the potential for increased risk of adverse reactions.

Pregnancy:
Celecoxib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In late pregnancy, starting at 30 weeks gestation, celecoxib should be avoided because it may cause premature closure of the ductus arteriosus.

Nursing mothers:
Because many drugs are excreted in human milk and because of the potential for serious 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 importance of the drug to the mother.

Drug 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. 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.

ACE Inhibitors and Angiotensin II Antagonists: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors and angiotensin II antagonists. This interaction should be given consideration in patients taking celecoxib concomitantly with ACE inhibitors and angiotensin II antagonists.

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 of aspirin with celecoxib may result in an increased 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 for cardiovascular prophylaxis.

Fluconazole: Concomitant administration of fluconazole at 200mg q.d. resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 CYP2C9 by fluconazole. Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium: Clinical studies showed that the mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450mg b.i.d. with celecoxib 200mg b.i.d. as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing celecoxib therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications.

Antacid: Co-administration of celecoxib with an aluminum and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations. No dose adjustment is required.

Glucocorticoids: Oral glucocorticoids should be used with caution since they increase the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

OVERDOSAGE
Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. 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. Monitor patients for signs and symptoms of gastrointestinal ulceration and/or hemorrhage. Monitor serum electrolytes, renal function and urinalysis after significant overdose.

STORAGE
Store at 25°C (Excursions permitted between 15°C-30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
CELBEXX (Celecoxib) Capsules 100mg is available in blister pack of 20's.
CELBEXX (Celecoxib) Capsules 200mg is available in blister pack of 20's.
CELBEXX PLUS (Celecoxib) Capsules 400mg is available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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