JOSWE

Flamex

Celecoxib

Cardiovascular risk: 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 duration of use. Patients with cardiovascular disease or risk factor for cardiovascular disease may be at greater risk (see warnings and clinical trials) Celecoxib is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see warnings)

Gastrointestinal risk: NSAIDs, including Celecoxib, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (see warnings)

DESCRIPTION: Celecoxib is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene-sulfonamide and is a diaryl-substituated pyrazole.

Indication and dosage: Carefully consider the potential benefits and other treatment options befor deciding the use Celecoxib. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see warning)

Flamex is indicated: for relief of the signs and symptoms of osteoarthritis. For relief of the signs and symptoms of rheumatoid arthritis in adults. For the relief of signs and symptoms of Ankylosing Spondylitis. For the management of acute pain in adults. For the treatment of primary dysmenorrhea. To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of Celecoxib treatment will persist after Celecoxib is discontinued. The efficacy and safety of Celecoxib treatment in patient with FAP beyond six months have not been studied (see WARNINGS and PRECAUTIONS sections)

CONTRAINDICATIONS: Celecoxib is contraindicated in patient with known hypersensitivity to celecoxib. Celecoxib should not be given to patient who have demonstrated allergic-type reactions to sulfonamides. Celecoxib shuld not be given to patient who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Sever, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS--ANAPHYLACTOID REACTIONS, and PRECAUTIONS - preexisting asthma). Celecoxib is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS)

WARNINGS: Cardiovascular effects Cardiovascular thrombotic events Chronic use of Celecoxib may cause an increased risk of serious adverse cardiovascular thrombotic event, myocardial infarction, and stroke, which can be fatal. In the APC trial, the relative risk for the composite endpoint of cardiovascular death, MI, or stroke was 34 (95% CI 14-8.5) for Celecoxib 400mg twice daily and 2.5 (95% CI 10-64) for the Celecoxib 200 mg twice daily compared to placebo. All NSAIDs , both COX-2 selective and nonselective, may have a similar risk. Patient with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patient treated with Celecoxib, the lowest effective dese should be used for the shortest duration possible. Physician and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV toxicity and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAIDs use. The concurrent use of aspirin and Celecoxib does increase the risk of serious GI events (see GI WARNINGS). 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 CONTRAINDICATIONS).

HYPERTENSION: As with all NSAIDs, Celecoxib can lead to the onest of new hypertension or worsening of pre-existing hypertension , either of which may contribute to the increased incidence of CV events. Patient taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Celecoxib, should be used with caution in patient with hypertension. Blood pressure should be monitored closely during the initiation of therapy with Celecoxib and throughout the course of therapy. The rates of hypertension from the CLASS trial in the Celecoxib, ibuprofen and diclofenac treated patient were 24% , 4.2% and 2.5%, respectively

CONGESTIVE HEART FAILURE AND EDEMA: Fluid retention and edema have been observed in some patients taking NSAIDs, including Celecoxib (see ADVERSE REACTIONS). In the CLASS study, the Kaplan-Meier cumulative rates at 9 months of peripheral edema in patients on Celecoxib 400 mg twice daily (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP) ibuprofen 800 mg three times daily and diclofenac 75 mg twice daily were a 4.5 % and 6.9% and 4.7%, respectively. Celecoxib should be used with caution in patients with fluid retention or heart failure.

GASTROINTESTINAL (GI) – RISK OF GI ULCERATION, BLEEDING, AND PERFORATION: NSAIDs, including Celecoxib, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs . only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the GLASS trial, and 2.19% for the subgroup on low dose ASA. Patients 65 years of age and older had an incidence of 1.40% at nine months, 3.06% when also taking ASA With longer duration of use of NSAIDs, there is a trend for increasing the likelihood of developing a serious GI events 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. Patients with a prior history with peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulant, longer duration of NSAIDs therapy, smoking, use of alcohol, older age, and poor general health status. 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. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during Celecoxib therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

RENAL EFFECT: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in the renal flow, which may precipitate over 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 NSAIDs 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.

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

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 symptoms complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal Bronchospasm , after taking aspirin or other NSAIDs (see contraindications and precautions- preexisting asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

SKIN REACTIONS: Celecoxib is a sulfonamide and can cause serious skin adverse events such as exfoliative dermatitis, Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TENS), 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 drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

PREGNANCY: In late pregnancy Celecoxib should be avoided because it may cause premature closure of ductus arteriosus (see precautions-pregnancy) 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 corticosteroids-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. the pharmacological activity of Celecoxib in reducing inflammation, as possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions. Hepatic effects: borderline elevation of one or more liver associated enzymes may occur in up to 15% of patients taking NSAIDs, and notable elevation 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 (see ADVERSE REACTIONS-post- marketing experience). In controlled clinical trials of Celecoxib, the incidence of borderline elevations (greater than or equal to 1.2 times and less than 3 times the upper limit of normal) of liver associated enzymes was 6% for Celecoxib and 5% for placebo, and approximately 0.2 %of patients taking Celecoxib and 0.3% of patients taking placebo had notable elevations of ALT and AST. 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. Hematological effects: anemia is sometimes seen in patients receiving Celecoxib. In controlled clinical trials the incidence of anemia was 0.6% with Celecoxib and 0.4% with placebo. Patients on long-term treatment with Celecoxib should have their hemoglobin or hematocrit checked if they exhibit any signs and symptoms of anemia or blood loss. Celecoxib dose not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages. Preexisting asthma: patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with sever 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 be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for patients

Patients should be informed of the following information before initiating therapy with Celecoxib and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. Celecoxib, like other NSAIDs, may cause serious CV side effects such as MI or stoke, which may result in hospitalization and even death. although serious CV events can occur without warnings symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice if they observe any of these signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNNINGS - CARDIOVASCULAR EFFECTS)

2. Celecoxib, like other NSAIDs, can cause gastrointestinal discomfort and, rarely, more serious side effects, such as ulcer and bleeding, which may result in hospitalization and even death. Although serious GI tract ulceration and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when they observe any signs or symptoms that are indicative of these disorders, including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up(see WARNINGS-GASTROINTESTINAL (GI) EFFECTS-RISK OF GASTROINTESTINAL ULCERATION, BLEEDING, AND PERFORATION).

3. patients should be advised to stop the drug immediately if they develop any type of rash and contact their physician as soon as possible. Celecoxib is a sulfonamide and can cause serious skin side effects such as exfoliative dermatitis, SJS, and TENS which may result in hospitalizations and even death. These reactions can occur with all NSAIDs, even non--sulfonamides. Although serious skin reactions may occur without warning, patient should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients with prior history of sulfa allergy should not take Celecoxib.

4. patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.

5.patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, Jaundice, right upper quadrant tenderness, and "flu-like" symptoms). Patients should be instructed that they should stop therapy and seek immediate medical therapy if these signs and symptoms occur.

6. patients should be informed of the signs and symptoms of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). Patients should be instructed to seek immediate emergency assistance if they develop any of these signs and symptoms (see WARNINGS-ANAPHYLACTOID REACTIONS).

7. patients should be informed that in late pregnancy Celecoxib should be avoided because it may cause premature closure of the ductus arteriosus.

8. patients with familial adenomatous polyposis (FAP) should be informed that Celecoxib has not been shown to reduce colorectal, duodenal or other FAP-related cancers, or the need for endoscopic surveillance, prophylactic or other FAP--related surgery. Therefore, all patients with FAP should be instructed to continue their usual care while receiving Celecoxib.

LABORATORY TESTS: because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have a CBC and a chemistry profile checked periodically. If abnormal liver tests or renal tests persist or worsen, Celecoxib should be discontinued.

In controlled clinical trials, elevated BUN occurred more frequently in patients receiving Celecoxib 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.

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.

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

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

Aspirin: Celecoxib can be used with low-dose aspirin. However, concomitant administration of aspirin with Celecoxib increases the rate of GI ulceration or other complications, compared to use of Celecoxib alone (see WARNINGS-GASTROINTESTINAL (GI) EFFECTS- RISK OF ULCERATION, BLEEDING, AND PERFORATION, AND WARNINGS-CARDIOVASCULAR EFFECTS).

Because of its lack of platelet effects, Celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. Fluconazole: concomitant administration of fluconazole at200 mg QD resulted in a two-fold increase in Celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole. Celecoxib should be introduced at the lower recommended dose in patients receiving fluconazole. 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.

Lithium: in a study conducted in healthy subjects, mean steady-state lithium plasma increased approximately 17% in subjects receiving lithium 450 mg BID with Celecoxib 200 mg BID as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored 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, after initiating or changing Celecoxib therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily dose of 2-5 mg of warfarin. In these subjects, Celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, In post-marketing experience, serious bleeding events, some of which were fatal, have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving Celecoxib concurrently with warfarin. Carcinogenesis, mutagenesis, impairment of fertility: 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 AUC 0-24 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 AUC 0-24 at 200 mg BID) for two years. celecoxib was not mutagenic in an Ames test and 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 AUC 0-24).

Pregnancy: Teratogenic effects: pregnancy category c. celecoxib at oral doses >- 150 mg/kg/day (approximately 2-fold human exposure at 200 mg BID as measured by AUC0-24, caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses >-30 mg/kg/day (approximately 6-fold human exposure based on the AUC0-24 at 200 mg BID)

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

Nonteratogenic effects: celecoxib produced pre-implantation and post-impalntation losses and reduced embryo/fetal survival in rats at oral dosages >-50 mg/kg/day (approximately 6-fold human exposure based on the AUC0-24 at 200 mg BID). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function, nor are they expected at clinical exposures. No studies have been conducted to evaluate the effect of Celecoxib on the closure of the ductus arteriosus in humans. Therefore, use of Celecoxib during the third trimester of pregnancy should be avoided.

Labor and delivery: celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 7-fold human exposure as measured by the AUC 0-24 at 200mg BID). The effects of Celecoxib on labor and delivery in pregnant women are unknown.

Nursing mothers: celecoxib is excreted in the milk of lactating rats at concentrations similar to those in 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 adverse reactions in nursing infants from Celecoxib, a decision should be made weather to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

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

Geriatric use Of the total number of patients who received Celecoxib in clinical trials, more than 3.300 were 65-74 years of age, while approximately 1.300 additional patients were 75 years and over. No substantial differences in effectiveness were observed between these subjects and younger subjects. In clinical studies comparing renal function as measured by the GFR, BUN and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the resultes were not different between elderly and young volunteers. However, as with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients (see WARNINGS GASTROINTESTINAL (GI) EFFECTS- RISK OF GI ULCERATION, BLEEDING, AND PERFORATION).

ADVERSE REACTIONS: 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 patient 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 (400mg 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 1 lists all adverse events, regardless of causality, occurring in >-2% of patients receiving Celecoxib from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group. Since these12 trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Table 1

Adverse events occurring in >-2% of Celecoxib patients

From Celecoxib premarkeing controlled arthritis trials

	Celecoxib (100-200 mg BID or 200mg QD) (n=4146)	Placebo (n=1864)	Naproxen 500 mg BID (n=1366)	Diclofenac 75 mg BID (n=387)	Ibuprofen 800 mg TID (n=345)
Gastrointestinal					
Abdominal pain	4.1	2.8	7.7	9.0	9.0
Diarrhea	5.6	3.8	5.3	9.3	5.8
Dyspepsia	8.8	6.2	12.2	10.9	12.8
flatulence	2.2	1.0	3.6	4.1	3.5
nausea	3.5	4.2	6.0	3.4	6.7
Body as a whole					
Back pain	2.8	3.6	2.2	2.6	0.9
Peripheral edema	2.1	1.1	2.1	1.0	3.5
Injury-accidental	2.9	2.3	3.0	2.6	3.2
Central and peripheral nervous system					
dizziness	2.0	1.7	2.6	1.3	2.3
headach	15.8	20.2	14.5	15.5	15.4
Psychiatric					
insomnia	2.3	2.3	2.9	1.3	1.4
Respiratory					
Pharyngitis	2.3	1.1	1.7	1.6	2.6
Rhinitis	2.0	1.3	2.4	2.3	0.6
Sinusitis	5.0	4.3	4.0	5.4	5.8
Upper respiratory tract infection	8.1	6.7	9.9	9.8	9.9
Skin					
Rash	2.2	2.1	2.1	1.3	1.2

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

The 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, face edema, 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, 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.

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

Male reproductive: Prostatic disorder.

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, weight increase.

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, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria.

Application site disorders: Cellulites, dermatitis contact, injection site reaction, skin nodule.

Special senses: Taste perversion.

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

Safety data from CLASS study:

Hematological events:

During this study, the incidence of clinically significant decreases in hemoglobin (>2 g/dL) confirmed by repeat testing was lower in patients on Celecoxib 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively, and the approved dose for FAP) compared to patients on either diclofenac 75 mg BID or ibupreofen 800 mg TID: 0.5%, 1.3% and 1.9%, respectively. The lower incidence of events with Celecoxib was maintained with or without ASA use.

Withdrawals/serious adverse events:

Kaplan-Meier cumulative rates at 9 months for withdrawals due to adverse events for Celecoxib, diclofenac and ibuprofen were 24%, 29%, and 26%, respectively. Rates for serious adverse events (i.e. those causing hospitalization or felt to be life threatening or otherwise medically significant) regardless of causality were not different across treatment groups, respectively, 8%, 7%, and 8%.

Adverse events from ankylosing spondylitis studies: a total of 378 patients were treated with Celecoxib in placebo- and active- controlled ankylosing spondylitis studies. Doses up to 400 mg QD were studied. The types of adverse events reported in the ankylosing spondylitis studies were similar to those reported in the arthritis studies.

Adverse events from analgesia and dysmenorrhea studies: approximately 1,700 patients were treated with Celecoxib in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain studies received a single dose of study medications. Doses up to 600 mg/day of Celecoxib were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies.

Adverse events from the controlled trial in familial adenomatous polyposis: the adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomized, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BID, and two at 400 mg BID) who had prior intestinal surgery.

Overdose

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.

Dosage and administration

Carefully consider the potential benefits and risks of Celecoxib and other treatment options before deciding to use Celecoxib. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see warnings)

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

Ankylosing spondylitis (AS): for the management of the signs and symptoms of AS, the recommended dose of Celecoxib is 200 mg daily single (once per day) or divided (twice per day) doses. If no effect is observed after 6 weeks, a trial of 400 mg daily may be worthwhile. If no effect is observed after 6 weeks on 400 mg daily, a response is not likely and consideration should be given to alternate treatment options.

Management of acute pain and treatment of primary dysmenorrhea: the recommended dose of Celecoxib is 400 mg initially, followed by an additional 200 mg doses 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 population

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%. The use of Celecoxib in patients with severe hepatic impairment is not recommended.

Presenataion:

Blister packs of 10's and 30's

Store below 30 C.

JOSWE

Flamex

- A medicament is a product that 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 dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTRIES
UNION OF ARAB PHARMACISTS

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Jordan Sweden Medical and Sterilization Co.
Na'ur - Jordan
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