SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	1.1 Product Name : CELMAC 200 (Celecoxib Capsules 200mg) CELMAC 400 (Celecoxib Capsules 400mg)
	1.2 Strength : CELMAC 200 (Celecoxib Capsules 200mg) Each hard gelatin capsule contains: Celecoxib USP … 200mg CELMAC 400 (Celecoxib Capsules 400mg) Each hard gelatin capsule contains: Celecoxib USP … 400mg
	1.3 Pharmaceutical Dosage Form : Capsule
2.	**Qualitative & Quantitative Composition:** CELMAC 200 (Celecoxib Capsules 200 mg) Each hard gelatin capsules contains: Celecoxib USP ...200mg Excipients ...q.s. Contains lactose, Tartrazine (E 102),Sunset Yellow FCF (E 110) CELMAC 400 (Celecoxib Capsules 400 mg) Each hard gelatin capsules contains: Celecoxib USP ...400mg Excipients ...q.s. Contains lactose, Tartrazine (E 102),Sunset Yellow FCF (E 110) For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	CELMAC 200 Violet (Cap) / white (Body) hard gelatin capsules of size “1”, containing white to off white coloured powder. CELMAC 400

	Dark yellow (Cap) / white (Body) hard gelatin capsules of size "00", containing white to off white coloured powder.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: CELECOXIB is indicated: • For the management of the signs and symptoms of Osteoarthritis • For the management of the signs and symptoms of Rheumatoid Arthritis • For the management of the signs and symptoms of Ankylosing Spondylitis • For the management of acute pain in adults • For the management of primary dysmenorrhea
	4.2 Posology and Method of administration: General Dosing Instructions Carefully consider the potential benefits and risks of Celecoxib and other treatment options before deciding to use Celecoxib. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. These doses can be given without regard to timing of meals. **Osteoarthritis** For OA, the dosage is 200 mg per day administered as a single dose or as 100 mg twice daily. **Rheumatoid Arthritis** For RA, the dosage is 100 mg to 200 mg twice daily. **Juvenile Rheumatoid Arthritis** For JRA, the dosage for pediatric patients (age 2 years and older) is based on weight. For patients ≥10 kg to ≤25 kg the recommended dose is 50 mg twice daily. For patients >25 kg the recommended dose is 100 mg twice daily. For patients who have difficulty swallowing capsules, the contents of a Celecoxib capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions. **Ankylosing Spondylitis** For AS, the dosage of Celecoxib is 200 mg daily in 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 For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage 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. **Special Populations** ***Hepatic Impairment*** In patients with moderate hepatic impairment (Child-Pugh Class B), reduce the dose by 50%. The use of CELECOXIB in patients with severe hepatic impairment is not recommended. ***Poor Metabolizers of CYP2C9 Substrates*** In adult patients who are known or suspected to be poor CYP2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), initiate treatment with half of the lowest recommended dose. In patients with JRA who are known or suspected to be poor CYP2C9 metabolizers, consider using alternative treatments.
	4.3 Contraindications: CELECOXIB is contraindicated in the following patients: • Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to celecoxib, any components of the drug product • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs, have been reported in such patients • In the setting of CABG surgery • In patients who have demonstrated allergic-type reactions to sulfonamides
	4.4 Special warning and precautions for use: ***Cardiovascular Thrombotic Events*** Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher

absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events 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 NSAID use. The concurrent use of aspirin and an NSAID, such as celecoxib, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

NSAIDs are contraindicated in the setting of CABG.

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of Celecoxib in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If CELECOXIB is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including celecoxib cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, 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 Celecoxib. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients

treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants; or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Complicated and symptomatic ulcer rates were 0.78% at nine months for all patients in the CLASS 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.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue Celecoxib until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding.

Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including celecoxib.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like"

symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash), discontinue Celecoxib immediately, and perform a clinical evaluation of the patient.

Hypertension

NSAIDs, including Celecoxib, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics or loop diuretics may have impaired response to these therapies when taking NSAIDs.

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of celecoxib may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]).

Avoid the use of Celecoxib in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If Celecoxib is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity and Hyperkalemia

Renal Toxicity

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 NSAID 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, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics, ACE inhibitors or the ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of celecoxib in patients with advanced renal disease. The renal effects of celecoxib may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating Celecoxib. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Celecoxib. Avoid the use of Celecoxib in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Celecoxib is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

Anaphylactic Reactions

Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin sensitive asthma. CELECOXIB is a sulfonamide and both NSAIDs and sulfonamides may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

Seek emergency help if any anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, Celecoxib is contraindicated in patients with this form of aspirin sensitivity. When Celecoxib is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

Serious Skin Reactions

Serious skin reactions have occurred following treatment with Celecoxib, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal.

Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of celecoxib at the first appearance of skin rash or any other sign of hypersensitivity. celecoxib is contraindicated in patients with previous serious skin reactions to NSAIDs.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as celecoxib. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue Celecoxib and evaluate the patient immediately.

Fetal Toxicity
Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including celecoxib, in pregnant women at about 30 weeks gestation and later. NSAIDs, including celecoxib, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including celecoxib, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit celecoxib use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if celecoxib treatment extends beyond 48 hours. Discontinue celecoxib if oligohydramnios occurs and follow up according to clinical practice.

Hematological Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with celecoxib has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including celecoxib, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs (e.g., aspirin), SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding.

Masking of Inflammation and Fever
The pharmacological activity of Celecoxib in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically.

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.

Disseminated Intravascular Coagulation (DIC)
Because of the risk of disseminated intravascular coagulation with use of celecoxib in pediatric patients with systemic onset JRA, monitor patients for signs and symptoms of abnormal clotting or bleeding, and inform patients and their caregivers to report symptoms as soon as possible.

Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

Interactions with other medicinal products and other forms of Interactions :

Table: Clinically Significant Drug Interactions with Celecoxib

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Celecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of Celecoxib and anticoagulants have an increased risk of serious bleeding

		compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
	Intervention:	Monitor patients with concomitant use of Celecoxib with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding.
	Aspirin	
	Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone.
	Intervention:	Concomitant use of celecoxib and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding. Celecoxib is not a substitute for low dose aspirin for cardiovascular protection.
	ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
	Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, ARBs, or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
	Intervention:	• During concomitant use of Celecoxib and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of Celecoxib and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function. • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.

Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of celecoxib with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
Digoxin	
Clinical Impact:	The concomitant use of Celecoxib with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of Celecoxib and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of celecoxib and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Celecoxib has no effect on methotrexate pharmacokinetics.
Intervention:	During concomitant use of Celecoxib and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of Celecoxib and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of Celecoxib and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of Celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy.
Intervention:	The concomitant use of Celecoxib with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of Celecoxib and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the

	pemetrexed prescribing information).
Intervention:	During concomitant use of Celecoxib and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
CYP2C9 Inhibitors or inducers	
Clinical Impact:	Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 (e.g., fluconazole) may enhance the exposure and toxicity of celecoxib whereas co-administration with CYP2C9 inducers (e.g., rifampin) may lead to compromised efficacy of celecoxib.
Intervention	Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2C9 inhibitors or inducers
CYP2D6 substrates	
Clinical Impact:	*In vitro* studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6 (e.g., atomoxetine), and celecoxib may enhance the exposure and toxicity of these drugs.
Intervention	Evaluate each patient's medical history when consideration is given to prescribing celecoxib. A dosage adjustment may be warranted when celecoxib is administered with CYP2D6 substrates
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with Celecoxib may increase the risk of GI ulceration or bleeding.
Intervention	Monitor patients with concomitant use of Celecoxib with corticosteroids for signs of bleeding.

4.6 Pregnancy and Lactation:

Pregnancy

Use of NSAIDs, including celecoxib, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of celecoxib use between about 20 and 30 weeks of gestation and avoid celecoxib use at about 30 weeks of gestation and later in pregnancy.

	Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including CELECOXIB, can cause premature closure of the fetal ductus arteriosus. *Oligohydramnios/Neonatal Renal Impairment:* If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If celecoxib treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue celecoxib and follow up according to clinical practice. Labor or Delivery There are no studies on the effects of celecoxib during labor or delivery. In animal studies, NSAIDs, including celecoxib, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth. **Lactation** Caution should be exercised when celecoxib is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for celecoxib and any potential adverse effects on the breastfed infant from the celecoxib or from the underlying maternal condition.
	4.7 Effects on ability to drive and use machine: Patients who experience dizziness, vertigo or somnolence while taking Celecoxib should refrain from driving or operating machinery.
	4.8 Undesirable Effects: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. Of the Celecoxib-treated patients in the pre-marketing 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 received a total daily dose of celecoxib of 200 mg (100 mg twice daily or 200 mg once daily)

or more, including more than 400 treated at 800 mg (400 mg twice daily). Approximately 3,900 patients 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.

Pre-marketing 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. Since these 12 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: Adverse Events Occurring in ≥2% of CELECOXIB Patients from Pre-marketing Controlled Arthritis Trials

	CBX N=4146	Placebo N=1864	NAP N=1366	DCF N=387	IBU N=345
CBX = CELECOXIB 100 mg to 200 mg twice daily or 200 mg once daily; NAP = Naproxen 500 mg twice daily;					
DCF = Diclofenac 75 mg twice daily;					
IBU = Ibuprofen 800 mg three times daily.					
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, Peripheral Nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	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 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 reactions occurred in 0.1% to 1.9% of patients treated with celecoxib (100 mg to 200 mg twice daily or 200 mg once daily):

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

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

General: Hypersensitivity, allergic reaction, chest pain, cyst NOS, edema generalized, face edema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain

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

Hearing and vestibular: Deafness, tinnitus

Heart rate and rhythm: Palpitation, tachycardia

Liver and biliary: Hepatic enzyme increased (including SGOT increased, SGPT increased)

Metabolic and nutritional: blood urea nitrogen (BUN) increased, creatine phosphokinase (CPK) increased, hypercholesterolemia, hyperglycemia, hypokalemia, NPN increased, creatinine increased, alkaline phosphatase increased, weight increased

Musculoskeletal: Arthralgia, arthrosis, myalgia, synovitis, tendinitis

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

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

Hemic: Anemia

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

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

Application site disorders: Cellulitis, dermatitis contact

Urinary: Albuminuria, cystitis, dysuria, hematuria, micturition frequency, renal calculus

The following serious adverse events (causality not evaluated) occurred in <0.1% of patients:

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

Gastrointestinal: **I**ntestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, esophageal perforation, pancreatitis, ileus

General: Sepsis, sudden death

Liver and biliary: Cholelithiasis

Hemic and lymphatic: Thrombocytopenia

Nervous: Ataxia, suicide

Renal: Acute renal failure

The following additional adverse reactions occurred in ≥0.1% and <1% of patients taking celecoxib, at an incidence greater than placebo in the long-term polyp prevention studies, and were either not reported during the controlled arthritis pre-marketing trials or occurred with greater frequency in the long-term, placebo-controlled polyp prevention studies:

Nervous system disorders: Cerebral infarction

Eye disorders: Vitreous floaters, conjunctival hemorrhage

Ear and labyrinth: Labyrinthitis

Cardiac disorders: Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy

Vascular disorders: Deep vein thrombosis

Reproductive system and breast disorders: Ovarian cyst

Investigations: Blood potassium increased, blood sodium increased, blood testosterone decreased

Injury, poisoning, and procedural complications: Epicondylitis, tendon rupture

Postmarketing Experience

The following adverse reactions have been identified during post approval use of Celecoxib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

Cardiovascular: Vasculitis, deep venous thrombosis

General: Anaphylactoid reaction, angioedema

Liver and biliary: Liver necrosis, hepatitis, jaundice, hepatic failure

Hemic and lymphatic**:** Agranulocytosis, aplastic anemia, pancytopenia, leucopenia

	Metabolic: Hypoglycemia, hyponatremia ***Nervous:*** Aseptic meningitis, ageusia, anosmia, fatal intracranial hemorrhage ***Renal:*** Interstitial nephritis
	4.9 Overdosage: Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare. 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. 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. Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.
5.	**Pharmacological properties**
	5.1 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.
	5.2 Pharmacokinetics Properties: **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 no. 1

Summary of single dose (200mg) disposition kinetics of celecoxib in healthy subjects				
Mean (%CV) PK Parameter Values				
C_{max} , ng/mL	T_{max}, hr	Effective $t_{1/2}$, hr	V_{SS}/F,L	CL/F , L/hr
705 (38)	2.8(37)	11.2(31)	429(34)	27.7(28)

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
	5.3 Preclinical Safety data: 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 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 AUC_{0-24}).
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: CELMAC 200/CELMAC 400 (Celecoxib Capsules) Lactose Monohydrate, Sodium Lauryl Sulphate , Croscarmellose Sodium, Povidone, Purified Water, Magnesium Stearate
	6.2 Incompatibilities: Not Applicable
	6.3 Shelf life: 2 Years.
	6.4 Special Precautions for storage: Do not store above 30°C, protect from light.
	6.5 Nature and contents of container: 10 capsules in Alu-Alu blister pack, 3 such blisters in a printed carton along with Pack Insert.
	6.6 Special precautions for disposal: Any unused product or waste material should be disposed of in accordance with local requirements.
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400067, India **Manufacturing Site Address:** Ajanta Pharma Limited B-4-5-6, MIDC Industrial Area

	Paithan, Aurangabad, 431148 Dist: Aurangabad Maharashtra, India. e-mail : info@ajantapharma.com
8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Jun 23, 2023