180.00 mm

490.00 mm

Product Name
Synerrv Celecoxib Capsules 400 mg

Qualitative and Quantitative Composition
Each 400 mg capsule contains 400 mg Celecoxib.

Dosage Form & Mode of Administration
Hard gelatin capsules for oral administration.

Product Description
Size '0', white to white opaque hard gelatin capsules, imprinted with 'CEL' on cap & '400 mg' on body in black ink, filled with white to off-white slug to granular powder.

Indication
For the management of acute pain in adults and for the treatment of primary dysmenorrhoea.
Relief of the acute and chronic pain and inflammation of rheumatoid arthritis and osteoarthritis.
Relief of signs and symptoms of ankylosing spondylitis.
For the management of low back pain (100 mg and 200 mg only).

Posology and Method of Administration
Celecoxib capsules can be taken with or without food.
Given the association between cardiovascular (CV) risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment.
Adults
Symptomatic Treatment of Osteoarthritis (OA): The recommended dose of celecoxib is 200 mg administered as a single dose or as 100 mg twice per day.
Symptomatic Treatment of Rheumatoid Arthritis (RA): The recommended dose of celecoxib is 100 mg or 200 mg twice per day.
Ankylosing Spondylitis (AS): The recommended dose of celecoxib is 200 mg administered as a single dose or 100 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.
Management of Acute Pain: The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily, as needed.
Treatment of Primary Dysmenorrhea: The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily, as needed.
Low Back Pain (LBP): Usual dosage for adults is 100 mg of celecoxib orally twice daily, morning and evening, or 200 mg once daily (100 mg and 200 mg only).
Elderly: No dosage adjustment is generally necessary. However, for elderly patients with a lower than average body weight (<50 kg), it is advisable to initiate therapy at the lowest recommended dose.
Hepatic Impairment: No dosage adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). Introduce celecoxib at half the recommended dose in arthritis or pain patients with moderate hepatic impairment (Child-Pugh Class B). Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied (see Special Warnings and Special Precautions for Use).
Renal Impairment: No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment (see Special Warnings and Special Precautions for Use).
Children: Celecoxib is not indicated for use in children.
CYP2C9 Poor Metabolizers: Patients who are known, or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as the risk of dose-dependent adverse effects is increased. Consider reducing the dose to half the lowest recommended dose (see Pharmacokinetic Properties).

Contraindication
Celecoxib is contraindicated in:
> Patients with known hypersensitivity to celecoxib or any other ingredient of the product.
> Patients with known sulfonamide hypersensitivity.
> Patients who have experienced asthma, urticaria or allergic-type reactions after taking acetylsalicylic acid (ASA [aspirin]) or other nonsteroidal anti-inflammatory drugs (NSAIDs), including other cyclooxygenase-2 (COX-2) specific inhibitors.
> Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see Special Warnings and Special Precautions for Use)
> Patients who have increased risk of cardiovascular disease (ischaemic heart disease and stroke).
> Patients with hypertension (high blood pressure) whose blood pressure is not under control.

Special Warnings and Precautions for Use

WARNING
RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Patients with risk factors of heart disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking patients and patients with peripheral arterial disease should only be treated with celecoxib after careful consideration.
Cardiovascular Effects
Cardiovascular Thrombotic Events: Celecoxib may cause an increased risk of serious CV thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with dose and duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with CV disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimize the potential risk for an adverse CV event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and symptoms of serious CV toxicity and the steps to take if they occur (see Pharmacodynamic Properties).
Celecoxib is not a substitute for acetylsalicylic acid for prophylaxis of CV thromboembolic diseases because of the lack of effect on platelet function. Because celecoxib does not inhibit platelet aggregation, anti-platelet therapies (e.g., acetylsalicylic acid) should not be discontinued.
Hypertension: As with all NSAIDS, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics 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 (see Pharmacodynamic Properties)
Fluid Retention and Edema: As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking celecoxib. Therefore, patients with pre-existing congestive heart failure (CHF) or hypertension should be closely monitored. Celecoxib should be used with caution in patients with compromised cardiac function, pre-existing edema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.
Gastrointestinal (GI) Effects
Upper and lower GI perforations, ulcers or bleeds have occurred in patients treated with celecoxib. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with celecoxib. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with CV disease, patients using concomitant glucocorticoids, antiplatelet drugs (such as aspirin), or other NSAIDs, patients using alcohol or patients with a prior history of, or active, GI disease, such as ulceration, GI bleeding or inflammatory conditions. 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 spontaneous reports of fatal GI events have been in elderly or debilitated patients.
Strategies to Minimize 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.
Renal Effects
NSAIDs including celecoxib may cause renal toxicity. Celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.
Caution should be used when initiating treatment in patients with dehydration. It is advisable to rehydrate patients first and then start therapy with celecoxib.
Advance Renal Disease
Renal function should be closely monitored in patients with advanced renal disease who are administered celecoxib (see Posology and Method of Administration)
Anaphylactoid Reactions
As with NSAIDs in general, anaphylactoid reactions have occurred in patients exposed to celecoxib (see Contraindications).
Serious Skin Reactions
Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic
epidermal necrolysis, have been reported very rarely in association with the use of celecoxib. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Hepatic Effects
Patients with severe hepatic impairment (Child-Pugh Class C) have not been studied. The use of celecoxib in patients with severe hepatic impairment is not recommended. Celecoxib should be used with caution when treating patients with moderate hepatic impairment (Child-Pugh Class B), and initiated at half the recommended dose (see Posology and Method of Administration)
Rare cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis, and hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib.
A patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with celecoxib.
Use with Oral Anticoagulants
The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban). In patients on concurrent therapy with warfarin or similar agents, serious bleeding events, some of them fatal, have been reported. Because increases in prothrombin time (INR) have been reported, anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant after initiating treatment with celecoxib or changing the dose (see Interaction with Other Medicinal Products and Other Forms of Interaction).
General
By reducing inflammation, celecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections.
The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.
CYP2D6 Inhibition
Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction may be necessary for individually dose-titrated medicinal products that are metabolised by CYP2D6 (see Interaction with Other Medicinal Products and Other Forms of Interaction).

Interaction with Other Medicinal Products and Other Forms of Interaction
General: Celecoxib metabolism is predominantly mediated via cytochrome P450 (CYP) 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Consider starting treatment at half the lowest recommended dose (see Posology and Method of Administration and Pharmacokinetic Properties).
Concomitant administration of celecoxib with inhibitors of CYP2C9 can lead to increases in plasma concentrations of celecoxib. Therefore, a dose reduction of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inhibitors.
Concomitant administration of celecoxib with inducers of CYP2C9, such as rifampicin, carbamazepine and barbiturates can lead to decreases in plasma concentrations of celecoxib. Therefore, a dose increase of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inducers.
Celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6.
Drug Specific
Interaction of celecoxib with warfarin or similar agents: (see Special Warnings and Special Precautions for Use).
Lithium: In healthy subjects, lithium plasma levels increased approximately 17% in subjects receiving lithium together with celecoxib. Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.
Aspirin: Celecoxib does not interfere with the anti-platelet effect of low-dose aspirin (see Special Warnings and Special Precautions for Use). Because of its lack of platelet effects, celecoxib is not a substitute for aspirin in the prophylactic treatment of CV disease.
Anti-hypertensives including Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin II antagonists (also known as angiotensin receptor blockers, [ARBs]), diuretics and beta-blockers: Inhibition of prostaglandins may diminish the effect of anti-hypertensives including ACEIs and/or ARBs, diuretics and beta-blockers. This interaction should be given consideration in patients taking celecoxib concomitantly with ACEIs and/or ARBs, diuretics and beta-blockers.
In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, angiotensin II antagonists or diuretics, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the clinical need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.
Cyclosporine: Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with cyclosporine.
Fluconazole and ketoconazole: Since celecoxib is predominantly metabolised by CYP2C9 it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of 200 mg single dose of celecoxib and 200 mg once daily of fluconazole, a potent CYP2C9 inhibitor, resulted in a mean increase in celecoxib C_{min} of 60% and in AUC of 130%. Ketoconazole, a CYP3A4 inhibitor, showed no clinically relevant inhibition in the metabolism of celecoxib.
Dextromethorphan and metoprolol: Concomitant administration of celecoxib 200 mg twice daily resulted in a 2.6-fold and a 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib inhibition to the CYP2D6 substrate metabolism via CYP2D6. Therefore, the dose of drugs as CYP2D6 substrate may need to be reduced when treatment with celecoxib is initiated or increased when treatment with celecoxib is terminated (see Special Warnings and Special Precautions for Use).
Diuretics: NSAIDs, in some patients, can reduce the natriuretic effect of furosemide and thiazides by inhibition of renal prostaglandin synthesis.
Methotrexate: No pharmacokinetic and clinically important interactions have been observed between celecoxib and methotrexate.
Oral contraceptives: Celecoxib has no clinically relevant effects.
Other drugs: No clinically important interactions have been observed with celecoxib and antacids (aluminum and magnesium), omeprazole, glibenclamide (glyburide), phenytoin, or tolbutamide.

Fertility, Pregnancy and Lactation
Based on the mechanism of action, the use of NSAIDs, including celecoxib, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including celecoxib, should be considered.
Pregnancy
There are no studies in pregnant women. Studies in animals have shown reproductive toxicity. The relevance of these data for humans is unknown.
Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus and should be avoided during the third trimester of pregnancy.
Celecoxib should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.
Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.
If used during second or third trimester of pregnancy, NSAIDs may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on celecoxib should be closely monitored for amniotic fluid volume.
Lactation
Celecoxib is excreted in milk at concentrations similar to those in plasma. Administration of celecoxib to lactating women has shown very low transfer of celecoxib into breast milk. Because of the potential for adverse reactions in nursing infants from celecoxib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the expected benefit of the drug to the mother.

Effects on Ability to Drive and Use Machines
The effect of celecoxib on ability to drive or use machinery has not been studied, but based on its pharmacodynamic properties and overall safety profile it is unlikely to have an effect.

Undesirable Effects
Adverse Drug Reactions with daily doses of 25 mg – 800 mg in Adult Populations

System Organ Class Frequency	Adverse Drug Reaction
Infections and other infestations Common Uncommon	 Bronchitis, sinusitis, upper respiratory tract infection, urinary tract infection Pharyngitis, rhinitis
Blood and lymphatic system disorders Uncommon Rare	 Anaemia Thrombocytopenia
Immune system disorders Uncommon	 Hypersensitivity
Psychiatric disorders Common Uncommon Rare	 Insomnia Anxiety Confusional state
Nervous system disorders Common Uncommon	 Dizziness Hypertonia, somnolence
Eye disorders Uncommon	 Vision blurred
Ear and labyrinth disorders Uncommon	 Tinnitus
Cardiac disorders Uncommon Rare	 Palpitations Cardiac failure congestive, arrhythmia, Tachycardia
Vascular disorders Common Rare	 Hypertension (including aggravated hypertension) Flushing
Respiratory, thoracic and mediastinal disorders Common	 Cough
Gastrointestinal disorders Common Uncommon Rare Very rare	 Vomiting, abdominal pain, diarrhoea, dyspepsia, flatulence Gastric ulcer, tooth disorder Duodenal ulcer, oesophageal ulcer Intestinal perforation, pancreatitis
Hepatobiliary disorders Uncommon	 Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)
Skin and subcutaneous tissue disorders Common Uncommon Rare Very Rare	 Pruritus (includes pruritus generalized), rash Urticaria, ecchymosis Angioedema, alopecia Dermatitis bullous
General disorders and administration site conditions Common Uncommon	 Oedema peripheral oedema Face oedema, influenza-like illness
Injury, poisoning and procedural conditions Uncommon	 Injury

Post Marketing Experience
Immune system disorders: Very rare: anaphylactic reaction
Psychiatric disorders: Rare: hallucination
Nervous system disorders: Very rare: cerebral haemorrhage, meningitis aseptic, ageusia, anosmia
Eye disorders: Uncommon: conjunctivitis
Vascular disorders: Very rare: vasculitis
Respiratory, thoracic and mediastinal disorders: Rare: pulmonary embolism, pneumonitis
Gastrointestinal disorders: Rare: gastrointestinal haemorrhage
Hepatobiliary disorders: Rare: hepatitis; Very rare: hepatic failure, hepatitis fulminant, hepatic necrosis (see Special Warnings and Special Precautions for Use), cholestasis, hepatitis cholestatic, jaundice
Skin and subcutaneous tissue disorders: Rare: photosensitivity reaction; Very rare: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis exfoliative
Renal and urinary disorders: Rare: renal failure acute (see Special Warnings and Special Precautions for Use), hyponatremia; Very rare: tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion
Reproductive system and breast disorders: Rare: menstrual disorder; Not known: infertility female (female fertility decreased) (see Fertility, Pregnancy and Lactation)
General disorders and administration site conditions: Uncommon: chest pain

Overdose
Clinical experience of overdose is limited. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided. Dialysis is unlikely to be an efficient method of drug removal because of high protein binding of the drug.

Pharmacodynamic Properties
Pharmacotherapeutic group: M01AH01
The mechanism of action of celecoxib is via inhibition of prostaglandin synthesis primarily by inhibition of COX-2. At therapeutic concentrations in humans, celecoxib does not inhibit cyclooxygenase 1 (COX-1). COX-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, in particular prostaglandin E2, causing inflammation, oedema and pain. Celecoxib acts as an anti-inflammatory, analgesic, and antipyretic agent in animal models by blocking the production of inflammatory prostanoids via COX-2 inhibition. In animal colon tumour models, celecoxib reduced the incidence and multiplicity of tumours.
Celecoxib has a very low affinity for the constitutively expressed COX-1 enzyme. Consequently, at therapeutic doses celecoxib has no effect on prostanoids synthesized by activation of COX-1 thereby not interfering with normal COX-1 related physiological processes in tissues, particularly the stomach, intestine and platelets.

Pharmacokinetic Properties
Absorption
When given under fasting conditions celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Oral bioavailability from capsules is about 99% relative to administration in suspension (optimally available oral dosage form). Under fasting conditions, both peak plasma levels (C_{max}) and area under the curve (AUC) are roughly dose proportional up to 200 mg twice daily; at higher doses there are less than proportional increases in C_{max} and AUC.
Distribution
Plasma protein binding, which is concentration independent, is about 97% at therapeutic plasma concentrations and celecoxib is not preferentially bound to erythrocytes in the blood.
Metabolism
Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been identified in human plasma: a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.
Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*3 polymorphism.
Patients who are known, or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose (see Posology and Method of Administration and Interactions with Other Medicinal Products and Other Forms of Interaction)
Excretion
Elimination of celecoxib is mostly by hepatic metabolism with less than 1% of the dose excreted unchanged in urine. After multiple dosing, elimination half-life is 8 to 12 hours and the rate of clearance is about 500 mL/min. With multiple dosing steady-state plasma concentrations are reached before day 5. The intersubject variability on the main pharmacokinetic parameters (AUC, C_{max}, elimination half-life) is about 30%. The mean steady-state volume of distribution is about 500 L/70 kg in young healthy adults indicating wide distribution of celecoxib into the tissues. The drug crosses the blood-brain barrier.
Food Effects
Dosing with food (high fat meal) delays absorption of celecoxib resulting in a T_{max} of about 4 hours and increases bioavailability by about 20% (see Posology and Method of Administration)
Overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in C_{max}, T_{max} or T1/2 after administration of capsule contents on applesauce.
Special Populations
Elderly
In the population >65 years there is a one and a half to two-fold increase in mean C_{max} and AUC for celecoxib. This is a predominantly weight-related rather than age-related change, celecoxib levels being higher in lower weight individuals and consequently higher in the elderly population who are generally of lower mean weight than the younger population. Therefore, elderly females tend to have higher drug plasma concentrations than elderly males. No dosage adjustment is generally necessary. However, for elderly patients with a lower than average body weight (<50 kg), initiate therapy at the lowest recommended dose.
Race
Approximately 40% higher AUC of celecoxib in the Black population compared to Caucasians. The cause and clinical significance of this finding is unknown.
Hepatic impairment: Plasma concentrations of celecoxib in patients with mild hepatic impairment (Child-Pugh Class A) are not significantly different from those of age and sex matched controls. In patients with moderate hepatic impairment (Child-Pugh Class B) celecoxib plasma concentrations are about twice those of matched controls (see Posology and Method of Administration)
Renal impairment: In elderly volunteers with age-related reductions in glomerular filtration rate (GFR) (mean GFR >65 mL/min/1.73 m2) and in patients with chronic stable renal insufficiency (GFR 35-60 mL/min/1.73 m2) celecoxib pharmacokinetics was comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance. Severe renal insufficiency would not be expected to alter clearance of celecoxib since the main route of elimination is via hepatic metabolism to inactive metabolites.
Renal effects: The relative roles of COX-1 and COX-2 in renal physiology are not completely understood. Celecoxib reduces the urinary excretion of PGE2 and 6-keto-PGF1a (a prostacyclin metabolite) but leaves serum thromboxane B2 (TXB2) and urinary excretion of 11-dehydro-TXB2, a thromboxane metabolite (both COX-1 products) unaffected. Specific studies have shown celecoxib produces no decreases in GFR in the elderly or those with chronic renal insufficiency. These studies have also shown transient reductions in fractional excretion of sodium. In studies in patients with arthritis a comparable incidence of peripheral oedema has been observed to that seen with non specific COX-inhibitors (which also possess COX-2 inhibitory activity). This was most evident in patients receiving concomitant diuretic therapy. However, increased incidences of hypertension and cardiac failure have not been observed and the peripheral oedema has been mild and self-limiting.

Special Precautions for Storage
Store below 30°C.

Shelf Life
Please refer to outer carton for expiry date.

Nature and Content of Container
Blisters of aluminum foil composite (paper/pet/aluminum/hsl) and PVDC coated rigid PVC/PE laminate
Pack Sizes: 10x10 Capsules

Manufacturer
Umedica Laboratories Pvt. Ltd.
Plot No. 221, IInd Phase, G.I.D.C.,
Vapi, Gujarat, 396195, India.

Product Registration Holder
Synerrv Sdn. Bhd.
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Leaflet Revision Date
30/08/2024

Minimum Font Size: Times New Roman, Size 7

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UMEDICA LABORATORIES PVT. LTD.
SPECIFICATION FOR ARTWORK APPROVAL

Format No.: FM/PDD/002-01-05			Ref. SOP No.: PDD/002
Artwork/SAP Code No. : AAAAAA		Old Version/SAP Code No.: New	Specification Version: 01
Product Name	: Synerrv Celecoxib Capsules 400mg	Company Name/Country	: Reg. Submission - Malaysia/Synerrv
Component Type	: Package Insert	Pack Style	: 10×10C
Description	: New Development Package Insert artwork as per RA & Malaysia/Synerrv for Registration.		
Specifications	: L×H (Layout No. : CL-1289) (AUTO CARTONATOR SIZE)	Site	: Umedica
~~Full Size~~ / Size	: 180×490 MM	Type / ~~Blister~~ / ~~Strip Size~~ / ~~Adhesive~~ / ~~Tube Type~~	: Front-Back
Size - Catch Cover / Foil / BOPP	: NA	~~Sachet Size~~/~~Pocket Size~~/Fold Size/~~Release Paper~~	: 180x30 MM
Space between Labels	: NA	Transparent Paper Thickness	: NA
GSM of Paper / ~~GSM of Aluminum Foil~~	: 40 GSM	Type of Paper / ~~GSM~~	: Bible Paper
Thickness of Foil	: NA	Type of Foil / Fold / Coating GSM	: NA
Cylinder	: NA	Lamination / Varnish / Material Grade	: NA
Repeat/Tolerence	: NA	Partition / Plate Size / Total GSM /	: NA
		Sealing / Embossing / Core Diameter	: NA
GSM/BF of Printed Shipper	: NA	Paper Grade / Flute Type / PLY of Shipper	: NA
(Top/Middle/Bottom and Flute layer	: NA		
Printing Colour	: BLACK		or as per Sample
Approved by Export/Marketing	:		[Approval attached with ADF]

CHECKLIST FOR CHECKING ARTWORK & SPECIFICATION

Brand Name and Generic Name(As per IP/BP/USP/ In-house Pharma-copeia)	Dosage Form and strength	Prefix Rx/ XRx	Mfg. Lic. No. / Code	Regulatory Agency Approval	Packing (Qty.) / Presentation	Dosage details if required	Size / Design	Composition /Label Claim	Schedule 'H','H1','G' or 'X' etc warning for local product / Red line for oral products	Item Code	QR Code/ Barcode (1D / 2D) as per requirement	Material and printing colours specifica-tion	Storage Condition as per pro-duct/Buyer requirement	Registration No. / Other requirement	Mfg. Name and Address, (Tel. No. and e-mail in the insert)	Marketed by / Distributors Name	Route of Admin. [in case of Inj./ Multidose Vial matter	Adequate Space (Batch details/2D barcode/ Embossing for Overprinting	Artwork Approved by Sign with Date
																			PDD Department
																			PPIC/Packing Department
																			QC Department
																			RA Department
																			QA Department

Note to Printer:
- Return the original approved artwork along with the sample.
- The overprinting area should be unvarnished.
- Machine proof must be verified against the approved hard copy in Light, Standard and Dark shade should be certified and signed by an authorized person.
- Any deviation must be brought to the notice of the Packaging Development Department immediately in the writing.
- For any clarification, please contact Packaging Development Department.