18x33cm / 2026 / 02/25

Vobrax Capsule 200mg

Asumed

■ **COMPOSITION**
Each capsule contains:
Celecoxib.....200mg

■ **PRODUCT DESCRIPTION**
#2 white capsules characterized with yellow ribbon ring and CH91 on surface, filled with white to off white granular powder inside for oral administration.

■ **INDICATION**
(1) For the management of acute pain in adults and for the treatment of primary dysmenorrhoea.
(2) Relief of the acute and chronic pain and inflammation of rheumatoid arthritis and osteoarthritis.
(3) Relief of signs and symptoms of ankylosing spondylitis.
(4) For the management of low back pain

■ **PHARMACOLOGICAL PROPERTIES**

■ ATC code: M01AH01
Pharmacotherapeutic group: anti-inflammatory and anti-rheumatic products, non-steroids, coxibs.

■ **PHARMACODYNAMIC PROPERTIES**
Mechanism of action: Celecoxib is an oral, selective, cyclooxygenase2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily). No statistically significant inhibition of COX-1 (assessed as ex vivo inhibition of thromboxane B2 [TxB2] formation) was observed in this dose range in healthy volunteers.

Pharmacodynamic effects: Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in human but its relevance to ulcer healing has not been established.
The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.
Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulfonamides (e.g. thiazides, furosemide) but differs from arylamine sulfonamides (e.g. sulfamethoxizole and other sulfonamide antibiotics).

A dose dependent effect on TxB2 formation has been observed after high doses of celecoxib.

■ **PHARMACOKINETIC PROPERTIES**
Absorption: Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption of celecoxib by about 1 hour resulting in a Tmax of about 4 hours and increases bioavailability by about 20%.

Distribution: Plasma protein binding is about 97% at therapeutic plasma concentrations and the drug is not preferentially bound to erythrocytes.

Biotransformation: 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 i.e., 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.

Elimination: Celecoxib is mainly eliminated by metabolism. Less than 1% of the dose is excreted unchanged in urine. The inter-subject variability in the exposure of celecoxib is about 10-fold. Celecoxib exhibits dose and time independent pharmacokinetics in the therapeutic dose range. Elimination half-life is 8-12 hours. Steady state plasma concentrations are reached within 5 days of treatment.

■ **RECOMMENDED DOSAGE**
Celecoxib capsules can be taken with or without food.
Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment.

Adults
(1) 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.
(2) Symptomatic Treatment of Rheumatoid Arthritis (RA): The recommended dose of celecoxib is 100 mg or 200 mg twice per day.
(3) 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.
(4) 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.
(5) 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.
(6) Low Back Pain (LBP): Usual dosage for adults is 100 mg of celecoxib orally twice daily, morning and evening after meal or 200 mg once daily.

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.

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.

■ **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

■ **CONTRAINDICATIONS**
(1) Patients with known hypersensitivity to the active substance or to any of the excipients and sulphonamides.
(2) Active peptic ulceration or gastrointestinal (GI) bleeding.
(3) Patients who have experienced asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid (aspirin) or other NSAIDs including COX-2 inhibitors.
(4) In pregnancy and in women of childbearing potential unless using an effective method of contraception.
(5) Breast-feeding.
(6) Severe hepatic dysfunction.
(7) Patients with estimated creatinine clearance <30 ml/min.
(8) Inflammatory bowel disease.
(9) Congestive heart failure (NYHA II-IV).
(10) Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
(11) Patients who have increased risk of cardiovascular disease (ischemic heart disease and stroke).

■ **WARNING AND PRECAUTIONS**
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.

Warning to prescriber when prescribing COX-2 inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes mellitus, smoking patients and patients with peripheral arterial disease.

Concomitant NSAID use
The concomitant use of celecoxib and a non- aspirin NSAID should be avoided.

Cardiovascular effects
As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. NSAIDs, including COX-2 selective inhibitors, have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with celecoxib after careful consideration.
COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued.

Fluid retention and oedema
As with other medicinal products known to inhibit prostaglandin synthesis fluid retention and oedema have been observed in patients taking celecoxib. Therefore, celecoxib should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention. Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.

Hypertension
As with all NSAIDS, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Therefore, blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

Hepatic and renal effects
Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.
NSAIDs, including celecoxib, may cause renal toxicity. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.
Some 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. Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib treatment.
If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of celecoxib therapy should be considered.

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.

CYP2C9 poor metabolisers
Patients known to be CYP2C9 poor metabolisers should be treated with caution.

Skin and systemic hypersensitivity reactions
Serious skin reactions, some of them fatal, including 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 reactions early in

the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (including anaphylaxis, angioedema and drug rash with eosinophilia and systemic symptoms (DRESS), or hypersensitivity syndrome) have been reported in patients receiving celecoxib. Patients with a history of sulphonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

General
Celecoxib may mask fever and other signs of inflammation.

Use with oral anticoagulants
In patients on concurrent therapy with warfarin, serious bleeding events, some of them fatal, have been reported. Increased prothrombin time (INR) with concurrent therapy has been reported. Therefore, this should be closely monitored in patients receiving warfarin/ coumarin-type oral anticoagulants, particularly when therapy with celecoxib is initiated or celecoxib dose is changed. Concomitant use of anticoagulants with NSAIDS may increase the risk of bleeding. Caution should be exercised when combining celecoxib with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).
Celecoxib capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

■ **Effects on Ability to Drive and Use Machine**
Patients who experience dizziness, vertigo or somnolence while taking Vobrax should refrain from driving or operating machinery.

■ **DRUG INTERACTIONS**

■ Pharmacodynamic interactions
Anticoagulants: Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of celecoxib in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with celecoxib is initiated or the dose of celecoxib is changed. Bleeding events in association with increases in prothrombin time have been reported, predominantly in the elderly, in patients receiving celecoxib concurrently with warfarin, some of them fatal.

Anti-hypertensives: NSAIDs may reduce the effect of antihypertensive medicinal products including ACE-inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers. As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients, patients on diuretics, or elderly patients) when ACE inhibitors, angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including celecoxib. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Ciclosporin and Tacrolimus: Coadministration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when celecoxib and any of these drugs are combined.

Acetylsalicylic acid: Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

Pharmacokinetic interactions

Effects of celecoxib on other drugs

CYP2D6 Inhibition: Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of drugs that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of drugs which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmic drugs, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated.
Concomitant administration of celecoxib 200 mg twice daily resulted in increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib CYP2D6 inhibition of the CYP2D6 substrate metabolism.

CYP2C19 Inhibition: Celecoxib shown some potential to inhibit CYP2C19 catalysed metabolism. Examples of drugs which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.

Methotrexate: Adequate monitoring for methotrexate-related toxicity should be considered when combining these two drugs.

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

Oral contraceptives: Celecoxib had no relevant effects on the pharmacokinetics of oral contraceptives.

Glibenclamide/tolbutamide: Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a relevant extent.

■ **Effects of other drugs on celecoxib**
CYP2C9 Poor Metabolisers: In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors such as fluconazole could result in further increases in celecoxib exposure. Such combinations should be avoided in known CYP2C9 poor metabolisers.

CYP2C9 Inhibitors and Inducers: Since celecoxib is predominantly metabolised by CYP2C9 it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

Ketoconazole and Antacids: Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib.

Paediatric population: None known.

■ **PREGNANCY & LACTATION**
Pregnancy: Potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. If a woman becomes pregnant during treatment, celecoxib should be discontinued.
During the second or third trimester of pregnancy, NSAIDs including celecoxib 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.

Celecoxib is contraindicated in pregnancy and in women who can become pregnant.

Lactation: Administration of celecoxib to a limited number of lactating women has shown a very low transfer of celecoxib into breast milk. Women who take celecoxib should not breastfeed.

■ **SIDE EFFECTS**

System Organ Class	Adverse Drug Reaction Frequency
Infections and infestations	**Common -** Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection
Blood and lymphatic system disorders	**Uncommon -** Anemia **Rare -** Leukopenia, thrombo-cytopenia **Very rare -** Pancytopenia
Immune system disorders	**Common -** Hyper-sensitivity **Very rare -** Anaphylactic shock, anaphylactic reaction
Metabolism and nutrition disorders	**Uncommon -** Hyperkalemia
Psychiatric disorders	**Common -** Insomnia **Uncommon -** Anxiety, depression, fatigue **Rare -** Confusional state, hallucinations
Nervous system disorders	**Common -** Dizziness, hypertonia, headache **Uncommon -** Cerebral infarction, paraesthesia, somnolence **Rare -** Ataxia, dysgeusia **Very rare -** Haemorrhage intracranial (including fatal intracranial haemorrhage), meningitis aseptic, epilepsy (including aggravated epilepsy), ageusia, anosmia
Eye disorders	**Uncommon -** Vision blurred, conjunctivitis **Rare -** Eye haemorrhage **Very rare -** Retinal artery occlusion, retinal vein occlusion
Ear and labyrinth disorders	**Uncommon -** Tinnitus, hypoacusis
Cardiac disorders	**Common -** Myocardial infarction **Uncommon -** Cardiac failure, palpitations, tachycardia **Rare -** Arrhythmia
Vascular disorders	**Very common -** Hyper-tension (including aggravated hyper-tension) **Rare -** Pulmonary embolism, flushing **Very rare -** Vasculitis
Respiratory, thoracic, and mediastinal disorders	**Common -** Rhinitis, cough, dyspnoea **Uncommon -** Bronchospasm **Rare -** Pneumonitis
Gastrointestinal disorders	**Common -** Nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia **Uncommon -** Constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of gastrointestinal inflammation), eructation **Rare -** Gastro-intestinal haemorrhage, duodenal ulcer, gastric ulcer, oesophageal ulcer, intestinal ulcer, and large intestinal ulcer, intestinal perforation; oesophagitis, melaena; pancreatitis, colitis
Hepatobiliary disorders	**Uncommon -** Hepatic function abnormal, hepatic enzyme increased (including increased SGOT and SGPT) **Rare -** Hepatitis **Very rare -** Hepatic failure (sometimes fatal or requiring liver transplant), hepatitis fulminant (some with fatal outcome), hepatic necrosis, cholestasis, hepatitis cholestatic, jaundice
Skin and subcutaneous tissue disorders	**Common -** Rash, pruritus (includes pruritus generalised) **Uncommon -** Urticaria, ecchymosis **Rare -** Angioedema, alopecia, photo-sensitivity **Very rare -** Dermatitis exfoliative, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis bullous
Musculoskeletal and connective Tissue disorder	**Common -** Arthralgia **Uncommon -** Muscle spasms (leg cramps) **Very rare -** Myositis
Renal and urinary disorders	**Uncommon -** Blood creatinine increase **Very rare -** Tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion
Reproductive system and breast disorders	**Rare -** Menstrual disorder **Frequency not known -** Infertility female (female fertility decreased)
General disorders and administrative site conditions	**Common -** Influenza-like illness, Oedema peripheral / fluid retention **Uncommon -** Face oedema, chest pain
Injury, poisoning and procedural complications	**Common -** Injury (accidental injury)

SIGNS AND SYMPTOMS OF OVERDOSE
In the event of suspected overdose, appropriate supportive medical care should be provided e.g. by eliminating the gastric contents, clinical supervision and, if necessary, the institution of symptomatic treatment. Dialysis is unlikely to be an efficient method of drug removal due to high protein binding.

STORAGE:
Store below 30°C.

PACKING:
10 capsules in an Alu/PVC blister, and 1 blister, packed in a printed box.
10 capsules in an Alu/PVC blister, and 3 blisters, packed in a printed box.
10 capsules in an Alu/PVC blister, and 10 blisters, packed in a printed box.

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