PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT
Revcox 200 mg Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 200 mg celecoxib.
Excipient(s) with known effect: lactose monohydrate.

3. PHARMACEUTICAL FORM
Capsule, hard.

Capsule: white body and orange cap, containing white to slightly yellow coloured pellets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
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.

4.2 Posology and method of administration
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
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 after meal, 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 Section 4.4 Special Warnings and Special Precautions for Use - Hepatic Effects).

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 section 4.4 Special Warnings and Special Precautions for Use – Renal Effects).

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 section 5.2 Pharmacokinetic Properties – Metabolism).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Known hypersensitivity to sulphonamides.
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients who have experienced asthma, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.
- Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 4.4 Special Warnings and Special Precautions for Use).
- Patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke).

4.4 Special warnings and precautions for use

Gastrointestinal (GI) effects
Upper and lower gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, 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 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

Cardiovascular effects
Celecoxib may increase number of serious cardiovascular (CV) events, mainly myocardial infarction (MI).

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. 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 patient and patient with peripheral arterial disease) should only be treated with celecoxib after careful consideration.

Contraindicated in patients who have increased risk of cardiovascular disease (ischeamic heart disease and stroke).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued.

Fluid retention and oedema
As with other active substances known to inhibit prostaglandin synthesis fluid retention and oedema have been observed in 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 oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia.

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

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 Section 4.2. 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.

Renal effects
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 older people. 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.

CYP 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 Section 4.5. Interaction with other medicinal products and other forms of interaction).

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

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 Section 4.5. Interaction with other medicinal products and other forms of interaction).

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

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.

Excipients
Revcox 200 mg capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 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 Section 4.2. Posology and method of administration and Section 5.2. Pharmacokinetic properties - Metabolism).

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.

Clinical pharmacokinetics study and *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.

Drug-specific
Interaction of celecoxib with warfarin or similar agents: (See Section 4.4. Special warnings and special precautions for use – Use with Oral Anticoagulants).

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 Section 4.4. Special warnings and special precautions for use - GI Effects). 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_{max} 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 Section 4.4. Special warnings and special precautions for use - Use with Oral Anticoagulants).

Diuretics: Clinical studies have shown that 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 in a clinical study between celecoxib and methotrexate.

Oral contraceptives: In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of a prototype combination oral contraceptive (1 mg norethindrone/0.035 mg ethinyl estradiol).

Other drugs: No clinically important interactions have been observed with celecoxib and antacids (aluminum and magnesium), omeprazole, glibenclamide (glyburide), phenytoin, or tolbutamide.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no studies in pregnant women. Studies in animals have shown reproductive toxicity, (see Section 5.3. Preclinical safety data). 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 upon discontinuation. Pregnant women on celecoxib should be closely monitored for amniotic fluid volume.

Breast-feeding

Studies in rats show that 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.

Fertility

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.

4.7 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.

4.8 Undesirable effects

System Organ Class	Frequency	Undesirable Effects
Infections and infestations	Common	Bronchitis, sinusitis, upper respiratory tract infection, urinary tract infection
	Uncommon	Pharyngitis, rhinitis
Blood and lymphatic system disorders	Uncommon	Anaemia
	Rare	Thrombocytopenia
	Very Rare	Pancytopenia
Immune system disorders	Uncommon	Allergy aggravated (hypersensitivity)

Psychiatric disorders	Common	Insomnia
	Uncommon	Anxiety
	Rare	Confusion (confusional state)
Nervous system disorders	Common	Dizziness
	Uncommon	Hypertonia somnolence
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Palpitations
	Rare	Cardiac failure congestive, arrhythmia, tachycardia
Vascular disorders	Common	Hypertension (including aggravated hypertension)
	Rare	Flushing
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting
	Uncommon	Gastric ulcer, tooth disorder
	Rare	Duodenal ulcer, oesophageal ulcer
	Very Rare	Intestinal perforation, pancreatitis
Hepatobiliary disorders	Uncommon	Abnormal hepatic function, elevation of hepatic enzymes (including increased SGOT and SGPT)
	Rare	Hepatitis
	Very Rare	Hepatic failure (sometimes fatal or requiring liver transplant), fulminant hepatitis (some with fatal outcome), liver necrosis, cholestasis, cholestatic hepatitis, jaundice
Skin and subcutaneous tissue disorders	Common	Pruritus (includes pruritus generalised), rash
	Uncommon	Urticaria, ecchymosis
	Rare	Angioedema, alopecia
	Very Rare	Dermatitis bullous
General disorders and administration site conditions	Common	Peripheral oedema/ fluid retention
	Uncommon	Face oedema, influenza-like illness
Injury, poisoning and procedural conditions	Common	Accidental injury (injury)

Post-marketing Experience
Adverse reactions identified from post-marketing experience are provided below. Frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%)), not known (cannot be estimated from the available data):

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 Section 4.4. Special warnings and special precautions for use – Hepatic Effects), 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 Section 4.4. Special warnings and special precautions for use – Renal Effects), 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 Section 4.6. Fertility, pregnancy and lactation)
General disorders and administration site conditions: Uncommon: chest pain

4.9 Overdose

There is limited clinical experience of overdose. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered to healthy subjects 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 active substance removal due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, Coxibs, ATC code: M01AH01

Mechanism of action

Celecoxib is an oral, selective, cyclooxygenase-2 (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.

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 man 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 thromboembolic 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. sulfamethoxazole and other sulfonamide antibiotics).

5.2 Pharmacokinetic properties

Absorption

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 the active substance 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 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.

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 Section 4.2. Posology and method of administration and Section 4.5. Interactions with other medicinal products and other forms of interaction).

Excretion

Celecoxib is mainly eliminated by hepatic metabolism. Less than 1% of the dose is 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. Preclinical studies indicate that 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 Section 4.2 Posology and method of administration).

In healthy adult volunteers, the 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 $T_{1/2}$ 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
A meta analysis of pharmacokinetic studies has suggested an 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 Section 4.2. 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 m^2) and in patients with chronic stable renal insufficiency (GFR 35-60 mL/min/1.73 m^2) 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 PGE_2 and 6-keto-$PGF_1\alpha$ (a prostacyclin metabolite) but leaves serum thromboxane B_2 (TXB_2) and urinary excretion of 11-dehydro-TXB_2, 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 edema 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 edema has been mild and self-limiting.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life
2 years

6.2 Special precautions for storage
Do not store above 30°C.

6.3 Packaging
Available pack sizes for Revcox 200 mg capsule are 30 and 100 capsules.

Not all available pack sizes may be marketed.

7. PRODUCT REGISTRATION HOLDER
Sandoz Products Malaysia Sdn. Bhd.
Unit 1202, Level 12, Uptown 1,
No. 1, Jalan SS 21/58, Damansara Uptown,
47400 Petaling Jaya, Selangor, Malaysia

8. DATE OF REVISION OF THE TEXT
May 2025