SUMMARY OF PRODUCT CHARACTERISTICS

CELDOL

Celecoxib Capsules 100 mg and 200 mg

R_x Only

NAME OF DRUG PRODUCT **:** Celecoxib Capsules 100 mg
Celecoxib Capsules 200 mg

(TRADE) NAME OF PRODUCT **:** CELDOL 100
CELDOL 200

STRENGTH **:** 100 mg and 200 mg.

PHARMACEUTICAL DOSAGE FORM: Capsules.

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Celecoxib Capsules 100 mg:

Each hard gelatin capsule contains Celecoxib Ph.Eur. 100 mg.

Celecoxib Capsules 200 mg:

Each hard gelatin capsule contains Celecoxib Ph.Eur. 200 mg.

PHARMACEUTICAL FORM:

Celecoxib Capsules 100 mg:

White cap and White body, Size '4' hard gelatin capsule filled with white to off white granular powder, imprinted with 'Y' on cap and '100' on body with blue ink.

Celecoxib Capsules 200 mg

White cap and White body, Size '2' hard gelatin capsule filled with white to off white granular powder, imprinted with 'Y' on cap and '200' on body with gold ink.

CLINICAL PARTICULARS:

Therapeutic indications

Celecoxib is indicated in adults for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

The decision to prescribe a selective cyclooxygenase-2 (COX-2) inhibitor should be based on an assessment of the individual patient's overall risks.

Posology and method of administration

Posology

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.

Osteoarthritis

The usual recommended daily dose is 200 mg taken once daily or in two divided doses. In some patients, with insufficient relief from symptoms, an increased dose of 200 mg twice daily may increase efficacy. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Rheumatoid arthritis

The initial recommended daily dose is 200 mg taken in two divided doses. The dose may, if needed, later be increased to 200 mg twice daily. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

Ankylosing spondylitis

The recommended daily dose is 200 mg taken once daily or in two divided doses. In a few patients, with insufficient relief from symptoms, an increased dose of 400 mg once daily or in two divided doses may increase efficacy. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

The maximum recommended daily dose is 400 mg for all indications.

Special populations

Elderly (>65 years)

As in younger adults, 200 mg per day should be used initially. The dose may, if needed, later be increased to 200 mg twice daily. Particular caution should be exercised in elderly with a body weight less than 50 kg.

Paediatric population

Celecoxib is not indicated for use in children.

CYP2C9 poor metabolisers

Patients who are known, or suspected to be CYP2C9 poor metabolisers 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.

Hepatic impairment

Treatment should be initiated at half the recommended dose in patients with established moderate liver impairment with a serum albumin of 25-35 g/l. Experience in such patients is limited to cirrhotic patients.

Renal impairment

Experience with Celecoxib in patients with mild or moderate renal impairment is limited, therefore such patients should be treated with caution.

Method of administration

Oral use.

Celecoxib may be taken with or without food. For patients who have difficulty swallowing capsules, the contents of a Celecoxib capsule can be added to applesauce, rice gruel, yogurt or mashed banana. To do so, the entire capsule contents must be carefully emptied onto a level teaspoon of cool or room temperature applesauce, rice gruel, yogurt or mashed banana and should be ingested immediately with 240 ml of water. The sprinkled capsule contents on applesauce, rice gruel or yogurt are stable for up to 6 hours under refrigerated conditions (2-8°C). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions and should be ingested immediately.

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, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic type reactions after taking acetylsalicylic acid (aspirin) or other NSAIDs including COX-2 inhibitors.

In pregnancy and in women of childbearing potential unless using an effective method of contraception.

Celecoxib has been shown to cause malformations in the two animal species studied. Thepotential for human risk in pregnancy is unknown, but cannot be excluded.

Breast-feeding.

Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).

Patients with estimated creatinine clearance <30 ml/min.

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

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. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly, glucocorticoids, patients using alcohol, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is further increase in the risk of gastrointestinal adverse effects for Celecoxib (gastrointestinal ulceration or other gastrointestinal complications), when Celecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

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. 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 drugs 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. Clinical trials with 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, 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 drugs 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).

Excipients

Celecoxib Capsules 100 mg and 200 mg contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interaction with other medicinal products and other forms of interaction

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 anti-hypertensive 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 2.6-fold and 1.5-fold 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

In vitro studies have shown some potential for Celecoxib to inhibit CYP2C19 catalysed metabolism. The clinical significance of this in vitro finding is unknown. Examples of drugs which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.

Methotrexate

In patients with rheumatoid arthritis Celecoxib had no statistically significant effect on the pharmacokinetics (plasma or renal clearance) of methotrexate (in rheumatologic doses). However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two drugs.

Lithium

In healthy subjects, co-administration of Celecoxib 200 mg twice daily with 450 mg twice daily of lithium resulted in a mean increase in C_{max} of 16% and in AUC of 18% of lithium. Therefore, patients on lithium treatment should be closely monitored when Celecoxib is introduced or withdrawn.

Oral contraceptives

In an interaction study, Celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethisterone/35 micrograms ethinylestradiol).

Glibenclamide/tolbutamide

Celecoxib does not affect the pharmacokinetics of tolbutamide (CYP2C9 substrate), or glibenclamide to a clinically 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 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%. 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.

Pregnancy and lactation.

Pregnancy

Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Celecoxib is contraindicated in pregnancy and in women who can become pregnant. If a woman becomes pregnant during treatment, Celecoxib should be discontinued.

Breast-feeding

Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. 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.

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.

Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence while taking Celecoxib should refrain from driving or operating machinery.

Undesirable effects

Adverse reactions are listed by system organ class and ranked by frequency in Table 1, reflecting data from the following sources:

- Adverse reactions reported in osteoarthritis patients and rheumatoid arthritis patients at incidence rates greater than 0.01% and greater than those reported for placebo during 12 placebo- and/or active-controlled clinical trials of duration up to 12 weeks at Celecoxib daily doses from 100 mg up to 800 mg. In additional studies using non-selective NSAID comparators, approximately 7400 arthritis patients have been treated with Celecoxib at daily doses up to 800 mg, including approximately 2300 patients treated for 1 year or longer. The adverse reactions observed with Celecoxib in these additional studies were consistent with those for osteoarthritis and rheumatoid arthritis patients listed in Table 1.
- Adverse reactions reported at incidence rates greater than placebo for subjects treated with Celecoxib 400 mg daily in long-term polyp prevention trials of duration up to 3 years (the Adenoma Prevention with Celecoxib (APC) and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials; see section 5.1, Pharmacodynamic properties:
  Cardiovascular safety – long-term studies involving patients with sporadic adenomatous polyps).

- Adverse drug reactions from post-marketing surveillance as spontaneously reported during a period in which an estimated >70 million patients were treated with Celecoxib (various doses, durations, and indications). Even though these were identified as reactions from post-marketing reports, trial data were consulted to estimate frequency.

  Frequencies are based on a cumulative meta-analysis with pooling of trials representing exposure in 38102 patients.

Table 1. Adverse Drug Reactions in Celecoxib Clinical Trials and Surveillance Experience (MedDRA Preferred Terms) [1,2]

	Adverse Drug Reaction Frequency					
System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Frequency Not Known
Infections and infestations		Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection				
Blood and lymphatic system disorders			Anaemia	Leukopenia, thrombocytopenia	Pancytopenia[4]	
Immune system disorders		Hyper-sensitivity			Anaphylactic shock, anaphylactic reaction[4]	
Metabolism and nutrition disorders			Hyperkalaemia			
Psychiatric disorders		Insomnia	Anxiety, depression, fatigue	Confusional state, Hallucinations[4]		
Nervous system disorders		Dizziness, hypertonia, headache[4]	Cerebral Infarction[1], paraesthesia, somnolence	Ataxia, dysgeusia	Haemorrhage intracranial (including fatal intracranial haemorrhage)[4], Meningitis aseptic[4] epilepsy (including aggravated epilepsy)[4], ageusia[4], anosmia[4]	
Eye disorders			Vision blurred, conjunctivitis[4]	Eye haemorrhage[4]	Retinal artery occlusion[4], retinal vein occlusion[4]	

Ear and labyrinth Disorders			Tinnitus, hypoacusis[1]			
Cardiac disorders		Myocardial infarction[1]	Cardiac failure, palpitations, tachycardia	Arrhythmia[4]		
Vascular disorders	Hypertension[1] (including aggravated hypertension)			Pulmonary embolism[4], flushing[4]	Vasculitis[4]	
Respiratory, thoracic, and mediastinal disorders		Rhinitis, cough, dyspnoea[1]	Bronchospasm[4]	Pneumonitis[4]		
Gastrointestinal disorders		Nausea[4], abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting[1], dysphagia[1]	Constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of gastrointestinal inflammation), eructation	Gastro-intestinal haemorrhage[4], duodenal ulcer, gastric ulcer, oesophageal ulcer, intestinal ulcer, and large intestinal ulcer; intestinal perforation; oesophagitis, melaena; pancreatitis, colitis[4]		
Hepatobiliary disorders			Hepatic function abnormal, hepatic enzyme increased (including increased SGOT and SGPT)	Hepatitis[4]	Hepatic failure[4] (sometimes fatal or requiring liver transplant), hepatitis fulminant[4] (some with fatal outcome), hepatic necrosis[4] , cholestasis[4], hepatitis cholestatic[4], jaundice[4]	
Skin and subcutaneous tissue disorders		Rash, pruritus (includes pruritus generalised)	Urticaria, ecchymosis[4]	Angioedema[4], alopecia, photosensitivity	Dermatitis exfoliative[4], erythema multiforme[4], Stevens-Johnson syndrome[4], toxic epidermal necrolysis[4], drug reaction with eosinophilia and systemic symptoms (DRESS)[4], acute generalised exanthematous	

					pustulosis (AGEP)[4], dermatitis bullous[4]	
Musculoskeletal and connective tissue disorders		Arthralgia[4]	Muscle spasms (leg cramps)		Myositis	
Renal and urinary disorders			Blood creatinine increased, blood urea increased	Renal failure acute[4], hyponatraemia	Tubulointerstitial nephritis[4], nephrotic syndrome[4], glomerulonephritis minimal lesion[4]	
Reproductive system and breast disorders				Menstrual disorder[4]		female (female fertility decreased)[3]
General disorders and administrative site conditions		Influenza-like illness, Oedema peripheral/ fluid retention	Face oedema, chest pain[4]			
Injury, poisoning and procedural complications		Injury (accidental Injury)				
	1. Adverse drug reactions that occurred in polyp prevention trials, representing subjects treated with Celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials). The adverse drug reactions listed above for the polyp prevention trials are only those that have been previously recognized in the post-marketing surveillance experience, or have occurred more frequently than in the arthritis trials. 2.Furthermore, the following *previously unknown* adverse reactions occurred in polyp prevention trials, representing subjects treated with Celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials): **Common:** angina pectoris, irritable bowel syndrome, nephrolithiasis, blood creatinine increased, benign prostatic hyperplasia, weight increased. **Uncommon:** helicobacter infection, herpes zoster, erysipelas, bronchopneumonia, labyrinthitis, gingival infection, lipoma, vitreous floaters, conjunctival haemorrhage, deep vein thrombosis, dysphonia, haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, allergic dermatitis, ganglion, nocturia, vaginal haemorrhage, breast tenderness, lower limb fracture, blood sodium increased. 3. Women intending to become pregnant are excluded from all trials, thus consultation of the trial database for the frequency of this event was not reasonable. 4. Frequencies are based on cumulative meta-analysis with pooling of trials representing exposure in 38102 patients.					

In final data (adjudicated) from the APC and PreSAP trials in patients treated with Celecoxib 400 mg daily for up to 3 years (pooled data from both trials), the excess rate over placebo for myocardial infarction was 7.6 events per 1000 patients (uncommon) and there was no excess rate for stroke (types not differentiated) over placebo.

Overdosage

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic drugs, NSAIDs, Coxibs.

Mechanism of action

Celecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily).

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. However, in healthy subjects, in small multiple dose studies with 600 mg BID (three times the highest recommended dose) Celecoxib had no effect on platelet aggregation and bleeding time compared to placebo.

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 T_{max} of about 4 hours and increases bioavailability by about 20%.

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.

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 intersubject 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.

PHARMACEUTICAL PARTICULARS

List of excipients

Capsule contents:

Lactose monohydrate, Hydroxypropyl Cellulose, Crospovidone (Type B), Povidone (K-30), Sodium Lauryl Sulfate, Sodium Stearyl Fumarate.

Capsule shell:

Gelatin

Titanium dioxide (E171)

Printing ink:

Shellac

FD&C Blue #2 Aluminum Lake (E132) for Celecoxib capsules 100 mg

Yellow Iron oxide (E172) for Celecoxib capsules 200 mg

Incompatibilities

Not applicable.

Shelf life

Please refer outer package for expiry date.

Special precautions for storage

Do not store above 30°C.

Nature and contents of container

Blister of 10 Capsules

MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Ltd.,
India.

DATE OF PREPARATION OF THIS LEAFLET

August 2016.