

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

CELEKOP-100 (Celecoxib Capsules 100mg)

2. Qualitative and quantitative composition

Each capsule contains Celecoxib EP.....100 mg

For the full list of excipients, Refer the Section 6.1

3. Pharmaceutical form

CELEKOP-100 (Celecoxib Capsules 100mg) are Size "2" opaque white with blue band printed "100" in white on body and "CEL" in white on cap

4. Clinical particulars

4.1 Therapeutic indications

CELECOXIB CAPSULES 100mg is indicated in the treatment of: Celecoxib is indicated for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2 Posology and method of administration

Posology

Osteoarthritis, 200mg daily in 1-2 divided doses, increased if necessary to max.200mg twice daily;

- Rheumatoid arthritis, 100mg twice daily, increased if necessary to 200mg twice daily;
- Alkylosing spondylitis, 200mg daily in 1-2 divided doses, increased if necessary to max. 400mg daily in 1-2 divided doses;
- Celecoxib Capsules are not recommended for use in children.

Method of administration

Administration via Oral route.

Oral: Swallow a Capsule with a glass of water as per dosage.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients.

- Known hypersensitivity to sulphonamides.
- Active peptic ulceration or gastrointestinal (GI) bleeding.
- 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.

4.4 Special warnings and precautions for use

Gastrointestinal (GI) effects

Upper 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 or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

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.

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. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, and the elderly 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.

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 (anaphylaxis and angioedema) 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.

4.5 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-hypertensive

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. In a 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients treated with celecoxib 200 mg BID, 48 % were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic

blood pressure increased >10 % compared to baseline), compared to 27 % of patients treated with placebo; this difference was statistically significant

Ciclosporin and tacrolimus

Co-administration 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 medicinal products are combined.

Acetylsalicylic acid

Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for CV prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid.

Pharmacokinetic interactions

Effects of celecoxib on other medicinal products

CYP2D6 inhibition

Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of medicinal products that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of medicinal products which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, antiarrhythmic medicinal products, 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 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 medicinal products 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 medicinal products.

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 area under the curve (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 medicinal products 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 (see sections 4.2 and 5.2).

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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and Lactation

Pregnancy

Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations. 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. The potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. 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 upon discontinuation. 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 Pfizer 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.

4.7 Effects on ability to drive and use machines

Celecoxib may have minor influence on the ability to drive and use machines. Patients who experience dizziness, vertigo or somnolence while taking celecoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

Gastro-intestinal disturbances including discomfort, nausea, diarrhoea, and occasionally bleeding, ulceration and dyspepsia. Other side-effects include hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity and haematuria. Blood disorders have also occurred. Fluid retention may occur (rarely precipitating CHF); Blood pressure may be raised. Dyspnoea, stomatitis, palpitation, dysphonia, cerebral infarction, fatigue, paraesthesia, lipoma, muscle cramps; taste disturbance, alopecia; seizures.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to report any suspected adverse reactions to the National Regulatory Agents.

4.9 Overdose

There is no 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 for nine days without clinically significant adverse effects. 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 medicinal product removal due to high protein binding.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and anti-rheumatic drugs, NSAIDs, 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 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 humans 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

5.2 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%. 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 Cmax, Tmax or T1/2 after administration of capsule contents on applesauce.

Distribution

Plasma protein binding is about 97 % at therapeutic plasma concentrations and the medicinal product 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. In a pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP2C9*1/*1, CYP2C9*1/*3, or CYP2C9*3/*3, the median C_{max} and AUC 0-24 of celecoxib on day 7 were approximately 4-fold and 7-fold, respectively, in subjects genotyped as CYP2C9*3/*3 compared to other genotypes. In three separate single-dose studies, involving a total of 5 subjects genotyped as CYP2C9*3/*3, single-dose AUC 0-24 increased by approximately 3-fold compared to normal metabolisers. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3-1.0 % among different ethnic groups.

Patients who are known, or suspected to be CYP2C9 poor metabolisers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. No clinically significant differences were found in Pharmacokinetic parameters of celecoxib between elderly African-Americans and Caucasians. The plasma concentration of celecoxib is approximately 100 % increased in elderly women (>65 years). Compared to subjects with normal hepatic function, patients with mild hepatic impairment had a mean increase in C_{max} of 53 % and in AUC of 26 % of celecoxib. The corresponding values in patients with moderate hepatic impairment were 41 % and 146 % respectively. The metabolic capacity in patients with mild to moderate impairment was best correlated to their albumin values. Treatment should be initiated at half the recommended dose in patients with moderate liver impairment (with serum albumin 25-35 g/l).

Patients with severe hepatic impairment (serum albumin <25 g/l) have not been studied and celecoxib is contraindicated in this patient group. There is little experience of celecoxib in renal impairment. The pharmacokinetics of celecoxib has not been studied in patients with renal impairment but is unlikely to be markedly changed in these patients. Thus, caution is advised when treating patients with renal impairment. Severe renal impairment is contraindicated.

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.

Preclinical safety data

Non-clinical safety data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, mutagenicity or carcinogenicity. Celecoxib at oral doses ≥ 150 mg/kg/day (approximately 2-fold human exposure at 200 mg twice daily as measured by AUC₀₋₂₄), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternbrae fused and sternbrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses ≥ 30 mg/kg/day (approximately 6-fold human exposure based on the AUC₀₋₂₄ at 200 mg twice daily) throughout organogenesis. These effects are expected following inhibition of prostaglandin synthesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses, and reduced embryo/fetal survival. Celecoxib was excreted in rat milk. In a peri-post natal study in rats, pup toxicity was observed. In a 2 year toxicity study an increase in nonadrenal thrombosis was observed in male rat at high doses.

6. Pharmaceutical Particulars

6.1 List of Excipients

Lactose Monohydrate, Croscarmellose Sodium, Sodium Lauryl Sulphate, Povidone (PVP K30), Magnesium Stearate, Purified water, Size "2" opaque white with blue band, reverse printed "100" in white on body and "CEL" in white on cap

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

36 Months

6.4 Special Precautions for storage

Store below 30°C in dry place. Protect from Moisture.

6.5 Nature and Content of container

Alu/PVC Blister

6.6 Special precautions for disposal and other handling

No special requirements.

Marketing Authorization Holder

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7. Marketing Authorization Number

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8. Date of first authorization/renewal of the authorization

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9. Date of revision of the text

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