

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 200 mg hard capsules
Onsenal 400 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg or 400 mg of celecoxib
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
White, opaque capsules with two gold bands marked 7767 and 200 (Onsenal 200 mg)
White, opaque capsules with two green bands marked 7767 and 400 (Onsenal 400 mg)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Onsenal is indicated for the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance (See section 4.4).

The effect of Onsenal-induced reduction of polyp burden on the risk of intestinal cancer has not been demonstrated (See section 4.4 and 5.1)

4.2 Posology and method of administration

The recommended oral dose is two 200 mg capsules twice per day, taken with food. (See section 5.2).

Usual medical care for FAP patients should be continued while on celecoxib. The maximum recommended daily dose is 800 mg.

Hepatic impairment: In patients with moderate hepatic impairment (serum albumin of 25-35 g/l), the daily recommended dose of celecoxib should be reduced by 50% (see section 4.3 and 5.2). Caution should be used as there is no experience in such patients at doses higher than 200 mg.

Renal impairment: Experience with celecoxib in patients with mild or moderate renal impairment is limited, therefore such patients should be treated with caution. (See section 4.3, 4.4 and 5.2).

Children: Celecoxib has not yet been studied in FAP for use in children and adolescents below the age of 18.

Elderly: The dose for elderly FAP patients has not been established. Special care should be used in such patients (see section 5.2).

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients (see section 6.1).

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 or non steroidal anti-inflammatory drugs (NSAIDs) including COX-2 (cyclooxygenase-2) inhibitors.

In pregnancy and in women who can become pregnant unless using an effective method of contraception. (See section 4.5, 4.6 and 5.3)

Breast feeding (See section 4.6 and 5.3).

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

Patients with renal insufficiency with estimated creatinine clearance <30ml/min.

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

Established ischaemic heart disease and/or cerebrovascular disease.

4.4 Special warnings and special precautions for use

Treatment with celecoxib in FAP has been studied for up to 6 months and has not been shown to reduce the risk of gastrointestinal or other form of cancer or the need for surgery. Therefore, the usual care of FAP patients should not be altered because of the concurrent administration of celecoxib. In particular, the frequency of routine endoscopic surveillance should not be decreased and FAP-related surgery should not be delayed.

Gastro-intestinal disorder

Upper gastrointestinal complications [perforations, ulcers or bleeds (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.

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

FAP patients carrying an ileorectal anastomosis or ileo pouch-anal anastomosis can develop anastomotic ulcerations. If an anastomotic ulcer is present, patients should not receive concomitant treatment with anticoagulants or acetyl salicylic acid.

Blood and lymphatic system disorder / Cardio-vascular disorder

Increased number of serious cardiovascular events, mainly myocardial infarction, has been found in a long-term placebo-controlled study in subjects with sporadic adenomatous polyps treated with celecoxib at doses of 200 mg BID and 400 mg BID compared to placebo (see 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with celecoxib after careful consideration (see 5.1).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore, antiplatelet therapies should not be discontinued (see section 5.1).

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.

In the event of elderly patients with mild to moderate cardiac dysfunction requiring therapy, special care and follow up is warranted.

Renal and hepatic disorders

Experience with celecoxib in patients with mild or moderate renal or hepatic impairment is limited, therefore such patients should be treated with caution. (See section 4.2 and 5.2).

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.

Other

Patients known to be CYP2C9 poor metabolisers should be treated with caution (see section 5.2).

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported in association with the use of NSAIDs including celecoxib during postmarketing surveillance (see section 4.8). Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in patients receiving celecoxib (see section 4.8). Patients with a history of sulphonamide allergy may be at greater risk of hypersensitivity reactions (see section 4.3). Celecoxib should be discontinued at the first sign of hypersensitivity.

Celecoxib may mask fever and other signs of inflammation.

In patients on concurrent therapy with warfarin, serious bleeding events have been reported. Caution should be exercised when combining celecoxib with warfarin and other oral anticoagulants (see section 4.5).

Onsenal 200 mg capsules contain lactose (49.8 mg). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The majority of the interaction studies have been performed with celecoxib doses of 200 mg BID (i.e. those used for osteoarthritis/rheumatoid arthritis). A more pronounced effect at 400 mg BID therefore cannot be excluded.

Anticoagulant activity should be monitored in patients taking warfarin or other anticoagulants, particularly in the first few days after initiating or changing the dose of celecoxib, since these

patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR. Bleeding events in association with increases in prothrombin time have been reported, in arthritis patients (mainly elderly) receiving celecoxib concurrently with warfarin, some of them fatal (see section 4.4).

NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. 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 or elderly patients) when ACE inhibitors or angiotensin II receptor antagonists 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.

Co-administration of NSAIDs and cyclosporin or tacrolimus have been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when celecoxib and any of these medicinal products are combined.

Celecoxib can be used with low dose acetylsalicylic acid, however it cannot be considered a substitute for acetylsalicylic acid for cardiovascular prophylaxis. 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. (see 5.1).

Pharmacokinetic interactions

Effects of celecoxib on other medicinal products

Celecoxib is a weak inhibitor of CYP2D6. During celecoxib treatment, the mean plasma concentrations of the CYP2D6 substrate dextromethorphan were increased by 136%. The plasma concentrations of medicinal products that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of medicines which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmics, 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.

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.

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.

Effects of other medicinal products on celecoxib

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.

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available for celecoxib. Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations (see section 4.3 and 5.3). 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.

Celecoxib is contraindicated in pregnancy and in women who can become pregnant unless using an effective method of contraception (see section 4.3).

If a woman becomes pregnant during treatment, celecoxib should be discontinued.

There are no studies on the excretion of celecoxib in human milk. Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Women who take celecoxib should not breastfeed.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

However, patients who experience dizziness, vertigo or somnolence while taking celecoxib should refrain from driving or operating machinery.

4.8 Undesirable effects

The adverse event profile reported for FAP patients was similar to that reported below for arthritis patients. Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial and was observed in 3 of 58 patients who had prior intestinal surgery: these events were minor and not of clinical concern. This occurrence is similar to that reported during routine surveillance in patients who did not receive NSAIDs.

The following reactions have been reported in arthritis patients receiving celecoxib.

[Very Common (>1/10), Common (\geq 1/100, <1/10) Uncommon (\geq 1/1000, <1/100) Rare (\geq 1/10,000, <1/1000) Very rare (<1/10,000 including isolated cases)]

Infections and infestations

Common: sinusitis, upper respiratory tract infection

Uncommon: urinary tract infection

Blood and the lymphatic system disorders

Uncommon: anaemia.

Rare: leucopenia, thrombocytopenia

Metabolism and nutrition disorders

Uncommon: hyperkalaemia

Psychiatric disorders

Common: insomnia

Uncommon: anxiety, depression, tiredness.

Nervous system disorders

Common: dizziness

Uncommon: blurred vision, hypertonia, paraesthesia

Rare: ataxia, taste alteration

Ear and labyrinth disorders

Uncommon: tinnitus

Cardiac disorders

Common: myocardial infarction *

Uncommon: heart failure, palpitations

Vascular disorders

Uncommon: ischaemic stroke*, hypertension, , hypertension aggravated

Respiratory, thoracic and mediastinal disorders

Common: pharyngitis, rhinitis

Uncommon: cough, dyspnoea

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, flatulence

Uncommon: constipation, eructation, gastritis, stomatitis, vomiting, , aggravation of gastrointestinal inflammation .

Rare: duodenal, gastric oesophageal, intestinal and colonic ulceration, dysphagia, intestinal perforation, oesophagitis, melaena.

Hepato-biliary disorders

Uncommon: abnormal hepatic function

Skin and subcutaneous tissue disorders

Common: rash.

Uncommon: urticaria.

Rare: alopecia, photosensitivity

Musculoskeletal and connective tissue disorders

Uncommon: leg cramps

General disorders and administration site conditions

Common: peripheral oedema/ fluid retention.

Investigations

Uncommon: increased SGOT and SGPT, increased creatinine, BUN increased

Reports from postmarketing experience include headache, nausea and arthralgia, also the following very rare (<1/10,000, including isolated cases):

Blood and lymphatic system disorders: pancytopenia.

Immune system disorders: serious allergic reactions, anaphylactic shock.

Psychiatric disorders: confusion, hallucinations.

Nervous system disorders: aggravated epilepsy.

Ear and labyrinth disorders: decreased hearing.

Vascular disorders: vasculitis.

Respiratory, thoracic and mediastinal disorders: bronchospasm.

Gastrointestinal disorders: gastrointestinal haemorrhage, acute pancreatitis.

Hepatobiliary disorders: hepatitis, jaundice.

Skin and subcutaneous tissue disorders: angioedema, isolated reports of skin exfoliation including: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme.

Musculoskeletal and connective tissue disorders: myositis.

Renal and urinary disorders: acute renal failure, interstitial nephritis.

*Foot Note:

The excess rate over placebo of myocardial infarction was estimated based on preliminary data from one long-term study in patients with colorectal polyps (median age: 59 years; (44-76)) treated with celecoxib 400mg BID for up to 3 years. It was $1.5-0.4=1.1\%$ (Common). In the same study, the excess for ischaemic stroke for 400 mg BID dose is: $0.75-0.38=0.36\%$ (Uncommon).

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 events. 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: Antineoplastic, ATC code: L01XX33

Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulphonamides (e.g. thiazides, furosemide) but differing from arylamine sulphonamides (e.g. sulphamethoxazole and other sulphonamide antibiotics).

Celecoxib is an oral, selective cyclooxygenase-2 (COX-2) inhibitor. No statistically significant inhibition of COX-1 (assessed as ex vivo inhibition of thromboxane B₂ [TxB₂] formation) was observed in healthy volunteers at the FAP therapeutic dose of 400 mg BID.

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. Elevated levels of COX-2 are found in many pre-malignant lesions (such as adenomatous colorectal polyps) and epithelial cancers. Familial Adenomatous Polyposis (FAP) is a genetic disease resulting from an autosomal dominant genetic alteration of a tumor suppressor gene, the adenomatous polyposis coli (APC) gene. Polyps with the APC mutation overexpress COX-2 and left untreated, these polyps continue to form and enlarge in the colon or rectum resulting in essentially a 100% chance of developing colorectal cancer. 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 thrombo-embolic reactions. COX-2 inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.

A dose-dependent effect on TxB_2 formation has been observed after high doses of celecoxib. However, in small multiple dose studies in healthy subjects with 600 mg BID celecoxib had no effect on platelet aggregation and bleeding time compared to placebo.

Experimental evidence shows that the mechanism(s) of action by which celecoxib leads to tumour death may be related to induction of apoptosis and inhibition of angiogenesis. Inhibition of COX-2 may have consequences on tumour viability that are unrelated to inflammation.

Celecoxib inhibits tumour formation in preclinical models of colon cancer, which express COX-2, whether induced by chemical (rat AOM model) or genetic (MIN mouse model) mutation.

Celecoxib has been shown to reduce the number and size of adenomatous colorectal polyps. A randomized double-blind placebo controlled study was conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype. The mean reduction in the number of colorectal polyps following six months of treatment was 28% (SD + 24%) for celecoxib 400 mg BID which was statistically superior to placebo (mean 5%, SD +16%). A meaningful reduction in duodenal adenoma area was also observed compared with placebo (14.5% celecoxib 400 mg BID versus 1.4% placebo), which however was not statistically significant.

Ongoing clinical Trials: Preliminary safety information from three long-term studies in Sporadic Adenomatous Polyps and Alzheimer's disease with celecoxib is available. In one of the three studies, there was a dose-related increase in cardiovascular events (mainly myocardial infarction, MI) at doses of 200mg BID and 400mg BID compared to placebo. The increased risk persisted throughout the study period (33 months). The relative risk for the composite endpoint (cardiovascular death, MI or stroke) was 3.2 (95% CI 1.3 – 8.0) for the higher dose and 2.5 (95% CI 1.0 – 6.3) for the lower dose of celecoxib, respectively, compared to placebo. Preliminary data from the other two long-term studies did not show a significantly increased cardiovascular risk with celecoxib 200mg BID and 400mg QD compared to placebo. This information will be updated as final data become available.

5.2 Pharmacokinetic properties

Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption by about 1 hour with an increase in total absorption (AUC) of 10 to 20%.

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. Plasma protein binding is about 97% at therapeutic plasma concentrations and celecoxib is not preferentially bound to erythrocytes. Elimination half-life is 8-12 hours. Steady state plasma concentrations are reached within 5 days of treatment. Pharmacological activity resides in the

parent substance. The main metabolites found in the circulation have no detectable COX-1 or COX-2 activity.

Celecoxib is metabolised in the liver by hydroxylation, oxidation and some glucuronidation. The phase I metabolism is mainly catalysed by CYP2C9. There is a genetic polymorphism of this enzyme. Less than 1% of the population are poor metabolisers and have an enzyme with decreased activity. Plasma concentrations of celecoxib are probably markedly increased in such patients. Patients known to be CYP2C9 poor metabolisers should be treated with caution.

No clinically significant differences were found in pharmacokinetic parameters of celecoxib between African-Americans and Caucasians.

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. When dosed at 200 mg per day 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. In FAP patients with moderate hepatic impairment (serum albumin of 25-35 g/l), the daily recommended dose of celecoxib should be reduced by 50%.

Patients with severe hepatic impairment (serum albumin <25 g/l) have not been studied and celecoxib is contraindicated in this patient group.

The pharmacokinetics of celecoxib has not been studied in patients with renal impairment but is unlikely to be markedly changed in these patients since it is mainly eliminated by hepatic metabolism. There is little experience of celecoxib in renal impairment and therefore caution is advised when treating patients with renal impairment. Severe renal impairment is a contraindication to use.

The plasma concentration of celecoxib is approximately 100% increased in elderly women (>65 years).

5.3 Preclinical safety data

Conventional embryo-foetal toxicity studies resulted in dose dependent occurrences of diaphragmatic hernia in rat foetuses and of cardiovascular malformations in rabbit foetuses at systemic exposures to free celecoxib approximately 3 times (rat) and 2 times (rabbit) higher than those achieved at the recommended daily human dose (800 mg). Diaphragmatic hernia was also seen in a peri-post natal toxicity study in rats, which included exposure during the organogenetic period. In the latter study, at the lowest systemic exposure where this anomaly occurred in a single animal, the estimated margin relative to the recommended daily human dose was 2 times more than the recommended daily human dose (800 mg).

In animals, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses. These effects are expected following inhibition of prostaglandin synthesis.

Celecoxib was excreted in rat milk. In a peri-post natal study in rats, pup toxicity was observed.

In a two-year toxicity study an increase in nonadrenal thrombosis was observed in male rat at high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Onsenal 200 mg Capsules contain:lactose monohydrate, sodium lauryl sulphate, povidone K30, croscarmellose sodium , magnesium stearate.

Capsule shells contain: Gelatin, titanium dioxide E171.

Printing ink contains: shellac , propylene glycol, iron oxide E172

Onsenal 400 mg Capsules contain: lactose monohydrate, sodium lauryl sulphate,, povidone K30, croscarmellos sodium, magnesium stearate.

Capsule shells contain: gelatin, titanium dioxide E171.

Printing ink contains shellac, propylene glycol, iron oxide E172, Brilliant Blue FCF E133.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Clear or opaque PVC/Aclar/Aluminium foil blisters (Onsenal 200 mg)

Opaque PVC/Aluminium foil blisters (Onsenal 400 mg)

Packs of 10 or 60 capsules

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmacia - Pfizer EEIG

Ramsgate Road

Sandwich

Kent CT13 9NJ

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/259/001-006

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

October 17, 2003

10. DATE OF REVISION OF THE TEXT