ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 200 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg of celecoxib.
Excipients: Lactose Monohydrate 49.8 mg For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
White, opaque capsules with two gold bands marked 7767 and 200.

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 sections 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 sections 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 sections 4.3, 4.4 and 5.2).

Paediatric patients: Experience with celecoxib in FAP patients below the age of 18 years is limited to a single pilot study in a very small population, in which patients were treated with celecoxib at doses up to 16 mg/kg daily, which corresponds to the recommended adult FAP dose of 800 mg daily (see section 5.1).

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.
Patients with the CYP2C9*3 allele, and, in particular those with CYP2C9*3*3 homozygous genotype, may be exposed to celecoxib levels that are higher than those for which safety has been studied in clinical trials. Therefore, the risk for high celecoxib exposure in poor

metabolizers should be considered carefully when treating FAP patients. Consider starting treatment at a reduced dose (see section 5.2).

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

- 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 (cyclooxigenase-2) selective inhibitors.
- In pregnancy and in women who can become pregnant unless using an effective method of contraception (see sections 4.5, 4.6 and 5.3)
- Breast feeding (see sections 4.6 and 5.3)
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10) (Class C).
- Patients with renal insufficiency 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

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). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid *vs*. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1).The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.

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 section 5.1).

As the cardiovascular risks of celecoxib were increased with the 400 mg twice daily dose in the APC trial (section 5.1), the response of the FAP patient to celecoxib should be re-examined periodically in

order to avoid unnecessary exposure in FAP patients for whom celecoxib is not effective (sections 4.2, 4.3, 4.8 and 5.1)

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

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.

In the event of elderly patients with mild to moderate cardiac dysfunction requiring therapy, special care and follow up is warranted. Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.

Renal and hepatic disorders
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, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.
Experience with celecoxib in patients with mild or moderate renal or hepatic impairment is limited, therefore such patients should be treated with caution (see sections 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.

Skin 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 (see section 4.8). 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 (see section 4.8). Patients with a history of sulphonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

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.

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.

Co-administration of NSAIDs and ciclosporin D derivatives 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 section 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 an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethistherone /35 microg ethinylestradiol).

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

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.

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

In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors (eg. fluconazole, amiodarone) 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).

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% (analogous studies have not been performed with amiodarone or other known CYP2C9 inhibitors). Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

4.6 Pregnancy and lactation

For celecoxib no clinical data on exposed pregnancies are available. Studies in animals (rats and rabbits) have shown reproductive toxicity (see sections 4.3 and 5.3). The potential risk for humans is unknown. 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.

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.

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

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 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). Because not all adverse drug reactions are reported to the MAH and included in the safety database, the frequencies of these reactions cannot be reliably determined.

TABLE 1	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1000)**	**Frequency Not Known (Post-marketing experience)[1]**
Infections and infestations	Sinusitis, upper respiratory tract infection, urinary tract infection			
Blood and lymphatic system disorders		Anemia	Leucopenia, thrombocytopenia	Pancytopenia
Immune system disorders	Allergy aggravated			Serious allergic reactions, anaphylactic shock, anaphylaxis
Psychiatric disorders	Insomnia	Anxiety, depression, tiredness	Confusion	Hallucinations
Metabolism and nutrition		Hyperkaelemia		
Nervous system disorders	Dizziness, hypertonia	Paraesthesia, somnolence	Ataxia, taste alteration	Headache, aggravated epilepsy, meningitis aseptic, ageusia , anosmia, fatal intracranial haemorrhage
Eye disorders		Blurred vision		Conjunctivitis, ocular haemorrhage, retinal artery or vein occlusion
Ear and labyrinth disorders		Tinnitus		Decreased hearing

Cardiac disorders		Heart failure, palpitations, tachycardia	Myocardial infarction[2]	Arrhythmia
Vascular disorders		Hypertension, hypertension aggravated		Flushing, vasculitis, pulmonary embolism
Respiratory, thoracic, and mediastinal disorders	Pharyngitis, rhinitis, cough	Dyspnoea		Bronchospasm
Gastrointestinal disorders	Abdominal pain, diarrhoea, dyspepsia, flatulence	Constipation, eructation, gastritis, stomatitis, vomiting, aggravation of gastrointestinal inflammation	Duodenal, gastric, oesophageal, intestinal, and colonic ulceration; dysphagia, intestinal perforation; oesophagitis, melaena; pancreatitis	Nausea, acute pancreatitis, gastrointestinal haemorrhage, colitis/colitis aggravated
Hepatobiliary disorders		Abnormal hepatic function, increased SGOT and SGPT	Elevation of hepatic enzymes	Hepatitis, hepatic failure jaundice
Skin and subcutaneous tissue disorders	Rash, pruritus	Urticaria	Alopecia, photosensitivity	Ecchymosis, bullous eruption, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema
Musculoskeletal and connective tissue disorders		Leg cramps		Arthralgia, myositis
Renal and urinary disorders		Increased creatinine, BUN increased		Acute renal failure, interstitial nephritis, hyponatraemia
Reproductive system and breast disorders				Menstrual disorder
General disorders and administration site conditions	Flu-like symptoms, peripheral oedema/ fluid retention			Chest pain

[1] Adverse drug reactions spontaneously reported to the safety surveillance database over a period in which an estimated >70 million patients were treated with celecoxib (various doses, durations, and indications). As a result, the frequencies of these adverse drug reactions cannot be reliably determined. Adverse drug reactions listed for the post-marketing population are only those that are not already listed for the arthritis trials (Table 1)

or the polyp prevention trials (Table 2).

[2] In a pooled analysis of 20 placebo-controlled studies with duration greater than 2 weeks up to 1 year in patients with OA and RA, the excess rate of myocardial infarction in patients treated with celecoxib 200 or 400 mg daily over placebo was 0.7 events per 1000 patients (Rare) and there was no excess of strokes.

The additional adverse reactions listed by system organ class and ranked by frequency in **Table 2** were reported at incidence rates greater than placebo for subjects treated with celecoxib 400 mg to 800 mg daily in long-term polyp prevention trials of duration up to 3 years (the APC and PreSAP trials; see Section 5.1, Pharmacodynamic properties: Cardiovascular Safety – Long-Term Studies Involving Patients With Sporadic Adenomatous Polyps).

TABLE 2	**Very Common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)
Infections and infestations		Ear infection, fungal infection (fungal infections were primarily nonsystemic)	Helicobacter infection, herpes zoster, erysipelas, wound infection, gingival infection, labrynthitis, bacterial infection
Neoplasms			Lipoma
Psychiatric			Sleep disorder
Nervous system disorders			Cerebral infarction
Eye disorders			Vitreous floaters; conjunctival hemorrhage
Ear and labyrinth disorders			Hypoacusis
Cardiac disorders		Angina pectoris; myocardial infarction	Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertropy
Vascular disorders	Hypertension*		Deep vein thrombosis; hematoma
Respiratory, thoracic, and mediastinal disorders		Dyspnoea	Dysphonia
Gastrointestinal disorders	Diarrhoea*	Nausea, gastroesophageal reflux disease, diverticulum, vomiting,* dysphagia, irritable bowel syndrome	Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
Skin and subcutaneous tissue disorders			Dermatitis allergic
Musculoskeletal and connective tissue disorders		Muscle spasms	Ganglion
Renal and urinary disorders		Nephrolithiasis, blood creatinine increased	Nocturia
Reproductive and breast disorders		Benign prostatic hyperplasia, prostatitis, prostatic specific antigen increased	Vaginal haemorrhage, breast tenderness, dysmenorrhea, ovarian cyst, menopausal symptoms
General disorders and administration		Edema	

site conditions			
Investigations		Weight increased	Blood levels increased: potassium, sodium, hemoglobin Blood levels decreased: hematocrit, testosterone
Injury, poisoning, and procedural complications			Foot fracture, lower limb fracture, epicondylitis, tendon rupture, fracture

* Hypertension, vomiting and diarrhoea are included in Table 2 because they were reported more frequently in these studies, which were of 3-year duration, compared to Table 1, which includes adverse reactions from studies of 12-week duration.

In final data (adjudicated) from the APC trial in patients treated with celecoxib 800 mg daily for up to 3 years, the excess rates over placebo were 11 events per 1000 patients for myocardial infarction (common); and 5 events per 1000 patients for stroke (uncommon; types of stroke not differentiated).

4.9 Overdose

There is no clinical experience of overdose in clinical trials. 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 sulfonamides (e.g. thiazides, furosemide) but differing from arylamine sulfonamides (e.g. sulfamethoxizole and other sulfonamide 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 B_2 [TxB_2] 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 overexpress 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 $\pm$ 24%) for celecoxib 400 mg BID which was statistically superior to placebo (mean 5%, SD $\pm$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.

Pilot Study in Juvenile FAP Patients: A total of 18 children 10 to 14 years of age who had genotype or phenotype positive FAP were treated with celecoxib 4 mg/kg/day (4 patients, compared to 2 patients treated with placebo), celecoxib 8 mg/kg/day (4 patients, compared to 2 patients treated with placebo), or celecoxib 16 mg/kg/day (4 patients, compared to 2 patients treated with placebo). Results demonstrated a statistically significant reduction in polyp burden in all celecoxib treatment groups compared to the corresponding placebo treatment groups. The greatest reduction was observed in patients treated with celecoxib 16 mg/kg/day, which corresponds to the recommended adult FAP dose of 800 mg daily. Safety data were reviewed in detail by a Data Safety Monitoring Committee, which concluded that celecoxib 16 mg/kg/day was a safe dose to recommend for further studies in juvenile FAP patients.

The long-term cardiovascular toxicity in children exposed to celecoxib has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to celecoxib or other COX-2 selective and non-selective NSAIDs (see section 4.4; cardiovascular effects.).

Cardiovascular Safety – Long-Term Studies Involving Subjects With Sporadic Adenomatous Polyps: Two studies involving subjects with sporadic adenomatous polyps were conducted with celecoxib i.e., the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In theAPC trial, there was a dose-related increase in the composite endpoint of cardiovascular death, myocardial infarction, or stroke (adjudicated) with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint.

In the APC trial, the relative risks compared to placebo for a composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) for placebo. The increases for both celecoxib dose groups versus placebo were mainly due to an increased incidence of myocardial infarction.

In the PreSAP trial, the relative risk compared to placebo for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9%

(12/628 subjects), respectively. The incidence of myocardial infarction (adjudicated) was 1.0% with (9/933 subjects) with celecoxib 400 mg once daily and 0.6% (4/628 subjects) with placebo.

Data from a third long-term study, ADAPT (The Alzheimer's Disease Anti-inflammatory Prevention Trial), did not show a significantly increased cardiovascular risk with celecoxib 200mg BID compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61 - 2.12) with celecoxib 200 mg twice daily. The incidence of myocardial infarction was 1.1% (8/717 patients) with celecoxib 200 mg twice daily and 1.2% (13/1070 patients) with placebo.

Data from pooled analysis of controlled randomized trials also suggest that cardiovascular risk may be associated with the use of celecoxib compared to placebo, with evidence for differences in risk based on celecoxib dose.

This medicinal product has been authorised under "Exceptional Circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency (EMA) will review any new information which may become available every year and this SPC will be updated as necessary.

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 metabolism is primarily mediated via cytochrome P450 CYP2C9. 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 CYP2C9 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 Cmax 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 metabolizers. 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 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution (see Section 4.2).

No clinically significant differences were found in pharmacokinetic parameters of celecoxib between 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. 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.

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

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)

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.
Packs of 10 or 60 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/259/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 October 2003/17 October 2008

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 400 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400 mg of celecoxib.
Excipients: Lactose Monohydrate 99.6 mg For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
White, opaque capsules with two green bands marked 7767 and 400.

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 sections 4.4 and 5.1)

4.2 Posology and method of administration

The recommended oral dose is one 400 mg capsule 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 sections 4.3 and 5.2). Caution should be used as there is no experience in such patients at doses higher than 400 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 sections 4.3, 4.4 and 5.2).

Paediatric patients: Experience with celecoxib in FAP patients below the age of 18 years is limited to a single pilot study in a very small population, in which patients were treated with celecoxib at doses up to 16 mg/kg daily, which corresponds to the recommended adult FAP dose of 800 mg daily (see section 5.1).

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.

Patients with the CYP2C9*3 allele, and, in particular those with CYP2C9*3*3 homozygous genotype, may be exposed to celecoxib levels that are higher than those for which safety has been studied in clinical trials. Therefore, the risk for high celecoxib exposure in poor

metabolizers should be considered carefully when treating FAP patients. Consider starting treatment at a reduced dose (see section 5.2).

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

- 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 (cyclooxigenase-2) selective inhibitors.
- In pregnancy and in women who can become pregnant unless using an effective method of contraception (see sections 4.5, 4.6 and 5.3)
- Breast feeding (see sections 4.6 and 5.3)
- Severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10) (Class C).
- Patients with renal insufficiency 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

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). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid *vs*. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1).

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

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 section 5.1).

As the cardiovascular risks of celecoxib were increased with the 400 mg twice daily dose in the APC trial (section 5.1), the response of the FAP patient to celecoxib should be re-examined periodically in order to avoid unnecessary exposure in FAP patients for whom celecoxib is not effective (sections 4.2, 4.3, 4.8 and 5.1).

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

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.

In the event of elderly patients with mild to moderate cardiac dysfunction requiring therapy, special care and follow up is warranted. Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.

Renal and hepatic disorders
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, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib.

Experience with celecoxib in patients with mild or moderate renal or hepatic impairment is limited, therefore such patients should be treated with caution (see sections 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.

Skin 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 (see section 4.8). 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 (see section 4.8). Patients with a history of sulphonamide allergy or any drug allergy may be at greater risk of serious skin reactions or hypersensitivity reactions (see section 4.3). Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

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 400 mg capsules contain lactose (99.6 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.

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.

Co-administration of NSAIDs and cyclosporine D derivatives 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 section 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 an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethistherone /35 microg ethinylestradiol).

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

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.

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

In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors (eg. fluconazole, amiodarone) 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).

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% (analogous studies have not been performed with amiodarone or other known CYP2C9 inhibitors). Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

4.6 Pregnancy and lactation

For celecoxib no clinical data on exposed pregnancies are available. Studies in animals (rats and rabbits) have shown reproductive toxicity (see sections 4.3 and 5.3). The potential risk for humans is unknown. 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.

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.

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

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 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). Because not all adverse drug reactions are reported to the MAH and included in the safety database, the frequencies of these reactions cannot be reliably determined.

TABLE 1	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1000)**	**Frequency Not Known (Post-marketing experience)[1]**
Infections and infestations	Sinusitis, upper respiratory tract infection, urinary tract infection			
Blood and lymphatic system disorders		Anemia	Leucopenia, thrombocytopenia	Pancytopenia
Immune system disorders	Allergy aggravated			Serious allergic reactions, anaphylactic shock, anaphylaxis
Psychiatric disorders	Insomnia	Anxiety, depression, tiredness	Confusion	Hallucinations
Metabolism and nutrition disorders		Hyperkaelemia		
Nervous system disorders	Dizziness, hypertonia	Paraesthesia, somnolence	Ataxia, taste alteration	Headache, aggravated epilepsy, meningitis aseptic, ageusia , anosmia, fatal intracranial haemorrhage
Eye disorders		Blurred vision		Conjunctivitis, ocular haemorrhage, retinal artery or vein occlusion
Ear and labyrinth disorders		Tinnitus		Decreased hearing
Cardiac disorders		Heart failure, palpitations,	Myocardial infarction[2]	Arrhythmia

		tachycardia		
Vascular disorders		Hypertension, hypertension aggravated		Flushing, vasculitis, pulmonary embolism
Respiratory, thoracic, and mediastinal disorders	Pharyngitis, rhinitis, cough	Dyspnoea		Bronchospasm
Gastrointestinal disorders	Abdominal pain, diarrhoea, dyspepsia, flatulence	Constipation, eructation, gastritis, stomatitis, vomiting, aggravation of gastrointestinal inflammation	Duodenal, gastric, oesophageal, intestinal, and colonic ulceration; dysphagia, intestinal perforation; oesophagitis, melaena; pancreatitis	Nausea, acute pancreatitis, gastrointestinal haemorrhage, colitis/colitis aggravated
Hepatobiliary disorders		Abnormal hepatic function, increased SGOT and SGPT	Elevation of hepatic enzymes	Hepatitis, hepatic failure jaundice
Skin and subcutaneous tissue disorders	Rash, pruritus	Urticaria	Alopecia, photosensitivity	Ecchymosis, bullous eruption, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema
Musculoskeletal and connective tissue disorders		Leg cramps		Arthralgia, myositis
Renal and urinary disorders		Increased creatinine, BUN increased		Acute renal failure, interstitial nephritis, hyponatraemia
Reproductive system and breast disorders				Menstrual disorder
General disorders and administration site conditions	Flu-like symptoms, peripheral oedema/ fluid retention			Chest pain

[1] Adverse drug reactions spontaneously reported to the safety surveillance database over a period in which an estimated >70 million patients were treated with celecoxib (various doses, durations, and indications). As a result, the frequencies of these adverse drug reactions cannot be reliably determined. Adverse drug reactions listed for the post-marketing population are only those that are not already listed for the arthritis trials (Table 1) or the polyp prevention trials (Table 2).

[2] In a pooled analysis of 20 placebo-controlled studies with duration greater than 2 weeks up to 1 year in patients with OA and RA, the excess rate of myocardial infarction in patients treated with celecoxib 200 or 400 mg daily over placebo was 0.7 events per 1000 patients (Rare) and there was no excess of strokes.

The additional adverse reactions listed by system organ class and ranked by frequency in **Table 2** were reported at incidence rates greater than placebo for subjects treated with celecoxib 400 mg to 800 mg

daily in long-term polyp prevention trials of duration up to 3 years (the APC and PreSAP trials; see Section 5.1, Pharmacodynamic properties: Cardiovascular Safety – Long-Term Studies Involving Patients With Sporadic Adenomatous Polyps).

TABLE 2	**Very Common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1000 to <1/100)
Infections and infestations		Ear infection, fungal infection (fungal infections were primarily nonsystemic)	Helicobacter infection, herpes zoster, erysipelas, wound infection, gingival infection, labrynthitis, bacterial infection
Neoplasms			Lipoma
Psychiatric			Sleep disorder
Nervous system disorders			Cerebral infarction
Eye disorders			Vitreous floaters; conjunctival hemorrhage
Ear and labyrinth disorders			Hypoacusis
Cardiac disorders		Angina pectoris; myocardial infarction	Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertropy
Vascular disorders	Hypertension*		Deep vein thrombosis; hematoma
Respiratory, thoracic, and mediastinal disorders		Dyspnoea	Dysphonia
Gastrointestinal disorders	Diarrhoea*	Nausea, gastroesophageal reflux disease, diverticulum, vomiting,* dysphagia, irritable bowel syndrome	Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
Skin and subcutaneous tissue disorders			Dermatitis allergic
Musculoskeletal and connective tissue disorders		Muscle spasms	Ganglion
Renal and urinary disorders		Nephrolithiasis, blood creatinine increased	Nocturia
Reproductive and breast disorders		Benign prostatic hyperplasia, prostatitis, prostatic specific antigen increased	Vaginal haemorrhage, breast tenderness, dysmenorrhea, ovarian cyst, menopausal symptoms
General disorders and administration site conditions		Edema	
Investigations		Weight increased	Blood levels increased: potassium, sodium, hemoglobin Blood levels decreased: hematocrit, testosterone
Injury, poisoning, and procedural			Foot fracture, lower limb fracture, epicondylitis, tendon rupture,

complications			fracture
* Hypertension, vomiting and diarrhoea are included in Table 2 because they were reported more frequently in these studies, which were of 3-year duration, compared to Table 1, which includes adverse reactions from studies of 12-week duration.			

In final data (adjudicated) from the APC trial in patients treated with celecoxib 800 mg daily for up to 3 years, the excess rates over placebo were 11 events per 1000 patients for myocardial infarction (common); and 5 events per 1000 patients for stroke (uncommon; types of stroke not differentiated).

4.9 Overdose

There is no clinical experience of overdose in clinical trials. Single doses up to 1400 mg and multiple doses up to 1400 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 sulfonamides (e.g. thiazides, furosemide) but differing from arylamine sulfonamides (e.g. sulfamethoxizole and other sulfonamide 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 B_2 [TxB_2] 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 overexpress 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 $\pm$ 24%) for celecoxib 400 mg BID which was statistically superior to placebo (mean 5%, SD $\pm$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.

Pilot Study in Juvenile FAP Patients: A total of 18 children 10 to 14 years of age who had genotype or phenotype positive FAP were treated with celecoxib 4 mg/kg/day (4 patients, compared to 2 patients treated with placebo), celecoxib 8 mg/kg/day (4 patients, compared to 2 patients treated with placebo), or celecoxib 16 mg/kg/day (4 patients, compared to 2 patients treated with placebo). Results demonstrated a statistically significant reduction in polyp burden in all celecoxib treatment groups compared to the corresponding placebo treatment groups. The greatest reduction was observed in patients treated with celecoxib 16 mg/kg/day, which corresponds to the recommended adult FAP dose of 800 mg daily. Safety data were reviewed in detail by a Data Safety Monitoring Committee, which concluded that celecoxib 16 mg/kg/day was a safe dose to recommend for further studies in juvenile FAP patients.

The long-term cardiovascular toxicity in children exposed to celecoxib has not been evaluated and it is unknown if the long-term risk may be similar to that seen in adults exposed to celecoxib or other COX-2 selective and non-selective NSAIDs (see section 4.4; cardiovascular effects).

Cardiovascular Safety – Long-Term Studies Involving Subjects With Sporadic Adenomatous Polyps: Two studies involving subjects with sporadic adenomatous polyps were conducted with celecoxib i.e., the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint of cardiovascular death, myocardial infarction, or stroke (adjudicated) with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint.

In the APC trial, the relative risks compared to placebo for a composite endpoint (adjudicated) of cardiovascular death, myocardial infarction, or stroke were 3.4 (95% CI 1.4 - 8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1 - 7.2) with celecoxib 200 mg twice daily. Cumulative rates for this composite endpoint over 3 years were 3.0% (20/671 subjects) and 2.5% (17/685 subjects), respectively, compared to 0.9% (6/679 subjects) for placebo. The increases for both celecoxib dose groups versus placebo were mainly due to an increased incidence of myocardial infarction.

In the PreSAP trial, the relative risk compared to placebo for this same composite endpoint (adjudicated) was 1.2 (95% CI 0.6 - 2.4) with celecoxib 400 mg once daily compared to placebo. Cumulative rates for this composite endpoint over 3 years were 2.3% (21/933 subjects) and 1.9% (12/628 subjects), respectively. The incidence of myocardial infarction (adjudicated) was 1.0% with (9/933 subjects) with celecoxib 400 mg once daily and 0.6% (4/628 subjects) with placebo.

Data from a third long-term study, ADAPT (The Alzheimer's Disease Anti-inflammatory Prevention Trial), did not show a significantly increased cardiovascular risk with celecoxib 200mg BID compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61 - 2.12) with celecoxib 200 mg twice daily. The incidence of

myocardial infarction was 1.1% (8/717 patients) with celecoxib 200 mg twice daily and 1.2% (13/1070 patients) with placebo.

Data from pooled analysis of controlled randomized trials also suggest that cardiovascular risk may be associated with the use of celecoxib compared to placebo, with evidence for differences in risk based on celecoxib dose.

This medicinal product has been authorised under "Exceptional Circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information which may become available every year and this SPC will be updated as necessary.

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 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 400 mg administered once daily in healthy volunteers, genotyped as either CYP2C9*1/*1, CYP2C9*1/*3, or CYP2C9*3/*3, the median Cmax 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 metabolizers. 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 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution (see Section 4.2).

No clinically significant differences were found in pharmacokinetic parameters of celecoxib between 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. 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.

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

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)
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

Opaque PVC/Aclar/Aluminium foil blisters.
Packs of 10 or 60 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/259/005-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 October 2003/17 October 2008

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

- Pfizer Manufacturing Deutschland GmbH, Heinrich-Mack-Strasse 35, 89257 Illertissen, Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the version dated 28 February 2005 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).
In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA

PSUR
The MAH shall continue to submit Periodic Safety Update Reports (PSURs) on a yearly basis.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical aspects

The MAH has previously committed to undertake a “Phase III placebo-controlled trial with celecoxib in genotype positive subjects with Familial Adenomatous Polyposis” (CHIP trial, Protocol A3191193) to generate further efficacy and safety data.

The MAH will submit a progress report for the CHIP trial, including an update on safety data, in the 8th annual reassessment and will submit a full study report for the completed study when available. The progress report will include full documentation of efforts to achieve the target for yearly recruitment: an increased number of 30 patients/year is expected.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton - 200 mg hard capsules (clear, opaque blister)

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 200 mg hard capsules
Celecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg celecoxib

3. LIST OF EXCIPIENTS

Lactose
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/259/001, 002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onsenal 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton - 200 mg hard capsules (clear, opaque blister)

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 200 mg hard capsules
Celecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg celecoxib

3. LIST OF EXCIPIENTS

Lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/259/003,004

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onsenal 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 200 mg capsules
Celecoxib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton - 400 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 400 mg hard capsules
Celecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 400 mg celecoxib

3. LIST OF EXCIPIENTS

Lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/259/005

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onsenal 400 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton - 400 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 400 mg hard capsules
Celecoxib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 400 mg celecoxib

3. LIST OF EXCIPIENTS

Lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/259/006

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Onsenal 400 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Onsenal 400 mg capsules
Celecoxib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Onsenal 200 mg hard capsules
celecoxib

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ONSENAL IS AND WHAT IT IS USED FOR

Onsenal belongs to a group of medicines called cyclo-oxygenase-2 (COX-2) inhibitors. Cyclo-oxygenase-2 is an enzyme that increases at inflammatory sites and in abnormally growing cells. Onsenal works by inhibiting COX-2, to which such dividing cells are sensitive. As a consequence the cells die.

Onsenal is used to reduce the number of gastrointestinal polyps in patients with Familial Adenomatous Polyposis (FAP). FAP is an inherited disorder in which the rectum and colon are covered with many polyps that might develop colorectal cancer. Onsenal should be used along with the usual care for FAP patients such as surgery and endoscopic surveillance.

2. BEFORE YOU TAKE ONSENAL

Do not take ONSENAL
- if you have had an allergic reaction to any of the ingredients of Onsenal
- if you have had an allergic reaction to a group of medicines called “sulphfonamides”. These include some antibiotics (Bactrim and Septra used in combination of sulfamethoxazole and trimethoprim), which can be used to treat infections
- if you have a stomach or duodenal ulcer, or bleeding in the stomach or intestines
- if after taking aspirin or another anti-inflammatory medicine you have had nasal polyps or severe nasal congestion, or any allergic reaction such as an itchy skin rash, swelling, breathing difficulties or wheezing
- women of childbearing potential unless using an effective method of contraception
- if you are breast feeding
- if you have inflammation of the colon (ulcerative colitis) or intestinal tract (Crohn’s disease)
- if you have severe liver disease
- if you have severe kidney disease
- if you have heart failure, established heart disease and /or cerebrovascular disease, e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages of blood vessels to the heart or brain
- if you have had an operation to clear or bypass blockages

- or if you have or have had problems with blood circulation (peripheral arterial disease) or if you have had surgery on the arteries of your legs

Take special care with ONSENAL
Some people will need special care from their doctors when they are taking Onsenal. Make sure that your doctor knows before you start taking Onsenal:
- if you have conditions which increase your risk of heart disease such as high blood pressure, diabetes, high cholesterol or if you smoke you should discuss with your doctor whether Onsenal is suitable for you
- if you have had a stomach or duodenal (intestinal) ulcer or bleeding in the stomach or intestines
- if your heart, liver, or kidneys are not working well, your doctor may want to keep a regular check on you
- if you have fluid retention (such as swollen ankles or feet)
- if you are dehydrated, for example by sickness or diarrhoea or if you are taking diuretic treatment (water tablets)
- if you have had a serious allergic reaction or a serious skin reaction to any medicines
- if you are taking acetylsalicylic acid
- if you are taking anticoagulants
- if you have intolerance to some sugars
- if you are being treated for an infection, because Onsenal may mask a fever which is a sign of an infection

  if you are over 65 years of age your doctor may want to keep a regular check on you

As with other non-steroidal, anti-inflammatory drugs (NSAIDs; eg. ibuprofen or diclofenac), this medicine may lead to an increase in blood pressure, and so your doctor may ask to monitor your blood pressure on a regular basis.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without a prescription.

Before you start taking Onsenal make sure your doctor knows if you are taking:
- ACE inhibitors or Angiotensin II receptor antagonists (used for high blood pressure and heart failure)
- Acetylsalcylic acid or other anti-inflammatory medicines
- Cyclosporin and tacrolimus (used for immune system suppression e.g. after transplants)
- Dextromethorphan (used as an antitussive in cough mixtures)
- Diuretics (used to treat fluid retention)
- Fluconazole (used to treat fungal infections)
- Lithium (used to treat depression)
- Rifampicin (used to treat bacterial infections)
- Warfarin (used to prevent blood from clotting) or other anticoagulants
- Other medicines to treat depression, sleep disorders, high blood pressure or an irregular heartbeat
- Neuroleptics (used to treat some mental disorders)
- Methotrexate (used to treat rheumatoid arthritis, psoriasis and leukaemia)
- Carbamazepine (used to treat epilepsy/seizures and some forms of pain or depression)
- Barbiturates (used to treat epilepsy/seizures and some sleep disorders)

Onsenal can be taken with low dose acetylsalicylic acid (aspirin). Ask your doctor for advice before taking both of these medicines together.

Taking ONSENAL with food and drink
You can take Onsenal with or without food.

Pregnancy and breast-feeding
You must not take Onsenal if you are pregnant or if it is possible that you become pregnant.
You must not take Onsenal if you are breast feeding.

Driving and using machines
If you feel dizzy or tired after taking Onsenal, do not drive or use machinery until you are feeling normal again.

Important information about some of the ingredients of Onsenal:
Onsenal contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ONSENAL

Always take Onsenal exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. The usual dose is 400 mg twice a day. You will usually take two 200 mg capsules twice a day.

The maximum recommended daily dose is 800 mg.

If you take more ONSENAL than you should
If you accidentally take too many capsules, tell your doctor or pharmacist as soon as possible.

If you forget to take ONSENAL
Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ONSENAL can cause side effects, although not everybody gets them.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

The side effects listed below were observed in arthritis patients who took medicines with the same active ingredient as Onsenal:

Stop taking the capsules and tell your doctor immediately
- If you have an allergic reaction such as skin rash, swelling of the face, wheezing or difficulty breathing
- If you have heart problems such as pain in the chest
- If you have liver failure (symptoms may include nausea (feeling sick), diarrhoea, jaundice (your skin or the whites of your eyes look yellow))
- If you have blistering or peeling of the skin
- If you have severe stomach pain or any sign of bleeding in the stomach or intestines, such as passing black or bloodstained bowel movements, or vomiting blood

Common side effects which may affect more than 1 person in 100, are listed below
- Fluid build up with swollen ankles, legs and/or hands
- Urinary infections
- Sinusitis (sinus inflammation, sinus infection, blocked or painful sinuses), blocked or runny nose, sore throat, coughs, colds, flu-like symptoms
- Dizziness, difficulty sleeping
- stomach ache, diarrhoea, indigestion, wind
- Rash, itching

- Muscle stiffness
- Worsening of existing allergies

Uncommon side effects which may affect more than 1 person in a 1000, are listed below:
- Heart failure, palpitations (awareness of heart beat), fast heart rate
- Worsening of existing high blood pressure
- Abnormalities in liver-related blood tests
- Abnormalities in kidney-related blood tests
- Anaemia (changes in red blood cells that can cause fatigue and breathlessness)
- Anxiety, depression, tiredness, drowsiness, tingling sensations (pins and needles)
- High levels of potassium in blood test results (can cause nausea (feeling sick), fatigue, muscle weakness or palpitations)
- Impaired or blurred vision, ringing in the ears, mouth pain and soresConstipation, burping, stomach inflammation (indigestion, stomach ache or vomiting), worsening of inflammation of the stomach or intestine.
- Leg cramps
- Raised itchy rash (hives)

Rare side effects which may affect more than 1 person in a 10,000, are listed below
- Ulcers (bleeding) in the stomach, gullet or intestines; or rupture of the intestine (can cause stomach ache, fever, nausea, vomiting, intestinal blockage), dark or black stools, inflammation of the gullet (can cause difficulty in swallowing), inflammation of the pancreas (can lead to stomach pain)
- Reduced number of white blood cells (which help protect the body from infection) and blood platelets (increased chance of bleeding or bruising)
- Difficulty coordinating muscular movements
- Feeling confused, changes in the way things taste
- Increased sensitivity to light
- Loss of hair

Additional reactions have been reported from actual use of the active ingredient of Onsenal (in post-marketing experience). The frequencies of these reactions are difficult to determine but are generally considered to be very rare (affecting less than 1 person in every 10,000)
- Bleeding within the brain causing death
- Serious allergic reactions (including potentially fatal anaphylactic shock) which can cause skin rash, swelling of the face, lips, mouth, tongue or throat, wheezing or difficulty breathing; difficulty swallowing
- Bleeding of the stomach or intestines (can lead to bloody stools or vomiting), inflammation of the intestine or colon, nausea (feeling sick)
- Serious skin conditions such as Stevens-Johnson syndrome, exfoliative dermatitis and toxic epidermal necrolysis (can cause rash, blistering or peeling of the skin)
- Liver failure, liver damage and severe liver inflammation (sometimes fatal or requiring liver transplant). Symptoms may include nausea (feeling sick), diarrhoea, jaundice, yellow discolouration of the skin or eyes, dark urine, pale stools, bleeding easily, itching or chills
- Kidney problems (possible kidney failure, inflammation of the kidneys)
- Blood clot in the blood vessels in the lungs. Symptoms may include sudden breathlessness, sharp pains when you breathe or collapse
- Irregular heartbeat
- Meningitis (inflammation of the membrane around the brain and spinal cord)
- Hallucinations
- Worsening of epilepsy (possible more frequent and/or severe seizures)
- Inflamed blood vessels (can cause fever, aches, purple blotches on the skin)
- Blockage of an artery or vein in the eye leading to partial or complete loss of vision, conjunctivitis, eye infection (pink eye), bleeding in the eye
- A reduction in the number of red and white blood cells and platelets (may cause tiredness, easy bruising, frequent nose bleeds and increased risk of infections)
- Chest pain

- Impaired sense of smell
- Skin discolouration (bruising), muscle pain and weakness, painful joints
- Menstrual disturbances
- Headache, flushing
- Low levels of sodium in blood test results (can cause loss of appetite, headache, nausea (feeling sick), muscle cramps and weakness)

In clinical studies where Onsenal was taken for up to 3 years to prevent spontaneous colon polyps, the following additional side effects have been observed (side effects marked with an asterisk were more common in these studies than in arthritis studies):

Very Common side-effects (affecting more than 1 person in every 10):
- High blood pressure*, diarrhoea*

Common
- Heart problems: heart attack*, angina (chest pain)
- Stomach problems: nausea, heartburn, diverticulum (a problem with the stomach or intestine that can become painful or infected), vomiting*, irritable bowel syndrome (can include stomach ache, diarrhoea, indigestion, wind)
- Kidney stones (which may lead to stomach or back pain, blood in urine), difficulty passing urine, increased creatinine (blood test result related to kidney function)
- Difficulty breathing
- Muscle spasms
- Oedema (water retention that can cause swelling)
- Enlarged or inflamed prostate, prostate specific antigen increased (lab test)
- Infections of various types
- Weight gain

Uncommon
- Stroke
- Unstable angina (chest pain), troubles with heart valves, rhythm, or coronary arteries, or enlarged heart
- Deep vein thrombosis (blood clot usually in the leg, which may cause pain, swelling or redness of the calf or breathing problems), bruising
- Stomach infection(which can cause irritation and ulcers of the stomach and intestines), bleeding from piles/haemorrhoids, frequent bowel movements, inflamed or bleeding gums/mouth sores
- Lower limb fracture, tendon rupture or inflammation
- Shingles, skin infection, allergic dermatitis (dry itchy rash)
- Floaters or haemorrhage in the eye causing blurred or impaired vision, vertigo due to inner ear troubles, difficulty speaking
- Difficulty sleeping, excessive urination at night
- Fatty lumps in skin or elsewhere, ganglion cyst (harmless swellings on or around joints and tendons in the hand or foot)
- Abnormal or heavy bleeding from the vagina, painful menstruation, breast pain, ovarian cyst, menopausal symptoms
- High levels of sodium or haemoglobin and low levels of hematocrit or testosterone in blood test results
- Decreased hearing
- Changes in blood counts

5. HOW TO STORE ONSENAL

Keep out of the reach and sight of children.

Do not store your capsules above 30°C.

Do not take the capsule after the ‘expiry date’ shown on the blister and carton. If your capsules are out of date, take them to your pharmacist who will get rid of them safely.

6. FURTHER INFORMATION

What ONSENAL contains

- The active substance is celecoxib
- The other ingredients are gelatin, lactose monohydrate, sodium lauryl sulphate, povidone K30, croscarmellose sodium, magnesium stearate and the colouring agent titanium dioxide E171.
- The printing ink contains also shellac, propylene glycol and iron oxide E172.

What ONSENAL looks like and contents of the pack

The capsules are white with ‘7767‘ and ‘200‘ marked in gold ink.
Onsenal is packed in blisters and supplied in boxes of 10 or 60 capsules.

Marketing Authrisation Holder

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

Manufacturer

Pfizer Manufacturing Deutschland GmbH
Heinrich-Mack-Strasse 35
89257 Illertissen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in.

This medicine has been authorised under "exceptional circumstances".
This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency (EMA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Onsenal 400 mg hard capsules
celecoxib

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ONSENAL IS AND WHAT IT IS USED FOR

Onsenal belongs to a group of medicines called cyclo-oxygenase-2 (COX-2) inhibitors. Cyclo-oxygenase-2 is an enzyme that increases at inflammatory sites and in abnormally growing cells. Onsenal works by inhibiting COX-2, to which such dividing cells are sensitive. As a consequence the cells die.

Onsenal is used to reduce the number of gastrointestinal polyps in patients with Familial Adenomatous Polyposis (FAP). FAP is an inherited disorder in which the rectum and colon are covered with many polyps that might develop colorectal cancer. Onsenal should be used along with the usual care for FAP patients such as surgery and endoscopic surveillance.

2. BEFORE YOU TAKE ONSENAL

Do not take ONSENAL
- if you have had an allergic reaction to any of the ingredients of Onsenal
- if you have had an allergic reaction to a group of medicines called “sulphonamides”. These include some antibiotics (Bactrim and Septra used in combination with sulfamethoxole and trimethoprim), which can be used to treat infections
- if you have a stomach or duodenal ulcer, or bleeding in the stomach or intestines
- if after taking aspirin or another anti-inflammatory medicine you have had nasal polyps or severe nasal congestion, or any allergic reaction such as an itchy skin rash, swelling, breathing difficulties or wheezing
- women of childbearing potential unless using an effective method of contraception
- if you are breast feeding
- if you have inflammation of the colon (ulcerative colitis) or intestinal tract (Crohn’s disease)
- if you have severe liver disease
- if you have severe kidney disease
- if you have heart failure, established heart disease and /or cerebrovascular disease, e.g. if you have had a heart attack, stroke, mini-stroke (TIA) or blockages of blood vessels to the heart or brain
- if you have had an operation to clear or bypass blockages

– or if you have or have had problems with blood circulation (peripheral arterial disease) or if you have had surgery on the arteries of your legs

Take special care with ONSENAL
– Some people will need special care from their doctors when they are taking Onsenal. Make sure that your doctor knows before you start taking Onsenal:
– if you have conditions which increase your risk of heart disease such as high blood pressure, diabetes, high cholesterol or if you smoke you should discuss with your doctor whether Onsenal is suitable for you
– if you have had a stomach or duodenal (intestinal) ulcer or bleeding in the stomach or intestines
– if your heart, liver, or kidneys are not working well, your doctor may want to keep a regular check on you
– if you have fluid retention (such as swollen ankles or feet)
– if you are dehydrated, for example by sickness or diarrhoea or if you are taking diuretic treatment (water tablets)
– if you have had a serious allergic reaction or a serious skin reaction to any medicines
– if you are taking acetylsalicylic acid
– if you are taking anticoagulants
– if you have intolerance to some sugars
– if you are being treated for an infection, because Onsenal may mask a fever which is a sign of an infection
– if you are over 65 years of age your doctor may want to keep a regular check on you

As with other non-steroidal, anti-inflammatory drugs (NSAIDs; eg. ibuprofen or diclofenac), this medicine may lead to an increase in blood pressure, and so your doctor may ask to monitor your blood pressure on a regular basis.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without a prescription.

Before you start taking Onsenal make sure your doctor knows if you are taking:
– ACE inhibitors or Angiotensin II receptor antagonists (used for high blood pressure and heart failure)
– Acetylsalcylic acid or other anti-inflammatory medicines
– Cyclosporin and tacrolimus (used for immune system suppression e.g. after transplants)
– Dextromethorphan (used as an antitussive in cough mixtures)
– Diuretics (used to treat fluid retention)
– Fluconazole (used to treat fungal infections)
– Lithium (used to treat depression)
– Rifampicin (used to treat bacterial infections)
– Warfarin (used to prevent blood from clotting) or other anticoagulants
– Other medicines to treat depression, sleep disorders, high blood pressure or an irregular heartbeat
– Neuroleptics (used to treat some mental disorders)
– Methotrexate (used to treat rheumatoid arthritis, psoriasis and leukaemia)
– Carbamazepine (used to treat epilepsy/seizures and some forms of pain or depression)
– Barbiturates (used to treat epilepsy/seizures and some sleep disorders)

Onsenal can be taken with low dose acetylsalicylic acid (aspirin). Ask your doctor for advice before taking both of these medicines together.

Taking ONSENAL with food and drink
You can take Onsenal with or without food.

Pregnancy and breast-feeding
You must not take Onsenal if you are pregnant or if it is possible that you become pregnant.
You must not take Onsenal if you are breast feeding.

Driving and using machines
If you feel dizzy or tired after taking Onsenal, do not drive or use machinery until you are feeling normal again.

Important information about some of the ingredients of Onsenal:
Onsenal contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ONSENAL

Always take Onsenal exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure. The usual dose is 400 mg twice a day. You will usually take one 400 mg capsule twice a day.

The maximum recommended daily dose is 800 mg.

If you take more ONSENAL than you should
If you accidentally take too many capsules, tell your doctor or pharmacist as soon as possible.

If you forget to take ONSENAL
Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, ONSENAL can cause side effects, although not everybody gets them.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

The side effects listed below were observed in arthritis patients who took medicines with the same active ingredient as Onsenal:

Stop taking the capsules and tell your doctor immediately…
If you have an allergic reaction such as skin rash, swelling of the face, wheezing or difficulty breathing

If you have heart problems such as pain in the chest
If you have liver failure (symptoms may include nausea (feeling sick), diarrhoea, jaundice (your skin or the whites of your eyes look yellow)
If you have blistering or peeling of the skin
If you have severe stomach pain or any sign of bleeding in the stomach or intestines, such as passing black or bloodstained bowel movements, or vomiting blood

Common side effects which may affect more than 1 person in 100, are listed below
- Fluid build up with swollen ankles, legs and/or hands
- Urinary infections
- Sinusitis (sinus inflammation, sinus infection, blocked or painful sinuses), blocked or runny nose, sore throat, coughs, colds, flu-like symptoms
- Dizziness, difficulty sleeping
- stomach ache, diarrhoea, indigestion, wind
- Rash, itching

- Muscle stiffness
- Worsening of existing allergies

Uncommon side effects which may affect more than 1 person in a 1000, are listed below
- Heart failure, palpitations (awareness of heart beat), fast heart rate
- Worsening of existing high blood pressure
- Abnormalities in liver-related blood tests
- Abnormalities in kidney-related blood tests
- Anaemia (changes in red blood cells that can cause fatigue and breathlessness)
- Anxiety, depression, tiredness, drowsiness, tingling sensations (pins and needles)
- High levels of potassium in blood test results (can cause nausea (feeling sick), fatigue, muscle weakness or palpitations)
- Impaired or blurred vision, ringing in the ears, mouth pain and sores
- Constipation, burping, stomach inflammation (indigestion, stomach ache or vomiting), worsening of inflammation of the stomach or intestine.
- Leg cramps
- Raised itchy rash (hives)

Rare side effects which may affect more than 1 person in a 10,000, are listed below
- Ulcers (bleeding) in the stomach, gullet or intestines; or rupture of the intestine (can cause stomach ache, fever, nausea, vomiting, intestinal blockage), dark or black stools, inflammation of the gullet (can cause difficulty in swallowing), inflammation of the pancreas (can lead to stomach pain)
- Reduced number of white blood cells (which help protect the body from infection) and blood platelets (increased chance of bleeding or bruising)
- Difficulty coordinating muscular movements
- Feeling confused, changes in the way things taste
- Increased sensitivity to light
- Loss of hair

Additional reactions have been reported from actual use of the active ingredient of Onsenal (in post-marketing experience). The frequencies of these reactions are difficult to determine but are generally considered to be very rare (affecting less than 1 person in every 10,000)
- Bleeding within the brain causing death
- Serious allergic reactions (including potentially fatal anaphylactic shock) which can cause skin rash, swelling of the face, lips, mouth, tongue or throat, wheezing or difficulty breathing; difficulty swallowing
- Bleeding of the stomach or intestines (can lead to bloody stools or vomiting), inflammation of the intestine or colon, inflammation of the pancreas, nausea (feeling sick)
- Serious skin conditions such as Stevens-Johnson syndrome, exfoliative dermatitis and toxic epidermal necrolysis (can cause rash, blistering or peeling of the skin)
- Liver failure, liver damage and severe liver inflammation (sometimes fatal or requiring liver transplant). Symptoms may include nausea (feeling sick), diarrhoea, jaundice, yellow discolouration of the skin or eyes, dark urine, pale stools, bleeding easily, itching or chills
- Kidney problems (possible kidney failure, inflammation of the kidneys)
- Blood clot in the blood vessels in the lungs. Symptoms may include sudden breathlessness, sharp pains when you breathe or collapse
- Irregular heartbeat
- Meningitis (inflammation of the membrane around the brain and spinal cord)
- Hallucinations
- Worsening of epilepsy (possible more frequent and/or severe seizures)
- Inflamed blood vessels (can cause fever, aches, purple blotches on the skin)
- Blockage of an artery or vein in the eye leading to partial or complete loss of vision, conjunctivitis, eye infection (pink eye), bleeding in the eye
- A reduction in the number of red and white blood cells and platelets (may cause tiredness, easy bruising, frequent nose bleeds and increased risk of infections)
- Chest pain

- Impaired sense of smell
- Skin discolouration (bruising), muscle pain and weakness, painful joints
- Menstrual disturbances
- Headache, flushing
- Low levels of sodium in blood test results (can cause loss of appetite, headache, nausea (feeling sick), muscle cramps and weakness)

In clinical studies where Onsenal was taken for up to 3 years to prevent spontaneous colon polyps, the following additional side effects have been observed (side effects marked with an asterisk were more common in these studies than in arthritis studies):

Very Common side-effects (affecting more than 1 person in every 10):
- High blood pressure*, diarrhoea*

Common
- Heart problems: heart attack*, angina (chest pain)
- Stomach problems: nausea, heartburn, diverticulum (a problem with the stomach or intestine that can become painful or infected), vomiting*, irritable bowel syndrome (can include stomach ache, diarrhoea, indigestion, wind)
- Kidney stones (which may lead to stomach or back pain, blood in urine), difficulty passing urine, increased creatinine (blood test result related to kidney function)
- Difficulty breathing
- Muscle spasms
- Oedema (water retention that can cause swelling)
- Enlarged or inflamed prostate, prostate specific antigen increased (lab test)
- Infections of various types
- Weight gain

Uncommon
- Stroke
- Unstable angina (chest pain), troubles with heart valves, rhythm, or coronary arteries, or enlarged heart
- Deep vein thrombosis (blood clot usually in the leg, which may cause pain, swelling or redness of the calf or breathing problems), bruising
- Stomach infection (which can cause irritation and ulcers of the stomach and intestines), bleeding from piles/haemorrhoids, frequent bowel movements, inflamed or bleeding gums/mouth sores
- Lower limb fracture, tendon rupture or inflammation
- Shingles, skin infection, allergic dermatitis (dry itchy rash)
- Floaters or haemorrhage in the eye causing blurred or impaired vision, vertigo due to inner ear troubles, difficulty speaking
- Difficulty sleeping, excessive urination at night
- Fatty lumps in skin or elsewhere, ganglion cyst (harmless swellings on or around joints and tendons in the hand or foot)
- Abnormal or heavy bleeding from the vagina, painful menstruation, breast pain, ovarian cyst, menopausal symptoms
- High levels of sodium or haemoglobin and low levels of hematocrit or testosterone in blood test results
- Decreased hearing
- Changes in blood counts

5. HOW TO STORE ONSENAL

Keep out of the reach and sight of children.

Do not store your capsules above 30°C.

Do not take the capsule after the 'expiry date' shown on the blister and carton. If your capsules are out of date, take them to your pharmacist who will get rid of them safely.

6. FURTHER INFORMATION

What ONSENAL contains

- The active substance is celecoxib
- The other ingredients are gelatin, lactose monohydrate, sodium lauryl sulphate, povidone K30, croscarmellose sodium, magnesium stearate and the colouring agent titanium dioxide E171.
- The printing ink contains also shellac, propylene glycol and iron oxide E172, Brilliant Blue FCF E 133.

What ONSENAL looks like and contents of the pack

The capsules are white with '7767' and '400' marked in green ink. Onsenal is packed in blisters and supplied in boxes of 10 or 60 capsules.

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