1. NAME OF THE MEDICINAL PRODUCT

Celecoxib NORMON 200 mg hard capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 200 mg celecoxib.

Excipients with known effect:

Each capsule contains 47.4 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

Hard capsules equipped with a yellow cap and a white body, containing white or almost white granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4).

Celecoxib Normon is indicated in adults.

4.2 Posology and method of administration

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see sections 4.3, 4.4, 4.8 and 5.1).

Posology:

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

Rheumatoid arthritis: The initial recommended daily dose is 200 mg taken **in two divided doses.** (*This posology cannot be administrated with this medicine. There are other medicines with a concentration of 100 mg celecoxib).*
The dose may, if needed, later be increased to 200 mg twice daily. In the absence of an increase in therapeutic benefit after two weeks, other therapeutic options should be considered.

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

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

Elderly (>65 years): As in younger adults, 200 mg per day should be used initially. The dose may, if needed, later be increased to 200 mg twice daily. Particular caution should be exercised in elderly with a body weight less than 50 kg (see sections 4.4 and 5.2).

Paediatric population: Celecoxib is not indicated for use in children.

Hepatic impairment: Treatment should be initiated at half the recommended dose in patients with established moderate liver impairment (with a serum albumin of 25-35 g/l). Experience in such patients is limited to cirrhotic patients (see sections 4.3, 4.4 and 5.2).

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).

CYP2C9 Poor Metabolizers: Patients who are known, or suspected to be CYP2C9 poor metabolizers based on genotyping or previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution as the risk of dose-dependent adverse effects is increased. Consider reducing the dose to half the lowest recommended dose (see section 5.2).

Method of administration:

Oral route.

Celecoxib Normon can be taken with or without food. The capsule should be swallowed whole with a drink of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known hypersensitivity to sulfonamides.

Active peptic ulceration or gastrointestinal bleeding.

Patients who have experienced asthma, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

In pregnancy and in women of childbearing potential unless using an effective method of contraception (see sections 4.5). Celecoxib has been shown to cause malformations in the two animal species studied (see sections 4.6 and 5.3). The potential for human risk in pregnancy is unknown, but cannot be excluded.

Breast feeding (see sections 4.6 and 5.3).

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

Patients with estimated creatinine clearance <30 ml/min.

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

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

4.4 Special warnings and precautions for use

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with celecoxib. Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and gastrointestinal bleeding.

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

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

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

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 twice a day and 400 mg twice a day compared to placebo (see section 5.1).

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-

evaluated periodically, especially in patients with osteoarthritis (see 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 effects. Therefore, antiplatelet therapies should not be discontinued (see section 5.1).

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking celecoxib. Therefore, celecoxib should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason, since prostaglandin inhibition may result in deterioration of renal function and fluid retention. Caution is also required in patients taking diuretic treatment or otherwise at risk of hypovolaemia.

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.

Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained.

NSAIDs, including celecoxib, may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. Patients at greatest risk for renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, angiotensin II receptor antagonists, and the elderly (see section 4.5). Such patients should be carefully monitored while receiving treatment with celecoxib.

Some cases of severe hepatic reactions, including fulminant hepatitis (some with fatal outcome), liver necrosis and, hepatic failure (some with fatal outcome or requiring liver transplant), have been reported with celecoxib. Among the cases that reported time to onset, most of the severe adverse hepatic events developed within one month after initiation of celecoxib treatment (see section 4.8).
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.

Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction may be necessary for individually dose-titrated drugs that are metabolised by CYP2D6 (see section 4.5).
Patients known to be CYP2C9 poor metabolisers should be treated with caution (see section 5.2.).

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 (including anaphylaxis, angioedema and drug rash with eosinophilia and systemic symptoms (DRESS, or hypersensitivity syndrome)) have been reported in patients receiving celecoxib (see section 4.8). Patients with a history of sulfonamide 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.

Celecoxib may mask fever and other signs of inflammation.

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

<u>Warnings about excipients:</u>

This medicine contains lactose. 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:
Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of celecoxib in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with celecoxib is initiated or the dose of celecoxib is changed. (see section 4.4). Bleeding events in association with increases in prothrombin time have been reported, predominantly in the elderly, in patients receiving celecoxib concurrently with warfarin, some of them fatal.

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, patients on diuretics, 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 twice a day 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 twice a day, 48% were considered unresponsive to lisinopril at the final clinic visit (defined as either diastolic blood pressure >90 mmHg or 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 or tacrolimus have been suggested to increase the nephrotoxic effect of ciclosporin and tacrolimus. Renal function should be monitored when celecoxib and any of these drugs are combined.

Celecoxib can be used with low dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis. In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid. (see section 5.1).

Pharmacokinetic interactions

Effects of celecoxib on other drugs:
Celecoxib is an inhibitor of CYP2D6. During celecoxib treatment, the plasma concentrations of the CYP2D6 substrate dextromethorphan were increased by 136%. The plasma concentrations of drugs that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of drugs which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmic drugs, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated.

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

In an interaction study, celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethistherone /35 µg 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 Cmax 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 drugs on celecoxib:
In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors 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 Cmax of 60% and in AUC of 130%. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data on exposed pregnancies are available for celecoxib. Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations (see sections 4.3 and 5.3). The potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, as with other drugs inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Celecoxib is contraindicated in pregnancy and in women who can become

pregnant (see sections 4.3 and 4.4). If a woman becomes pregnant during treatment, celecoxib should be discontinued.

Breast-feeding

Celecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. Administration of celecoxib to a limited number of lactating women has shown a very low transfer of celecoxib into breast milk. Women who take celecoxib should not breastfeed.

4.7 Effects on ability to drive and use machines

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

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, 7400 arthritis patients have been treated with celecoxib at daily doses up to 800 mg, including approximately 2300 patients treated for 1 year or longer. The adverse reactions observed with celecoxib in these additional studies were consistent with those for osteoarthritis and rheumatoid arthritis patients listed in **Table 1**.
- Adverse reactions reported at incidence rates greater than placebo for subjects treated with celecoxib 400 mg daily in long-term polyp prevention trials of duration up to 3 years (the APC and PreSAP trials; see section 5.1, Pharmacodynamic properties: Cardiovascular Safety – Long-Term Studies Involving Patients With Sporadic Adenomatous Polyps).

- Adverse reactions from post-marketing experience 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 marketing authorisation holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

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

Adverse Drug Reaction Frequency					
System organ class	**Very common** (≥ 1/10)	**Common** (≥1/100 to < 1/10)	**Uncommon** (≥1/1.000 to 1/100)	**Rare** (≥1/10.000 to < 1/1.000)	**Frequency not known** (cannot be estimated from the available data) (Post-marketing experience)[3]
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
Metabolism and nutrition disorders			Hyperkaelemia		
Psychiatric disorders		Insomnia	Anxiety, depression, tiredness	Confusion	Hallucinations
Nervous system disorders		Dizziness, hypertonia	Paraesthesia, somnolence, cerebral infarction[1]	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, hypoacusis[1]		
Cardiac disorders		Myocardial infarction[1]	Heart failure, palpitations, tachycardia		Arrhythmia
Vascular	Hypertension[1]		Hypertension		Flushing,

disorders			aggravated		vasculitis, pulmonary embolism
Respiratory, thoracic, and mediastinal disorders		Pharyngitis, rhinitis, cough, dyspnoea[1]			Bronchospasm
Gastrointestinal disorders		Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting[1], dysphagia[1]	Constipation, eructation, gastritis, stomatitis, aggravation of gastrointestinal inflammation	Duodenal, gastric, oesophageal and colonic ulceration, intestinal perforation, oesophagitis, melaena, pancreatitis	Nausea, gastrointestinal haemorrhage, colitis/colitis aggravated
Hepatobiliary disorders			Abnormal hepatic function, increased SGOT and SGPT	Elevation of hepatic enzymes	Hepatic failure (sometimes fatal or requiring liver transplant), fulminant hepatitis (some with fatal outcome), liver necrosis, hepatitis, jaundice
Skin and subcutaneous tissue disorders		Rash, pruritus	Urticaria	Alopecia, photosensitivity	Ecchymosis, bullous eruption, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS) or hypersensitivity syndrome, angioedema, acute generalised exanthematous pustulosis
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 NOS
General disorders and administrative site conditions		Flu-like symptoms, peripheral oedema/fluid			Chest pain

		retention			

[1] Adverse drug reactions that occurred in polyp prevention trials, representing subjects treated with celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials). The adverse drug reactions listed above for the polyp prevention trials are only those that have been previously recognized in post-marketing surveillance experience, or have occurred more frequently than in the arthritis trials.

[2] Furthermore, the following previously unknown adverse reactions occurred in polyp prevention trials, representing subjects treated with celecoxib 400 mg daily in 2 clinical trials of duration up to 3 years (the APC and PreSAP trials): **Common**: angina pectoris, irritable bowel syndrome, nephrolithiasis, blood creatinine increased, benign prostatic hyperplasia, weight increased. **Uncommon**: helicobacter infection, herpes zoster, erysipelas, bronchopneumonia, labyrinthitis, gingival infection, lipoma, vitreous floaters, conjunctival haemorrhage, deep vein thrombosis, dysphonia, haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, allergic dermatitis, ganglion, nocturia, vaginal haemorrhage, breast tenderness, lower limb fracture, blood sodium increased.

[3] 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 or the polyp prevention trials.

In final data (adjudicated) from the APC and PreSAP trials in patients treated with celecoxib 400 mg daily for up to 3 years (pooled data from both trials; see section 5.1 for results from individual trials), the excess rate over placebo for myocardial infarction was 7.6 events per 1000 patients (uncommon) and there was no excess rate for stroke (types not differentiated) over placebo.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

There is no clinical experience of overdose. Single doses up to 1200 mg and multiple doses up to 1200 mg twice daily have been administered to healthy subjects for nine days without clinically significant adverse effects. In the event of suspected overdose, appropriate supportive medical care should be provided e.g. by eliminating the gastric contents, clinical supervision and, if necessary, the institution of symptomatic treatment.

Dialysis is unlikely to be an efficient method of drug removal due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: M01AH01.

Celecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range (200-400 mg daily). No statistically significant inhibition of COX-1 (assessed as ex vivo inhibition of thromboxane B2 [TxB2] formation) was observed in this dose range in healthy volunteers.

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX 1 inhibiting NSAIDs and COX 2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane.

Celecoxib is a diaryl-substituted pyrazole, chemically similar to other non-arylamine sulfonamides (e.g. thiazides, furosemide) but differs from arylamine sulfonamides (e.g. sulfamethoxizole and other sulfonamide antibiotics).

A dose dependent effect on TxB2 formation has been observed after high doses of celecoxib. However, in healthy subjects, in small multiple dose studies with 600 mg twice per day (three times the highest recommended dose) celecoxib had no effect on platelet aggregation and bleeding time compared to placebo.

Several clinical studies have been performed confirming efficacy and safety in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Celecoxib was evaluated for the treatment of the inflammation and pain of osteoarthritis of the knee and hip in approximately 4200 patients in placebo and active controlled trials of up to 12 weeks duration. It was also evaluated for treatment of the inflammation and pain of rheumatoid arthritis in approximately 2100 patients in placebo and active controlled trials of up to 24 weeks duration. Celecoxib at daily doses of 200 mg - 400 mg provided pain relief within 24 hours of dosing. Celecoxib was evaluated for the symptomatic treatment of ankylosing spondylitis in 896 patients in placebo and active controlled trials of up to 12 weeks duration. Celecoxib at doses of 100 mg twice per day, 200 mg once per day, 200 mg twice per day and 400mg once per day in these studies demonstrated significant improvement in pain, global disease activity and function in ankylosing spondylitis.
Five randomised double-blind controlled studies have been conducted including scheduled upper gastrointestinal endoscopy in approximately 4500 patients free from initial gastrointestinal ulceration (celecoxib doses from 50 mg - 400 mg twice per day). In twelve week endoscopy studies celecoxib (100 - 800 mg per day) was associated with a significantly lower risk of gastroduodenal ulcers compared with naproxen (1000 mg per day) and ibuprofen (2400 mg per day). The data were inconsistent in comparison with diclofenac (150 mg per day). In two of the 12-week studies the percentage of patients with endoscopic gastroduodenal ulceration were not significantly different between placebo and celecoxib 200 mg twice per day and 400 mg twice per day.

In a prospective long-term safety outcome study (6 to 15 month duration, CLASS study), 5,800 osteoarthritis and 2,200 rheumatoid arthritis patients received celecoxib

400 mg twice per day (4-fold and 2-fold the recommended osteoarthritis and rheumatoid arthritis doses, respectively), ibuprofen 800 mg TID or diclofenac 75 mg twice per day (both at therapeutic doses). Twenty-two percent of enrolled patients took concomitant low-dose acetylsalicylic acid (≤325 mg/day), primarily for cardiovascular prophylaxis. For the primary endpoint complicated ulcers (defined as gastrointestinal bleeding, perforation or obstruction) celecoxib was not significantly different than either ibuprofen or diclofenac individually. Also for the combined NSAID group there was no statistically significant difference for complicated ulcers (relative risk 0.77, 95 % CI; 0.41-1.46, based on entire study duration). For the combined endpoint, complicated and symptomatic ulcers, the incidence was significantly lower in the celecoxib group compared to the NSAID group, relative risk 0.66, 95% CI; 0.45-0.97 but not between celecoxib and diclofenac. Those patients on celecoxib and concomitant low-dose acetylsalicylic acid experienced 4 fold higher rates of complicated ulcers as compared to those on celecoxib alone. The incidence of clinically significant decreases in haemoglobin (>2 g/dL), confirmed by repeat testing, was significantly lower in patients on celecoxib compared to the NSAID group (relative risk 0.29, 95% CI; 0.17- 0.48). The significantly lower incidence of this event with celecoxib was maintained with or without acetylsalicylic acid use.

In a prospective randomised 24 week safety study in patients who were aged ≥60 years or had a history of gastroduodenal ulcers (users of ASA excluded), the percentages of patients with decreases in haemoglobin (≥2 g/dL) and/or haematocrit (≥10%) of defined or presumed gastrointestinal origin were lower in patients treated with celecoxib 200 mg twice daily (N=2238) compared to patients treated with diclofenac prolonged-release 75 mg twice daily plus omeprazole 20 mg once daily (N=2246) (0.2% vs. 1.1% for defined gastrointestinal origin, p = 0.004; 0.4% vs. 2.4% for presumed gastrointestinal origin, p = 0.0001). The rates of clinically manifest gastrointestinal complications such as perforation, obstruction or haemorrhage were very low with no differences between the treatment groups (4-5 per group).

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% (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 200 mg twice daily compared to placebo. The relative risk compared to placebo for a similar composite endpoint (cardiovascular death, myocardial infarction, 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.

5.2 Pharmacokinetic properties

Absorption

Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption by about 1 hour.

Distribution

Celecoxib exhibits dose- and time-independent pharmacokinetics in the therapeutic dose range. Plasma protein binding is about 97% at therapeutic plasma concentrations and the drug 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 drug. The main metabolites found in the circulation have no detectable COX-1 or COX-2 activity.

Biotransformation

Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been identified in human plasma i.e., a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9*3 polymorphism.

In a pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP2C9*1/*1, CYP2C9*1/*3, or CYP2C9*3/*3, the median 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 PK parameters of celecoxib between elderly African-Americans and Caucasians.
The plasma concentration of celecoxib is approximately 100% increased in elderly women (>65 years).

Elimination
Celecoxib is mainly eliminated by metabolism. Less than 1% of the dose is excreted unchanged in urine. The inter-subject variability in the exposure of celecoxib is about 10-fold.

Hepatic failure
Compared to subjects with normal hepatic function, patients with mild hepatic impairment had a mean increase in Cmax of 53% and in AUC of 26% of celecoxib. The corresponding values in patients with moderate hepatic impairment were 41% and 146% respectively. The metabolic capacity in patients with mild to moderate impairment was best correlated to their albumin values. Treatment should be initiated at half the recommended dose in patients with moderate liver impairment (with serum albumin 25-35g/L). Patients with severe hepatic impairment (serum albumin <25 g/l) have not been studied and celecoxib is contraindicated in this patient group.

Renal impairment
There is little experience of celecoxib in renal impairment. The pharmacokinetics of celecoxib has not been studied in patients with renal impairment but is unlikely to be markedly changed in these patients. Thus caution is advised when treating patients with renal impairment. Celecoxib is contraindicated in severe renal impairment.

5.3. Preclinical safety data

Conventional embryo-fetal toxicity studies resulted in dose dependent occurrences of diaphragmatic hernia in rat fetuses and of cardiovascular malformations in rabbit fetuses at systemic exposures to free drug approximately 5X (rat) and 3X (rabbit) higher than those achieved at the maximum recommended daily human dose (400 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 maximum recommended daily human dose was 3X.

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.

Based on conventional studies, genotoxicity or carcinogenicity, no special hazard for humans was observed, beyond those addressed in other sections of the SmPC. 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

Capsule content:
Lactose monohydrate
Sodium laurilsulfate
Povidone
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Capsule shells:
Gelatin
Titanium dioxide (E-171)
Yellow iron oxide (E-172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30ºC. Protect from humidity.

6.5 Nature and contents of container

Aluminium/PVDC-PE or aluminium/PVC-PVDC(60) blisters. Each pack contains 30 hard capsules.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

April 2014.

10. DATE OF REVISION OF THE TEXT