

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1328/057/001

Case No: 2033989

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, Ruislip, Middlesex, HA4 0NU, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Celebrex 100 mg capsules.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **20/08/2007** until **28/09/2011**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Celebrex 100 mg capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg celecoxib

Excipient: Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Product imported from France:

Opaque, white with two blue bands marked 7767 and 100.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis.

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, 4.4).

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 (4.3, 4.4, 4.8 and 5.1).

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

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

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

Celebrex may be taken with or without food.

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 4.4 and 5.2).

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 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 4.3, 4.4 and 5.2).

Children: Celecoxib is not indicated for use in children.

4.3 Contraindications

History of hypersensitivity to the active substance or to any of the excipients (see 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 NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

In pregnancy and in women of childbearing potential unless using an effective method of contraception (See 4.5).

Celecoxib has been shown to cause malformations in the two animal species studied (See 4.6 and 5.3). The potential for human risk in pregnancy is unknown, but cannot be excluded.

Breast feeding (See 4.6 and 5.3).

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

Patients with estimated creatinine clearance <30ml/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

The use of Celebrex may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Celebrex should be considered.

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

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 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).

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

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 (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 5.1).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thromboembolic 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.

Compromised renal or hepatic function and especially cardiac dysfunction are more likely in the elderly and therefore medically appropriate supervision should be maintained. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs.

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 4.5).

Patients known to be CYP2C9 poor metabolisers should be treated with caution (see 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 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 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 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 4.5).

Celebrex 100 mg and 200 mg capsules contain lactose (149.7 mg and 49.8 mg, respectively). 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 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 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.

Coadministration of NSAIDs and cyclosporin or tacrolimus have been suggested to increase the nephrotoxic effect of cyclosporin and tacrolimus. Renal function should be monitored when celecoxib and any of these 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 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 (1mg norethisterone/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 450mg 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 drugs on celecoxib

Since celecoxib is predominantly metabolised by CYP2C9 it should be used at half the recommended dose in patients receiving fluconazole. Concomitant use of 200 mg single dose of celecoxib and 200 mg once daily of fluconazole, a potent CYP2C9 inhibitor, resulted in a mean increase in celecoxib C_{max} of 60% and in AUC of 130%. Concomitant use of inducers of CYP2C9 such as rifampicin, carbamazepine and barbiturates may reduce plasma concentrations of celecoxib.

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

4.6 Pregnancy and lactation

No clinical data on exposed pregnancies are available for celecoxib. Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations (see 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 4.3 and 4.4). If a woman becomes pregnant during treatment, celecoxib should be discontinued.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Approximately 7400 patients were treated with celecoxib in controlled trials and of those approximately 2300 have received it for 1 year or longer. The following events have been reported in patients receiving celecoxib in 12 placebo and/or active controlled trials. Side-effects listed have a rate equal or greater than placebo, and the discontinuation rate due to side effects was 7.1% in patients receiving celecoxib and 6.1% in patients receiving placebo.

Additional reactions reported from post-marketing experience in >70 million treated patients include headache, nausea and arthralgia, and the reactions included as very rare, in italics in the list below.

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

Infections and infestations

Common: sinusitis, upper respiratory tract infection

Uncommon: urinary tract infection

Blood and the lymphatic system disorders

Uncommon: anaemia

Rare: leucopenia, thrombocytopenia

Very rare: *pancytopenia*

Immune system disorders :

Very rare: *serious allergic reactions, anaphylactic shock*

Metabolism and nutrition disorders

Uncommon: hyperkalaemia

Psychiatric disorders

Common: insomnia

Uncommon: anxiety, depression, tiredness.

Very rare: *confusion, hallucinations.*

Nervous system disorders

Common: dizziness

Uncommon: blurred vision, hypertonia, paraesthesia

Rare: ataxia, taste alteration

Very rare: *aggravated epilepsy, meningitis aseptic, ageusia, anosmia*

Ear and labyrinth disorders

Uncommon: tinnitus

Very rare: *decreased hearing*

Cardiac disorders

Uncommon: myocardial infarction*, heart failure, palpitations

Vascular disorders

Uncommon: hypertension, hypertension aggravated

Rare: ischaemic stroke*

Very rare: *vasculitis.*

Respiratory, thoracic and mediastinal disorders

Common: pharyngitis, rhinitis

Uncommon: cough, dyspnoea

Very rare: *bronchospasm.*

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, dyspepsia, flatulence

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

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

Very rare: *gastrointestinal haemorrhage, acute pancreatitis, colitis/colitis aggravated.*

Hepato-biliary disorders

Uncommon: abnormal hepatic function

Very rare: *hepatitis, jaundice, hepatic failure.*

Skin and subcutaneous tissue disorders

Common: rash

Uncommon: urticaria

Rare: alopecia, photosensitivity

Very rare: *angioedema, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis*

Musculoskeletal and connective tissue disorders

Uncommon: leg cramps

Very rare: *myositis*

Renal and urinary disorders:

Very rare: *acute renal failure, interstitial nephritis*

Reproductive system and breast disorders:

Very rare: *menstrual disorder NOS*

General disorders and administration site conditions

Common: peripheral oedema/ fluid retention

Investigations

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

*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.

In preliminary data from two studies in patients with colorectal polyps treated with celecoxib 400 mg daily (see Section 5.1) the excess rate over placebo of myocardial infarction over 3 years was 7 events per 1000 patients (Uncommon). In the same studies, the excess rate for clearly identified ischaemic stroke for the 400 mg daily dose (not including events that were haemorrhagic or of unknown aetiology) was 0.5 event per 1000 over 3 years (Rare). For all strokes, there was no increased event rate with celecoxib compared with placebo.

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: 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. sulfamethoxazole and other sulfonamide antibiotics).

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

Several clinical studies have been performed confirming efficacy and safety in osteoarthritis and rheumatoid arthritis. Celecoxib was evaluated for the treatment of the inflammation and pain of OA 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 RA 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. Five randomised double-blind controlled studies have been conducted including scheduled upper gastrointestinal endoscopy in approximately 4500 patients free from initial ulceration (celecoxib doses from 50 mg-400 mg BID). 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 BID and 400 mg BID.

In a prospective long-term safety outcome study (6 to 15 month duration, CLASS study), 5,800 OA and 2,200 RA patients received celecoxib 400 mg BID (4-fold and 2-fold the recommended OA and RA doses, respectively), ibuprofen 800 mg TID or diclofenac 75 mg BID (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 statically 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.

Ongoing Clinical Trials: Preliminary safety information from three long-term studies involving patients with Sporadic Adenomatous Polyps or who were predisposed to developing Alzheimer's disease treated with celecoxib is available. In one of the three studies, the APC (Prevention of Sporadic Colorectal Adenomas with Celecoxib), there was a dose-related increase in cardiovascular events (mainly myocardial infarction, MI) at celecoxib doses of 200 mg BID and 400 mg BID compared to placebo. The increased risk became apparent after approximately 1 year of treatment. The relative risk (RR) for the composite endpoint (cardiovascular death MI or stroke) was 3.4 (95% CI 1.4 – 8.5) for the higher dose and 2.5 (95% CI 1.0 – 6.4) for the lower dose of celecoxib compared to placebo. The absolute risk for the composite endpoint was 3.0% for the higher dose of celecoxib, 2.2% for the lower dose of celecoxib, and 0.9% for placebo. Preliminary data from the other two long-term studies did not show a significantly increased cardiovascular risk with celecoxib 200 mg BID and 400 mg QD compared to placebo. This information will be updated as final data become available.

5.2 Pharmacokinetic properties

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

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 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.

Celecoxib is metabolised in the liver by hydroxylation, oxidation and some glucuronidation.

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

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

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

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

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

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

Capsules contain:

Lactose monohydrate
Sodium lauryl sulphate
Povidone K30
Croscarmellose sodium
Magnesium stearate.

Capsule shells contain:

Gelatin
Titanium dioxide (E171)
Ink contains indigotine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30⁰C.

6.5 Nature and contents of container

Clear PVC blisters or aluminium cold-formed blisters. Pack of 30 capsules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

B&S Healthcare
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8 Parallel Product Authorisation Number

PPA 1328/57/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 29th September 2006

10 DATE OF REVISION OF THE TEXT

August 2007