SUMMARY OF PRODUCT CHARACTERISTICS

COLCIBRA
(Celecoxib 100/200 mg capsules)

1. NAME OF THE MEDICINAL PRODUCT

COLCIBRA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COLCIBRA

Each capsule contains:
Celecoxib …….100 mg

Each capsule contains:
Celecoxib …….200 mg

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Celecoxib is indicated in adults for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

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

4.2 Posology and method of administration

Colcibra is available at the strength of 100 and 200 mg only and may not be suitable for all the dosing recommendations mentioned below. In such cases, other approved strength must be used**.**

Posology

As the cardiovascular (CV) 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**, and **4.8**).

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.

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 400 mg 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.

Special populations

Elderly
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
Colcibra is not indicated for use in children.

CYP2C9 poor metabolisers
Patients who are known, or suspected to be CYP2C9 poor metabolisers 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**).

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
Limited experience has been reported with celecoxib in patients with mild or moderate renal impairment, therefore such patients should be treated with caution (see **sections 4.3**, **4.4** and **5.2**).

Method of administration

Oral use
Colcibra may be taken with or without food. For patients who have difficulty swallowing capsules, the contents of a celecoxib capsule can be added to applesauce, rice gruel, yogurt or mashed banana. To do so, the entire capsule contents must be carefully emptied onto a level teaspoon of cool or room temperature applesauce, rice gruel, yogurt or mashed banana and should be ingested immediately with 240 ml of water. The sprinkled capsule contents on applesauce, rice gruel or yogurt are stable for up to 6 hours under refrigerated conditions (2-8°C). The sprinkled capsule contents on mashed banana should not be stored under refrigerated conditions and should be ingested immediately.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of this product listed in section 6.1.
- Known hypersensitivity to sulfonamides.
- 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 (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors.
- In pregnancy and in women of childbearing potential unless using an effective method of contraception (see **section 4.6**). Celecoxib has been reported 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

Gastrointestinal (GI) effects
Upper and lower gastrointestinal complications (perforations, ulcers or bleedings [PUBs]), some of them resulting in fatal outcome, have been reported 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 antiplatelet drugs (such as acetylsalicylic acid) or glucocorticoids concomitantly, patients using alcohol, 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 reported in long-term clinical trials.

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

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

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. NSAIDs, including COX-2 selective inhibitors, have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk. 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 and 4.8**).

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

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.

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

Hypertension
As with all NSAIDS, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Therefore, blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

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

NSAIDs, including celecoxib, may cause renal toxicity. Clinical trials with celecoxib have reported 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, angiotensin converting enzyme (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.

CYP2D6 inhibition
Celecoxib inhibits CYP2D6. Although it is not a strong inhibitor of this enzyme, a dose reduction may be necessary for individually dose-titrated medicinal products that are metabolised by CYP2D6 (see **section 4.5**).

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

Skin and systemic hypersensitivity reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib (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.

General
Celecoxib may mask fever and other signs of inflammation.

Use with oral anticoagulants
In patients on concurrent therapy with warfarin, serious bleeding events, some of them fatal, have been reported. Increased prothrombin time (INR) with concurrent therapy has been reported. Therefore, this should be closely monitored in patients receiving warfarin/coumarin-type oral anticoagulants, particularly when therapy with celecoxib is initiated or celecoxib dose is changed (see **section 4.5**). Concomitant use of anticoagulants with NSAIDS may increase the risk of bleeding. Caution should be

exercised when combining celecoxib with warfarin or other oral anticoagulants, including novel anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban).

COLCIBRA contains lactose
COLCIBRA contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

COLCIBRA contains sodium
COLCIBRA contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Anticoagulants
Anticoagulant activity should be monitored particularly in the first few days after initiating or changing the dose of celecoxib in patients receiving warfarin or other anticoagulants since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with celecoxib is initiated or the dose of celecoxib is changed (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.

Anti-hypertensives
NSAIDs may reduce the effect of anti-hypertensive medicinal products including ACE-inhibitors, angiotensin II receptor antagonists, diuretics and beta-blockers. As for NSAIDs, the risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients, patients on diuretics, or elderly patients) when ACE-inhibitors, angiotensin II receptor antagonists, and/or diuretics are combined with NSAIDs, including celecoxib (see **section 4.4**). 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 reported clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted in no clinically significant

increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients treated with celecoxib 200 mg BID, 48% were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic blood pressure increased >10% compared to baseline), compared to 27% of patients treated with placebo; this difference was statistically significant.

Ciclosporin and tacrolimus
Co-administration of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin or tacrolimus, respectively. Renal function should be monitored when celecoxib and any of these medicinal products are combined.

Acetylsalicylic acid
Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for CV prophylaxis. As with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of celecoxib alone has been reported for concomitant administration of low-dose acetylsalicylic acid.

Pharmacokinetic interactions

Effects of celecoxib on other medicinal products

CYP2D6 inhibition
Celecoxib is an inhibitor of CYP2D6. The plasma concentrations of medicinal products that are substrates of this enzyme may be increased when celecoxib is used concomitantly. Examples of medicinal products which are metabolised by CYP2D6 are antidepressants (tricyclics and SSRIs), neuroleptics, anti-arrhythmic medicinal products, etc. The dose of individually dose-titrated CYP2D6 substrates may need to be reduced when treatment with celecoxib is initiated or increased if treatment with celecoxib is terminated.

An increase of 2.6-fold and 1.5-fold in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively, have been reported with concomitant administration of celecoxib 200 mg twice daily. These increases are due to celecoxib inhibition of the CYP2D6 substrate metabolism.

CYP2C19 inhibition
In vitro studies have reported some potential for celecoxib to inhibit CYP2C19 catalysed metabolism has been reported. The clinical significance of this is unknown. Examples of

medicinal products which are metabolised by CYP2C19 are diazepam, citalopram and imipramine.

Methotrexate
In patients with rheumatoid arthritis celecoxib had no statistically significant effect on the pharmacokinetics (plasma or renal clearance) of methotrexate (in rheumatologic doses). However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two medicinal products.

Lithium
A mean increase in C_{max} and AUC of 16% and 18%, respectively, of 450 mg twice daily of lithium has been reported with co-administration of celecoxib 200 mg twice daily in healthy subjects. Therefore, patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Oral contraceptives
No clinically relevant effects of celecoxib on the pharmacokinetics of oral contraceptives (1 mg norethisterone /35 micrograms ethinylestradiol) have been reported.

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

Effects of other medicinal products on celecoxib

CYP2C9 poor metabolisers
In individuals who are CYP2C9 poor metabolisers and demonstrate increased systemic exposure to celecoxib, concomitant treatment with CYP2C9 inhibitors such as fluconazole could result in further increases in celecoxib exposure. Such combinations should be avoided in known CYP2C9 poor metabolisers (see **sections 4.2** and **5.2**).

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

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

Paediatric population
Interaction studies have only been reported in adults.

4.6 Fertility, Pregnancy and lactation

Pregnancy
Studies in animals (rats and rabbits) have reported reproductive toxicity, including malformations (see **sections 4.3**and **5.3**). Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from reported epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. The potential for human risk in pregnancy is unknown, but cannot be excluded. Celecoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester.

During the second or third trimester of pregnancy, NSAIDs including celecoxib may cause fetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible upon discontinuation.

Celecoxib is contraindicated in pregnancy and in women who can become pregnant (see **sections 4.3** and **4.4**). If a woman becomes pregnant during treatment, celecoxib should be discontinued.

Lactation
Celecoxib has been reported to be excreted in the milk of lactating rats at concentrations similar to those in plasma. A very low transfer of celecoxib into breast milk has been reported in lactating women after administration of celecoxib. Women who take celecoxib should not breastfeed.

Fertility
Based on the mechanism of action, the use of NSAIDs, including celecoxib, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.

4.7 Effects on ability to drive and use machines

Celecoxib may have minor influence on the ability to drive and use machines.

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

4.8 Undesirable effects

Adverse reactions reported with celecoxib are listed by system organ class and ranked by frequency in table below:

Table: Adverse drug reactions reported with celecoxib (MedDRA preferred terms)

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)	**Very Rare** (<1/10,000)	**Frequency Not Known (cannot be estimated from reported data)**
Infections and infestations		Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection				
Blood and lymphatic system disorders			Anaemia	Leukopenia, thrombo-cytopenia	Pancytopenia	
Immune system disorders		Hypersensitivity			Anaphylactic shock, anaphylactic reaction)	
Metabolism and nutrition disorders			Hyperkalaemia			
Psychiatric disorders		Insomnia	Anxiety, depression, fatigue	Confusional state, hallucinations		
Nervous system		Dizziness, hypertonia,	Cerebral infarction,	Ataxia, dysgeusia	Haemorrhage intracranial	

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)	**Very Rare** (<1/10,000)	**Frequency Not Known (cannot be estimated from reported data)**
disorders		headache	paraesthesia, somnolence		(including fatal intracranial haemorrhage), meningitis aseptic, epilepsy (including aggravated epilepsy), ageusia, anosmia	
Eye disorders			Vision blurred, conjunctivitis	Eye haemorrhage	Retinal artery occlusion, retinal vein occlusion	
Ear and labyrinth disorders			Tinnitus, hypoacusis			
Cardiac disorders		Myocardial infarction	Cardiac failure, palpitations, tachycardia	Arrhythmia		
Vascular disorders	Hyper-tension (including aggravated hyper-tension)			Pulmonary embolism, flushing	Vasculitis	
Respiratory, thoracic, and mediastinal disorders		Rhinitis, cough, dyspnoea	Bronchospasm	Pneumonitis		
Gastrointestinal disorders		Nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia	Constipation, gastritis, stomatitis, gastrointestinal inflammation	Gastro-intestinal haemorrhage, duodenal ulcer, gastric ulcer,		

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)	**Very Rare** (<1/10,000)	**Frequency Not Known (cannot be estimated from reported data)**
			(including aggravation of gastrointestinal inflammation), eructation	oesophageal ulcer, intestinal ulcer, large intestinal ulcer, intestinal perforation, oesophagitis, melaena; pancreatitis, colitis		
Hepatobiliary disorders			Hepatic function abnormal, hepatic enzyme increased (including increased SGOT and SGPT)	Hepatitis	Hepatic failure (sometimes fatal or requiring liver transplant), hepatitis fulminant (some with fatal outcome), hepatic necrosis, cholestasis, hepatitis cholestatic, jaundice	
Skin and subcutaneous tissue disorders		Rash, pruritus (includes pruritus generalised)	Urticaria, ecchymosis	Angioedema, alopecia, photo-sensitivity	Dermatitis exfoliative, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction	

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)	**Very Rare** (<1/10,000)	**Frequency Not Known (cannot be estimated from reported data)**
					with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis bullous	
Musculoskeletal and connective tissue disorders		Arthralgia	Muscle spasms (leg cramps)		Myositis	
Renal and urinary disorders			Blood creatinine increased, blood urea increased	Renal failure acute, hypo-natraemia	Tubulo-interstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion	
Reproductive system and breast disorders				Menstrual disorder		Infertility female (female fertility decreased)
General disorders and administrative site conditions		Influenza-like illness, oedema peripheral/ fluid retention	Face oedema, chest pain			
Injury, poisoning and		Injury (accidental injury)				

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)	**Very Rare** (<1/10,000)	**Frequency Not Known (cannot be estimated from reported data)**
procedural complications						

SGOT - serum glutamic oxaloacetic transaminase

SGPT - serum glutamic pyruvic transaminase

Furthermore, the following adverse reactions have been reported with celecoxib 400 mg daily:

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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and antirheumatic drugs, NSAIDs, Coxibs, ATC code: M01AH01.

Mechanism of action

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

Pharmacodynamic effects

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

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 reported after high doses of celecoxib. However, in healthy subjects, 600 mg BID (three times the highest recommended dose) celecoxib has been reported to have no effect on platelet aggregation and bleeding time compared to placebo.

5.2 Pharmacokinetic properties

Absorption

Celecoxib is reported to be well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delay absorption of celecoxib by about 1 hour resulting in a T_{max} of about 4 hours and increases bioavailability by about 20%.

In healthy adult volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in C_{max}, T_{max} or $T_{1/2}$ after administration of capsule contents on applesauce.

Distribution
Plasma protein binding is reported to be about 97% at therapeutic plasma concentrations and the medicinal product is not preferentially bound to erythrocytes.

Biotransformation
Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, inactive as COX-1 or COX-2 inhibitors, have been reported 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 reported pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP2C9*1/*1, CYP2C9*1/*3, or CYP2C9*3/*3, the median C_{max} and AUC_{0-24} of celecoxib on day 7 were reported as approximately 4-fold and 7-fold, respectively, in subjects genotyped as CYP2C9*3/*3 compared to other genotypes. In three reported separate single dose studies, involving a total of 5 subjects genotyped as CYP2C9*3/*3, single-dose AUC_{0-24} has been reported to increase by approximately 3-fold compared to normal metabolisers. It is estimated that the frequency of the homozygous *3/*3 genotype is 0.3-1.0 % among different ethnic groups.

Patients who are known, or suspected to be CYP2C9 poor metabolisers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution (see **section 4.2**).

No clinically significant differences in PK parameters of celecoxib has been reported between elderly African-Americans and Caucasians. The plasma concentration of celecoxib has been reported to be approximately 100% increased in elderly women (>65 years).

A mean increase in C_{max} of 53% and in AUC of 26% of celecoxib has been reported in patients with mild hepatic impairment compared to subjects with normal hepatic function. 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 reported in patients with renal impairment but is unlikely to be markedly changed in these patients. Thus caution is advised when treating patients with renal impairment. Severe renal impairment is contraindicated.

Elimination
Celecoxib has been reported to be mainly eliminated by metabolism. Less than 1% of the dose is reported to be excreted unchanged in urine. The inter-subject variability in the exposure of celecoxib is reported as about 10-fold. Celecoxib exhibits dose- and time-independent pharmacokinetics in the therapeutic dose range. Elimination half-life is reported as be 8-12 hours. Steady state plasma concentrations are reached within 5 days of treatment.

5.3 Preclinical safety data

Reported non-clinical safety data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, mutagenicity or carcinogenicity.

Celecoxib at oral doses ≥150 mg/kg/day (approximately 2-fold human exposure at 200 mg twice daily as measured by AUC_{0-24}), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternebrae fused and sternebrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was reported when rats were given celecoxib at oral doses ≥30 mg/kg/day (approximately 6-fold human exposure based on the AUC_{0-24} at 200 mg twice daily) throughout organogenesis. These effects are expected following inhibition of prostaglandin synthesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses, and reduced embryo/fetal survival.

Celecoxib has been reported to excrete in rat milk. In a reported peri-post natal study in rats, pup toxicity was observed. In a reported 2 year toxicity study, an increase in nonadrenal thrombosis was observed in male rat at high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate, Povidone, Silica, Colloidal Anhydrous, Sodium Lauryl Sulfate, Croscarmellose sodium, Purified Water, Magnesium Stearate.

6.2 Incompatibilities

NA

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30 ^{0}C

6.5 Nature and contents of container

PVC blister pack.

6.6 Special precautions for disposal and other handling

NA

7. MARKETING AUTHORISATION HOLDER

Ranbaxy Nigeria Limited

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

August 2022

REFERENCE

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