FRONT SIDE

220 mm

around gastric ulcers in human 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 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).

5.2 Pharmacokinetic properties
***Pharmacokinetic Properties*:**
Absorption: Celecoxib is well absorbed reaching peak plasma concentrations after approximately 2-3 hours. Dosing with food (high fat meal) delays absorption of celecoxib by about 1 hour resulting in a T_{max} of about 4 hours and increases bioavailability by about 20%.
Distribution: Plasma protein binding is about 97 % at therapeutic plasma concentrations and the drug 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 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.
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. Celecoxib exhibits dose- and time-independent pharmacokinetics in the therapeutic dose range. Elimination half-life is 8-12 hours. Steady state plasma concentrations are reached within 5 days of treatment.

5.3 Preclinical safety data
Conventional embryo-foetal toxicity studies resulted in dose-dependent occurrences of diaphragmatic hernia in rat foetuses and of cardiovascular malformations in rabbit foetuses at systemic exposures to free 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.
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.

6 Pharmaceutical Particulars
6.1 List of excipients
Colloidal Anhydrous Silica
Maize Starch
Croscarmellose Sodium
Hypromellose
Sodium Lauryl Sulphate
Microcrystalline Cellulose
Purified Talc
Magnesium Stearate
Empty Hard Gelatin Capsules size "1"

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 Months from the date of manufacture.

6.4. Special precautions for storage
Store at temperature not exceeding 30°C, protect from moisture.
Keep out of the reach and sight of children.

6.5 Nature and contents of container
10x10 Capsules in Alu-PVC Blister pack.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Manufactured by :
ZIM LABORATORIES LIMITED
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441 501,
Maharashtra State, India

zim
Zeal & Innovation in Medicine

8. Marketing Authorization Number(S)
NA

9. Date of First Authorization/Renewal of the Authorization
NA

10. Date of Revision of the Text
30 Jun 2019

*PB400/X/XX/XX

COLCIBID-200
Celecoxib Capsules 200 mg

1. Name of the Finished Pharmaceutical Product
1.1 Trade Name : COLCIBID-200 (Celecoxib Capsules 200 mg)
1.2 Strength : 200 mg
1.3 Pharmaceutical Form : *"Hard Gelatin Capsule"*

2. Qualitative And Quantitative Composition
Each hard gelatin capsule capsule contain:
Celecoxib BP 200 mg
For the full list of excipients, see section 6.1

3. Pharmaceutical Form
"Hard Gelatin Capsule
Green transparent/ clear transparent, Size '1' hard gelatin capsule filled with granular powder."

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.

4.2 Posology and method of administration
Posology:
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.
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 (>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.
Paediatric population: Celecoxib 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.
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.
Renal impairment: Experience with celecoxib in patients with mild or moderate renal impairment is limited, therefore such patients should be treated with caution.
Mode of Administration:
For oral use.
Celecoxib may be taken with or without food.

4.3 Contraindication
- Hypersensitivity to the active substance or to any of the excipients of this formulation.
- 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 (aspirin) or other NSAIDs including COX-2 inhibitors.
- In pregnancy and in women of childbearing potential unless using an effective method of contraception. The potential for human risk in pregnancy is unknown, but cannot be excluded.
- Breast-feeding.
- 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.

160 mm

BACK SIDE

4.4 Special warnings and special precautions for use

Gastrointestinal (GI) effects: Upper and lower gastrointestinal complications, 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, glucocorticoids, 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, when Celecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

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

Cardiovascular effects: 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.

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.

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.

Skin and systemic hypersensitivity reactions: 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. 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).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

- *Anticoagulants:* 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 when ACE inhibitors, angiotensin II receptor antagonists, and/or diuretics 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.
- *Ciclosporin and Tacrolimus:* Coadministration 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 drugs are combined.
- *Acetylsalicylic acid:* Celecoxib can be used with low-dose acetylsalicylic acid but is not a substitute for acetylsalicylic acid for cardiovascular prophylaxis.

Pharmacokinetic interactions:

Effects of celecoxib on other drugs

CYP2D6 Inhibition: Celecoxib is an inhibitor of CYP2D6. 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.

Concomitant administration of celecoxib 200 mg twice daily resulted in 2.6-fold and 1.5-fold increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates), respectively. These increases are due to celecoxib CYP2D6 inhibition of the CYP2D6 substrate metabolism.

CYP2C19 Inhibition: In reported 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.

Methotrexate: In patients with rheumatoid arthritis celecoxib had no statistically significant effect on the pharmacokinetics of methotrexate. However, adequate monitoring for methotrexate-related toxicity should be considered when combining these two drugs.

Lithium: Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Oral contraceptives: Celecoxib had no clinically relevant effects on the pharmacokinetics of oral contraceptives (1 mg norethisterone /35 micrograms ethinylestradiol).

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

Effects of other drugs on celecoxib

CYP2C9 Poor Metabolisers: 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.

CYP2C9 Inhibitors and Inducers: 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 and Antacids: Ketoconazole or antacids have not been observed to affect the pharmacokinetics of celecoxib.

Paediatric population: Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy: Celecoxib is contraindicated in pregnancy and in women who can become pregnant. If a woman becomes pregnant during treatment, celecoxib should be discontinued.

Breast-feeding: 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

The following adverse reactions of Celecoxib reported with frequencies: 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

Very common: Hyper-tension

Common: Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection, Hyper-sensitivity, Insomnia, Dizziness, hypertonia, headache, Myocardial infarction, Rhinitis, cough, dyspnoea, Nausea, abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dysphagia, Rash, pruritus, Arthralgia, Influenza-like illness, Oedema peripheral/ fluid retention, accidental injury.

Uncommon: Anaemia, Hyperkalaemia, Anxiety, depression, fatigue, Cerebral infarction, paraesthesia, somnolence, Vision blurred, conjunctivitis, Tinnitus, hypoacusis, Cardiac failure, palpitations, tachycardia, Bronchospasm, Constipation, gastritis, stomatitis, gastrointestinal inflammation, eructation, Hepatic function abnormal, hepatic enzyme increased, Urticaria, ecchymosis, Muscle spasms, Blood creatinine increased, blood urea increased, Face oedema, chest pain.

Rare: Leukopenia, thrombo-cytopenia, Confusional state, hallucinations, Ataxia, dysgeusia, Eye haemorrhage, Arrhythmia, Pulmonary embolism, flushing, Pneumonitis, Gastro-intestinal haemorrhage, duodenal ulcer, gastric ulcer, oesophageal ulcer, intestinal ulcer, large intestinal ulcer, intestinal perforation; oesophagitis, melaena; pancreatitis, colitis, Hepatitis, Angioedema, alopecia, photo-sensitivity, Renal failure acute, hypo-natraemia, Menstrual disorder.

Very Rare: Pancytopenia, Anaphylactic shock, anaphylactic reaction, Haemorrhage intracranial, meningitis aseptic, epilepsy, ageusia, anosmia, Retinal artery occlusion, retinal vein occlusion, Vasculitis, Hepatic failure, hepatitis fulminant, hepatic necrosis, cholestasis, hepatitis cholestatic, jaundice, Dermatitis exfoliative, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), dermatitis bullous, Myositis, Tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion,

Not Known: Infertility female

4.9 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, Coxibs.

ATC code: M01AH01

Mechanism of action: Celecoxib is an oral, selective, cyclooxygenase-2 (COX-2) inhibitor within the dose range (200-400 mg daily). No statistically significant inhibition of COX-1 was observed in this dose range.

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 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

220 mm

160 mm