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CEBREX™

1. Name of the Medicinal Product

1.1 Product name

CEBREX™

1.2 Strength

200 mg and 400 mg

1.3 Pharmaceutical dosage form

Hard capsules for oral use

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

Active Ingredient: celecoxib.

2.2 Quantitative declaration

CEBREX 200 mg hard capsules

Each capsule contains 200 mg celecoxib.

CEBREX 400 mg hard capsules

Each capsule contains 400 mg celecoxib.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Hard capsules for oral use

CEBREX 200 mg hard capsules

200 mg capsules: Hard gelatin capsules, white opaque cap with gold ink band containing in white “7767”, white opaque body with gold ink band containing in white “200” (containing white to off-white granulation).

CEBREX 400 mg hard capsules

400 mg capsules: Hard gelatin capsules, white opaque cap with green ink band containing in white “7767”, white opaque body with green ink band containing in white “400” (containing white to off-white granulation).

4. Clinical Particulars

4.1 Therapeutic indications

Symptomatic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA).

Relief of signs and symptoms of ankylosing spondylitis (AS).

Management of acute pain.

Treatment of primary dysmenorrhea.

Management of low back pain.

4.2 Posology and method of administration

Celecoxib capsules, at doses up to 200 mg twice per day, can be taken with or without food.

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.

Symptomatic Treatment of Osteoarthritis (OA): The usual recommended dose of celecoxib is 200 mg administered as a single dose. 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 2 weeks, other therapeutic options should be considered.

Symptomatic Treatment of Rheumatoid Arthritis (RA): The recommended dose of celecoxib is 200 mg twice per day.

Ankylosing Spondylitis (AS): The recommended dose of celecoxib is 200 mg administered as a single dose. Some patients may benefit from a total daily dose of 400 mg.

Management of Acute Pain: The recommended dose of celecoxib is 400 mg initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily or 400 mg once daily as needed.

Treatment of Primary Dysmenorrhea: The recommended dose of celecoxib is 400 mg, initially, followed by an additional 200 mg dose, if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily or 400 mg once daily as needed.

Low Back Pain (LBP): The recommended dose of celecoxib is 200 mg or 400 mg daily, administered as a 200 mg single dose, or as 100 or 200 mg twice per day. Some patients may benefit from a total daily dose of 400 mg.

CYP2C9 Poor Metabolizers: 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. Consider starting treatment at half the lowest recommended dose (see sections 4.5 and 5.2).

Pediatric Patients: Celecoxib has not been studied in subjects under 18 years of age.

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).

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).

Method of administration

Cebrex 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 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 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 ischemic 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 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 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 demonstrated in long-term clinical trials (see section 5.1).

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 found in a long-term placebo-controlled study in subjects with sporadic adenomatous polyps treated with celecoxib at doses of 200 mg bis in die (BID) and 400 mg BID 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. 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, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, 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).

Fluid retention and oedema

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

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 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, 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 metabolized by CYP2D6 (see section 4.5).

CYP2C9 poor metabolizers

Patients known to be CYP2C9 poor metabolizers 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).

Excipients

Cebrex 200 mg and 400 mg capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Cebrex 200 mg and 400 mg 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 28-day clinical study in patients with lisinopril-controlled Stage I and II hypertension, administration of celecoxib 200 mg BID resulted in no clinically significant increases, when compared to placebo treatment, in mean daily systolic or diastolic blood pressure as determined using 24-hour ambulatory blood pressure monitoring. Among patients treated with celecoxib 200 mg BID, 48% were considered unresponsive to lisinopril at the final clinic visit (defined as either cuff diastolic blood pressure >90 mmHg or cuff diastolic blood pressure increased >10% compared to baseline), compared to 27% of patients treated with placebo; this difference was statistically significant.

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. 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 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 metabolized 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.

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 inhibition of the CYP2D6 substrate metabolism.

CYP2C19 inhibition

In vitro studies have shown some potential for celecoxib to inhibit CYP2C19 catalyzed metabolism. The clinical significance of this in vitro finding is unknown. Examples of medicinal products which are metabolized 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

In healthy subjects, co-administration of celecoxib 200 mg twice daily with 450 mg twice daily of lithium resulted in a mean increase in C_{max} of 16% and in area under the curve (AUC) of 18% of lithium. Therefore, patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn.

Oral contraceptives

In an interaction study, 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 medicinal products on celecoxib

CYP2C9 poor metabolizers

In individuals who are CYP2C9 poor metabolizers 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 metabolizers (see sections 4.2 and 5.2).

CYP2C9 inhibitors and inducers

Since celecoxib is predominantly metabolized 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.

Pediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

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.

Pregnancy

Studies in animals (rats and rabbits) have shown reproductive toxicity, including malformations (see sections 4.3 and 5.3). Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from 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.

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 Cebrex should not breastfeed.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

Adverse reactions are listed by system organ class and ranked by frequency in **Table 1**, reflecting data from the following sources:

- Adverse reactions reported in osteoarthritis patients and rheumatoid arthritis patients at incidence rates greater than 0.01% and greater than those reported for placebo during 12 placebo- and/or active-controlled clinical trials of duration up to 12 weeks at celecoxib daily doses from 100 mg up to 800 mg. In additional studies using non-selective NSAID comparators, approximately 7400 arthritis patients have been treated with celecoxib at daily doses up to 800 mg, including approximately 2 300 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 Adenoma Prevention with Celecoxib (APC) and Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trials; see section 5.1, Cardiovascular safety – long-term studies involving patients with sporadic adenomatous polyps).
- Adverse drug reactions from post-marketing surveillance as spontaneously reported during a period in which an estimated >70 million patients were treated with celecoxib (various doses, durations, and indications). Even though these were identified as reactions from post-marketing reports, trial data was consulted to estimate frequency. Frequencies are based on a cumulative meta-analysis with pooling of trials representing exposure in 38102 patients.

Table 1. Adverse drug reactions in celecoxib clinical trials and surveillance 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)	**Very rare** (<1/10,000)	**Not known (cannot be estimated from available data)**
Infections and infestations		Sinusitis, upper respiratory tract infection, pharyngitis, urinary tract infection				
Blood and lymphatic system disorders			Anaemia	Leukopenia, thrombo-cytopenia	Pancytopenia[4]	

	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)	**Not known (cannot be estimated from available data)**
Immune system disorders		Hyper-sensitivity			Anaphylactic shock[4], anaphylactic reaction[4]	
Metabolism and nutrition disorders			Hyperkalaemia			
Psychiatric disorders		Insomnia	Anxiety, depression, fatigue	Confusional state, hallucinations[4]		
Nervous system disorders		Dizziness, hypertonia, headache[4]	Cerebral infarction[1], paraesthesia, somnolence	Ataxia, dysgeusia	Haemorrhage intracranial (including fatal intracranial haemorrhage)[4], meningitis aseptic[4], epilepsy (including aggravated epilepsy)[4], ageusia[4], anosmia[4]	
Eye disorders			Vision blurred, conjunctivitis[4]	Eye haemorrhage[4]	Retinal artery occlusion[4], retinal vein occlusion[4]	
Ear and labyrinth disorders			Tinnitus, hypoacusis[1]			

	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)	**Not known (cannot be estimated from available data)**
Cardiac disorders		Myocardial infarction[1]	Cardiac failure, palpitations, tachycardia	Arrhythmia[4]		
Vascular disorders	Hypertension[1] (including aggravated hypertension)			Pulmonary embolism[4], flushing[4]	Vasculitis[4]	
Respiratory, thoracic, and mediastinal disorders		Rhinitis, cough, dyspnoea[1]	Bronchospasm[4]	Pneumonitis[4]		

	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)	**Not known (cannot be estimated from available data)**
Gastrointestinal disorders		Nausea[4], abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting[1], dysphagia[1]	Constipation, gastritis, stomatitis, gastrointestinal inflammation (including aggravation of gastrointestinal inflammation), eructation	Gastro-intestinal haemorrhage[4], duodenal ulcer, gastric ulcer, oesophageal ulcer, intestinal ulcer, large intestinal ulcer, intestinal perforation, oesophagitis, melaena, pancreatitis, colitis[4]		

	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)	**Not known (cannot be estimated from available data)**
Hepatobiliary disorders			Hepatic function abnormal, hepatic enzyme increased (including increased SGOT and SGPT)	Hepatitis[4]	Hepatic failure[4] (sometimes fatal or requiring liver transplant), hepatitis fulminant[4] (some with fatal outcome), hepatic necrosis[4], cholestasis[4], hepatitis cholestatic[4], jaundice[4]	

	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)	**Not known (cannot be estimated from available data)**
Skin and subcutaneous tissue disorders		Rash, pruritus (includes pruritus generalised)	Urticaria, ecchymosis[4]	Angioedema[4], alopecia, photo-sensitivity	Dermatitis exfoliative[4], erythema multiforme[4], Stevens-Johnson syndrome[4], toxic epidermal necrolysis[4], drug reaction with eosinophilia and systemic symptoms (DRESS)[4], acute generalised exanthematous pustulosis (AGEP)[4], dermatitis bullous[4]	
Musculoskeletal and connective tissue disorders		Arthralgia[4]	Muscle spasms (leg cramps)		Myositis[4]	
Renal and urinary disorders			Blood creatinine increased, blood urea increased	Renal failure acute[4], hypo-natraemia[4]	Tubulointerstitial nephritis[4], nephrotic syndrome[4], glomerulonephritis minimal lesion[4]	

	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)	**Not known (cannot be estimated from available data)**
Reproductive system and breast disorders				Menstrual disorder[4]		Infertility female (female fertility decreased)[3]
General disorders and administrative site conditions		Influenza-like illness, oedema peripheral/ fluid retention	Face oedema, chest pain[4]			
Injury, poisoning and procedural complications		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)	**Not known (cannot be estimated from available data)**

SGOT - serum glutamic oxaloacetic transaminase

SGPT - serum glutamic pyruvic transaminase

[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 recognised in the 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] Women intending to become pregnant are excluded from all trials, thus consultation of the trial database for the frequency of this event was not reasonable.

[4] Frequencies are based on cumulative meta-analysis with pooling of trials representing exposure in 38102 patients.

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.

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

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, 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 B_2 [TxB_2] formation) was observed 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 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 humans 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 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.

Clinical efficacy and safety

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 BID, 200 mg QD, 200 mg BID and 400 mg QD 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 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 was 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), 5800 osteoarthritis and 2200 rheumatoid arthritis patients received celecoxib 400 mg BID (4-fold and 2-fold the recommended osteoarthritis and rheumatoid arthritis doses, respectively), ibuprofen 800 mg ter in die (TID) or diclofenac 75 mg BID (both at therapeutic doses). Twenty-two percent of enrolled patients took concomitant low-dose acetylsalicylic acid ($\leq$325 mg/day), primarily for CV 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 acetylsalicylic acid (ASA) excluded], the percentages of patients with decreases in haemoglobin (≥2 g/dL) and/or haematocrit (≥10%) of defined or presumed GI origin were lower in patients treated with celecoxib 200 mg twice daily (N=2238) compared to patients treated with diclofenac SR 75 mg twice daily plus omeprazole 20 mg once daily (N=2246) (0.2% vs. 1.1% for defined GI origin, p=0.004; 0.4% vs. 2.4% for presumed GI origin, p=0.0001). The rates of clinically manifest GI 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 Patients with Sporadic Adenomatous Polyps

Two studies involving patients 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 CV 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 CV 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 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 was 2.3% (21/933), compared to 1.9% (12/628) for placebo group. The incidence of myocardial infarction (adjudicated) was with 1.0% (9/933) with celecoxib

400 mg once daily and 0.6% (4/628) with placebo.

Data from a third long-term study, ADAPT (The Alzheimer's Disease Anti-inflammatory Prevention Trial), did not show a significantly increased CV risk with celecoxib 200 mg twice daily compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61-2.15) 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.

Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION)

The PRECISION study was a double-blind study of cardiovascular safety in OA or RA patients with or at high risk for cardiovascular disease comparing Celecoxib (200-400 mg daily) with Naproxen (750-1000 mg daily) and Ibuprofen (1800-2400 mg daily). The primary endpoint, Antiplatelet Trialists Collaboration (APTC), was an independently adjudicated composite of cardiovascular death (including haemorrhagic death), non-fatal myocardial infarction or non-fatal stroke. The study was planned with 80% power to evaluate non-inferiority. All patients were prescribed open-label esomeprazole (20-40 mg) for gastro protection. Patients who were taking low-dose Aspirin were permitted to continue therapy, at baseline nearly half of the subjects were on Aspirin. Secondary and tertiary endpoints included cardiovascular, gastrointestinal and renal outcomes. The Average Dose dispensed was 209±37 mg/day for Celecoxib, 2045±246 for Ibuprofen and 852±103 for Naproxen.

Regarding the primary endpoint, Celecoxib, as compared with either naproxen or ibuprofen, met all four pre-specified non-inferiority requirements, see **Table 2**.

Other independently adjudicated secondary and tertiary endpoints included cardiovascular, gastrointestinal and renal outcomes. Additionally, there was a 4-month substudy focusing on the effects of the three drugs on blood pressure as measured by ambulatory monitoring (ABPM).

Table 2. Primary Analysis of the Adjudicated APTC Composite Endpoint

Intent-To-Treat Analysis (ITT, through month 30)			
	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**

N	8,072	8,040	7,969
Subjects with Events	188 (2.3%)	218 (2.7%)	201 (2.5%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.93 (0.76, 1.13)	0.86 (0.70, 1.04)	1.08 (0.89, 1.31)
Modified Intent-To-Treat Analysis (mITT, on treatment through month 43)			
	Celecoxib 100-200 mg bid	**Ibuprofen 600-800 mg tid**	**Naproxen 375-500 mg bid**
N	8,030	7,990	7,933
Subjects with Events	134 (1.7%)	155 (1.9%)	144 (1.8%)
Pairwise Comparison	**Celecoxib vs. Naproxen**	**Celecoxib vs. Ibuprofen**	**Ibuprofen vs. Naproxen**
HR (95% CI)	0.90 (0.72, 1.14)	0.81 (0.64, 1.02)	1.12 (0.889, 1.40)

HR - hazard Ratio

BID - bis in die

TID - ter in die

The results were overall numerically similar in the celecoxib and comparator groups for the secondary and tertiary endpoints and there were overall no unexpected safety findings.

Taken together the PRECISION study indicates that celecoxib at the lowest approved dose of 100 mg twice daily is non-inferior to ibuprofen dosed in the range of 600 mg-800 mg three times daily or naproxen dosed in the range of 375 mg-500 mg twice daily with respect to cardiovascular adverse effects. The cardiovascular risks of the NSAID class, including coxibs, are dose-dependent, therefore, the results for celecoxib 200 mg daily on the composite cardiovascular endpoint cannot be extrapolated to dosing regimens using the higher doses of celecoxib.

Analgesia, including Primary Dysmenorrhea

In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, celecoxib relieved pain that was rated by patients as moderate to severe. Single doses of celecoxib provided pain relief within 60 minutes (see Section 4.2).

Low Back Pain (LBP)

Celecoxib was used to treat patients who had pre-existing non-neuropathic LBP of duration $\geqslant$12

weeks. In the table shown below, efficacy results in 5 clinical trials are presented using the Patient's Assessment of Pain Intensity (100 mm visual analog scale) from baseline to end of treatment:

Patient's Assessment of Pain Intensity in LBP Clinical Trials

Study ID (Duration) Treatment (TDD)	**N**	**Baseline Pain Intensity[c]**	**Change in Pain Intensity[c]**	**P-Value for Treatment Difference[c]**
Study 244 (12				
Placebo	177	76.6	-30.1	--
Celecoxib 200 mg	183	73.6	-35.9	0.0503
Study 245 (12				
Placebo	191	75.7	-26.2	--
Celecoxib 200 mg	183	72.8	-32.2	0.0427
Study 1165 (6 Weeks)[b]				
Celecoxib 400 mg	402	65.5	-34.6	0.008
Tramadol 200 mg	389	66.1	-30.4	--
Study 1338 (6 Weeks)[b]				
Celecoxib 400 mg	386	65.9	-34.8	0.595
Tramadol 200 mg	385	66.6	-34.4	--
Study 1174 (4 Weeks)				
Placebo	410	65.1	-26.2	--
Celecoxib 400 mg	410	65.0	-31.7	<0.001
Loxoprofen 180 mg	407	65.6	-29.3	Not Evaluated

N = Number of patients providing data at baseline and end of treatment. TDD = Total daily dose.

[a] Patient's Assessment of Pain Intensity a co-primary efficacy measure in these studies, along with Patient's Global Assessment of Low Back Pain (treatment differences significantly favored celecoxib over placebo in Studies 244 and 245) and the Roland-Morris Disability Questionnaire (treatment difference significantly favored celecoxib over placebo in Study 244).

[b] The primary efficacy measure in these studies was the percentage of patients who experienced at least 30% improvement on the Numerical Rating Scale (NRS) Pain Assessment, for which results in both studies showed statistical superiority for celecoxib over tramadol.

[c] Based on least-squares means from Analysis of Covariance models, with changes in pain intensity calculated by subtracting baseline value from end-of-treatment value; p-values were calculated based on least-squares mean differences between treatment groups.

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 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, which is concentration independent, is about 97% at therapeutic plasma concentrations and celecoxib is not preferentially bound to erythrocytes in the blood.

Metabolism

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: 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 C_{max} 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 sections 4.2).

No clinically significant differences were found in Pharmacokinetic 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.

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

Non-clinical safety data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, mutagenicity or carcinogenicity beyond those addressed in sections 4.4, 4.6, and 5.1.

Celecoxib at oral doses $\geq$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 observed 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 was excreted in rat milk. In a peri-post natal study in rats, pup toxicity was observed.

In a 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

Capsules (200 mg and 400 mg) contain lactose monohydrate, sodium lauryl sulfate, polyvidone, croscarmellose sodium, and magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

PVC blister with aluminum foil backing containing 1, 2, 3, 5, 7, 10 or 20 capsules in a carton of 1,

2, 3, 4, 5, 6, 10, 20, 50 or 100 blisters

Not all pack size may be marketed.

7. Marketing Authorization Holder

Viatris Healthcare (Thailand) Limited

8. Marketing Authorization Numbers

Cebrex (Capsules 200 mg) Reg. No. 1C 55/59 (N)
Cebrex (Capsules 400 mg) Reg. No. 1C 15152/62 (N)

9. Date of Authorization

Cebrex (Capsules 200 mg): 23 May 2016
Cebrex (Capsules 400 mg): 2 January 2020

10. Date of Revision of the Text

04 August 2022

Warning (based on the Ministry of Public Health's Announcement)

1. Is contraindicated in patients who are hypersensitive to this drug, in pregnant and lactating women.
2. Is contraindicated in patients who have coronary artery surgery in the immediately post-operative period.
3. Is contraindicated in patients with cardiovascular or cerebrovascular diseases.
4. If there is erythema multiforme or flu-like symptom after use, stop using this drug and consult the physician immediately.
5. Is contraindicated in patients who have ever been hypersensitive to this drug and patients with history of sulfonamide hypersensitivity.
6. If the following symptoms occur during using this drug e.g., fever, erythema multiforme, vesicle, skin lesions and other lesions appear in the mucous membranes (such as in the mouth cavity, throat, nasal cavity, sexual organs) and conjunctivitis, stop using this drug and consult the physician immediately as this may be Stevens-Johnson syndrome.

7. Is contraindicated in patients who have had myocardial infarction or congestive heart failure (NYHA II-IV).
8. Is contraindicated in patients who have had coronary heart disease (stenosed or occluded) or paresis, paralysis due to cerebrovascular accident.
9. Use with caution in patients with risk factors for developing coronary heart disease, e.g., hypertension, hyperlipidemia, diabetes, smoking, elderly, etc.
10. Use with caution in patients with hepatic and renal disorders.

คำเตือน (ตามประกาศกระทรวงสาธารณสุข)

1. ห้ามใช้ในผู้ที่แพ้ยานี้ สตรีมีครรภ์และสตรีระยะให้นมบุตร
2. ห้ามใช้ในผู้ที่ได้รับการผ่าตัดหลอดเลือดหัวใจในระยะหลังผ่าตัดใหม่ๆ (immediately postoperative period)
3. ห้ามใช้ยานี้ในผู้ป่วยโรคเกี่ยวกับหลอดเลือดหัวใจ หรือหลอดเลือดสมอง
4. หากใช้ยานี้แล้วมีอาการผื่นแดง หรือมีอาการคล้ายเป็นหวัด ให้หยุดยาและรีบปรึกษาแพทย์ทันที
5. ห้ามใช้ในผู้ที่เคยแพ้ยานี้และผู้ที่มีประวัติแพ้ยาในกลุ่ม sulfonamide
6. เมื่อใช้ยานี้หากมีอาการดังต่อไปนี้ เช่น ไข้ ผื่นแดง ตุ่มน้ำพอง มีการหลุดลอกของผิวหนัง และบริเวณเยื่อบุต่างๆ เช่น ในช่องปาก ลำคอ จมูก อวัยวะสืบพันธุ์ และเยื่อบุตาอักเสบ ให้หยุดยาและปรึกษาแพทย์เพราะอาจเป็น Stevens-Johnson syndrome
7. ห้ามใช้ยานี้ในผู้ป่วยภาวะกล้ามเนื้อหัวใจตาย หรือผู้ป่วยที่มีภาวะหัวใจล้มเหลวเลือดคั่ง (congestive heart failure NYHA II-IV)
8. ห้ามใช้ยานี้ในผู้ป่วยที่เคยเป็นโรคหลอดเลือดหัวใจตีบตัน หรือเคยมีภาวะอัมพฤกษ์ อัมพาตอันเกิดจากโรคหลอดเลือดสมอง
9. ระมัดระวังการใช้ยานี้ในผู้ที่มีปัจจัยเสี่ยงต่อการเกิดโรคหลอดเลือดหัวใจ เช่น ความดันโลหิตสูง ระดับไขมันในเลือดสูง โรคเบาหวาน ผู้สูบบุหรี่ ผู้สูงอายุ เป็นต้น
10. ระมัดระวังการใช้ยานี้ในผู้ป่วยที่มีความผิดปกติของตับและไต