For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

CLODREL PLUS/CLODREL FORTE

1. Generic Name

Clopidogrel and Aspirin Tablets I.P.

2. Qualitative and quantitative Composition:

CLODREL PLUS

Each film coated bilayered tablet contains:

Clopidogrel Bisulphate I.P. eq to Clopidogrel ….. 75 mg

Colour: Lake of Sunset Yellow

Aspirin I.P. ……. 75 mg

(In coated form)

The excipients used are Hydroxy Propyl Methyl Cellulose, Ethyl cellulose, PEG – 6000, Iso Propyl Alcohol, Methylene Chloride, Lactose Anhydrous, Microcrystalline Cellulose (AVI.PH-112), Crosspovidone XL-10, Colloidal Silicon Dioxide, Hydrogenated Castor Oil, Colloidal Hydrated Silica, Lake of Sunset Yellow, Stearic Acid, Talc, Citric Acid Anhydrous, Glyceryl Dibehenate, Sodium Starch Glycolate, Methanol

CLODREL FORTE

Each film coated bilayered tablet contains:

Clopidogrel Bisulphate I.P. eq to Clopidogrel ….. 75 mg

Colour: Lake of Sunset Yellow

Aspirin I.P. ……. 150 mg

(In coated form)

The excipients used are Hydroxy Propyl Methyl Cellulose, Ethyl cellulose, PEG – 6000, Iso Propyl Alcohol, Methylene Chloride, Lactose Anhydrous, Microcrystalline Cellulose (AVI.PH-112), Crosspovidone XL-10, Colloidal Silicon Dioxide, Hydrogenated Castor Oil, Colloidal Hydrated Silica, Lake of Sunset Yellow, Stearic Acid, Talc, Citric Acid Anhydrous, Glyceryl Dibehenate, Sodium Starch Glycolate, Methanol.

3. Dosage form and strength

Dosage form: 75 mg + 75 mg, 75 mg + 150 mg

Strength: Film coated bilayered tablet

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the treatment of angina, myocardial infarction, and stroke.

4.2. Posology and method of administration

Posology

Adults and elderly

CLODREL PLUS should be given as a single daily 75 mg/75 mg dose.

CLODREL FORTE should be given as a single daily 75 mg/150 mg dose.

Clopidogrel/Aspirin fixed-dose combination is used following initiation of therapy with clopidogrel, and Aspirin given separately, and replaces the individual clopidogrel and Aspirin products.

- In patients with non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months. If the use of Clopidogrel/ Aspirin is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.
- In patients with ST segment elevation acute myocardial infarction: Therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting. If the use of Clopidogrel/ Aspirin is discontinued, patients may benefit with continuation of one antiplatelet medicinal product.

If a dose is missed:

Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.

For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

Paediatric population

The safety and efficacy of Clopidogrel/ Aspirin in children and adolescents under 18 years old have not been established. Clopidogrel/Acetylsalicylic acid is not recommended in this population.

Method of administration

For oral use. It may be given with or without food.

4.3. Contraindications

Due to the presence of clopidogrel and acetylsalicylic acid (aspirin) in the medicine, CLOPIDOGREL ASPIRIN 75/75 mg PD is contraindicated in case of:

- hypersensitivity to clopidogrel, acetylsalicylic acid or to any of the ingredients of CLOPIDOGREL ASPIRIN 75/75 mg PD
- active or history of pathological bleeding such as recurrent peptic ulcer/haemorrhage/perforations or intracranial haemorrhage
- safety and efficacy in children below the age of 18 have not been established. ASA has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A medical practitioner should be consulted before aspirin is used in these patients' safety and efficacy in pregnancy and lactation have not been established.
- severe hepatic impairment
- thrombocytopenia and platelet dysfunction.

In addition, due to the presence of ASA, CLOPIDOGREL ASPIRIN 75/75 mg PD is also contraindicated in:

- patients with hypersensitivity (allergy) to non-steroidal anti-inflammatory drugs (NSAIDs) and syndrome of asthma, rhinitis, and nasal polyps. Patients with pre-existing mastocytosis, in whom

the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).

- patients with severe renal impairment
- patients with heart failure
- patients with a history of gastrointestinal bleeding, ulceration, or perforation
- (PUBs) related to previous NSAIDs.
- pregnancy and lactation

4.4. Special warnings and precautions for use

Recent transient ischaemic attack or stroke

In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of aspirin and clopidogrel has been shown to increase major bleeding.

Acquired haemophilia

Following use of clopidogrel, acquired haemophilia has been reported. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and CLOPIDOGREL ASPIRIN 75/75 mg PD should be discontinued.

Fluid retention and oedema

In view of the inherent potential of NSAIDs, including ASA, to cause fluid retention, heart failure may be precipitated in some compromised patients. As fluid retention and oedema have been reported in association with CLOPIDOGREL ASPIRIN 75/75 mg PD therapy, caution is required in patients with a history of hypertension and/or heart failure.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding, ulceration and perforation (PUBs) which may be fatal. Due to the presence of ASA caution is required in the following:

- patients with a history of asthma or allergic disorders since they are at increased risk of hypersensitivity reactions.
- patients with gout since low doses of ASA increase serum uric acid concentrations
- children: as there is an association between ASA and Reye's syndrome (a very rare disease which can be fatal) when ASA is given to children
- alcohol may increase the risk of gastrointestinal injury when taken with ASA. Alcohol should therefore be used with caution in patients taking CLOPIDOGREL ASPIRIN 75/75 mg PD. Patients should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking CLOPIDOGREL ASPIRIN 75/75 mg PD
- in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, CLOPIDOGREL ASPIRIN 75/75 mg PD must be administered under close medical supervision due to the risk of haemolysis.
- concomitant treatment with levothyroxine and salicylates, specifically at doses greater than 2,0 g/day, should be avoided.

Bleeding and haematological disorders

CLOPIDOGREL ASPIRIN 75/75 mg PD produces irreversible inhibition of platelet aggregation for the life of the platelet, which is 7-10 days. Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever such suspected clinical symptoms arise during the course of treatment. As there is a risk of bleeding intensity, concomitant administration of CLOPIDOGREL ASPIRIN 75/75 mg PD with warfarin is not recommended.

Caution is required when administering CLOPIDOGREL ASPIRIN 75/75 mg PD to patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions associated with bleeding diathesis as well as in patients receiving treatment with other non-steroidal anti-inflammatory medicines including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers, or thrombolytics. Patients should be monitored continuously and carefully for any signs of bleeding (including occult bleeding) especially but not limited to during the first weeks of treatment and/or after invasive cardiac procedures or surgery.

CLOPIDOGREL ASPIRIN 75/75 mg PD should be discontinued 7 days prior to surgery in those patients who are to undergo elective surgery where an antiplatelet effect is not desired.

The concomitant administration of CLOPIDOGREL ASPIRIN 75/75 mg PD with oral anticoagulants is not recommended since it may increase the intensity of bleeding.

CLOPIDOGREL ASPIRIN 75/75 mg PD prolongs bleeding time and should therefore be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intra-ocular).

Spinal and epidural anaesthesia should not be administered to a patient taking CLOPIDOGREL ASPIRIN 75/75 mg PD or for 7 days thereafter. No lumbar puncture should be done during these 7 days due to risk of haematoma formation following lumbar puncture or spinal and epidural anaesthesia.

Patients should be told that it may take longer than usual to stop bleeding whilst on CLOPIDOGREL ASPIRIN 75/75 mg PD therapy, and that they should report any unusual bleeding (site or duration) to their medical practitioner.

Patients should inform medical practitioners and dentists that they are taking CLOPIDOGREL ASPIRIN 75/75 mg PD before any surgery is scheduled and before any new medicine is taken.

Gastrointestinal

In patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia), peptic ulcer, gastroduodenal haemorrhage or minor upper gastrointestinal symptoms, CLOPIDOGREL ASPIRIN 75/75 mg PD should be used with caution as the condition may be exacerbated or may be due to gastric ulceration which in turn may lead to gastric bleeding.

In patients with a history of ulcers, and the elderly the risk of gastrointestinal bleeding, ulceration, or perforation (PUBs) is higher with increasing doses of CLOPIDOGREL ASPIRIN 75/75 mg PD.

Should gastrointestinal bleeding, perforation or ulceration occur in patients receiving CLOPIDOGREL ASPIRIN 75/75 mg PD, therapy should be stopped.

Gastrointestinal side effects including stomach pain, heartburn, nausea, vomiting, and GI bleeding may occur. Although minor upper GI symptoms (such as dyspepsia) are common and can occur anytime during therapy, medical practitioners should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be told about signs and symptoms of GI side effects and what steps to take if they occur.

In patients concomitantly receiving nicorandil and NSAIDs including acetylsalicylic acid (ASA) and lysine acetylsalicylate (LAS), there is an increased risk for severe complications such as gastrointestinal ulceration, perforation, and haemorrhage.

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported. CLOPIDOGREL ASPIRIN 75/75 mg PD should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics:

In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy.

Use of medicines that induce the activity of CYP2C19 would be expected to result in increased medicine levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.

CYP2C8 substrates

Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

Cross-reactivity among thienopyridines

As cross-reactivity among thienopyridines has been reported, patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel)

Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological reactions such as thrombocytopenia and neutropenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for cross-reactivity is advised.

Hepatic impairment

CLOPIDOGREL ASPIRIN 75/75 mg PD is contraindicated in patients with severe hepatic impairment.

Caution is advised in patients with mild and moderate hepatic impairment.

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore, CLOPIDOGREL ASPIRIN 75/75 mg PD should be used with caution in this population.

Renal impairment

CLOPIDOGREL ASPIRIN 75/75 mg PD is contraindicated in patients with severe renal Impairment.

Therapeutic experience with CLOPIDOGREL ASPIRIN 75/75 mg PD is limited in patients with mild to moderate renal impairment.

CLOPIDOGREL ASPIRIN 75/75 mg PD should therefore be used with caution in this population.

4.5. Drugs interactions

There are no studies on the concomitant use of clopidogrel and acetylsalicylic acid with other medicines. The information below was obtained with clopidogrel or ASA alone. Safety of CLOPIDOGREL ASPIRIN 75/75 mg PD and the concomitant use with the medicines mentioned below have not been established.

Medicines associated with bleeding risk

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicines associated with bleeding risk should be undertaken with caution.

Nicorandil

In patients concomitantly receiving nicorandil and NSAIDs including acetylsalicylic acid (ASA) and lysine acetylsalicylate (LAS), there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage.

Injectable anticoagulants

In healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel, however, as a pharmacodynamic interaction between CLOPIDOGREL ASPIRIN 75/75 mg PD and heparin is possible, concomitant use should be undertaken with caution.

Thrombolytics

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction with the incidence of clinically significant bleeding being similar to that as observed when thrombolytic medicines and heparins are co-administered with acetylsalicylic acid. However, the concomitant use of CLOPIDOGREL ASPIRIN 75/75 mg PD with thrombolytic medicines should be undertaken with caution.

Oral anticoagulants

Concomitant administration of warfarin with CLOPIDOGREL ASPIRIN 75/75 mg PD is not recommended due to the increased risk of bleeding.

Glycoprotein IIb/IIIa inhibitors

CLOPIDOGREL ASPIRIN 75/75 mg PD should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions and who receive concomitant glycoprotein IIb/IIIa inhibitors.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

In healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, the concomitant use of NSAIDs, including Cox-2 inhibitors, is not recommended with CLOPIDOGREL ASPIRIN 75/75 mg PD.

When they are dosed concomitantly, experimental data suggests that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is likely for occasional ibuprofen use.

Selective Serotonin Reuptake Inhibitors (SSRIs)

The concomitant administration of SSRIs with clopidogrel should be undertaken with caution as SSRIs affect platelet activation and increase the risk of bleeding.

Other concomitant therapy with clopidogrel:

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicines that induce the activity of this enzyme would be expected to result in increased medicine levels of the active metabolite of clopidogrel. Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.

Inhibitors of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicine that inhibit the activity of this enzyme would be expected to result in reduced medicine levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole and esomeprazole) should be discouraged. If a proton pump inhibitor is to be used concomitantly with CLOPIDOGREL ASPIRIN 75/75 mg PD, consider using one with less CYP2C19 inhibitory activity.

Other medicinal products

No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel was not significantly influenced by the co administration of phenobarbital or estrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Data from studies with human liver microsomes indicated that clopidogrel could inhibit the activity of one of the Cytochrome P450 (CYP) enzymes (CYP2C9). This could potentially lead to increased plasma levels of medicines such as phenytoin, tolbutamide, torsemide, tamoxifen, fluvastatin and NSAIDs which are metabolised by CYP2C9. Data indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

CYP2C8 substrate medicines

Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and medicines primarily cleared by CYP2C8 metabolism (e.g. repaglinide, paclitaxel) should be undertaken with caution.

Rosuvastatin

Clopidogrel has been shown to increase rosuvastatin exposure in patients by 1.4-fold (AUC) without effect on Cmax, after repeated administration of a 75 mg clopidogrel dose.

Other concomitant therapy with ASA

Interactions with the following medicinal products have been reported with ASA:

Uricosurics

Caution is required because ASA may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Methotrexate

Due to the presence of ASA, methotrexate used at doses higher than 20 mg/week should be used with caution with CLOPIDOGREL ASPIRIN 75/75 mg PD as it can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Metamizole

Metamizole may reduce the effect of ASA on platelet aggregation when taken concomitantly. Therefore, this combination should be used with caution in patients taking low-dose ASA for cardio-protection.

NSAIDs

Use of two or more NSAIDs concomitantly could result in an increase in side effects.

Corticosteroids

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Selective serotonin reuptake inhibitors (SSRIs)

Increased risk of gastrointestinal bleeding.

Acetazolamide

Due to the increased risk of metabolic acidosis, caution is recommended when co administering salicylates with acetazolamide.

Varicella vaccine

Cases of Reye's syndrome have occurred following the use of salicylates during varicella infections. It is therefore recommended that patients not be given salicylates for an interval of six weeks after receiving the varicella vaccine.

Levothyroxine

Thyroid hormone levels should be monitored as salicylates, specifically at doses greater than 2,0 g/day, may inhibit binding of thyroid hormones to carrier proteins and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels.

Valproic acid

The concomitant administration of salicylates and valproic acid may result in decreased valproic acid protein binding and inhibition of valproic acid metabolism resulting in increased serum levels of total and free valproic acid.

Tenofovir

Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

Other interactions with ASA

Interactions with the following medicinal products with higher (anti-inflammatory) doses of ASA have also been reported: angiotensin converting enzyme (ACE) inhibitors, acetazolamide, anticonvulsants (phenytoin and valproic acid), beta blockers, diuretics, and oral hypoglycaemic medicines.

Alcohol

Alcohol, when taken with ASA, may increase the risk of gastrointestinal injury. Therefore, alcohol should be used with caution in patients taking CLOPIDOGREL ASPIRIN 75/75 mg PD.

Other interactions with clopidogrel and ASA

More than 30 000 patients who entered clinical trials with clopidogrel plus ASA, at maintenance doses lower than or equal to 325 mg received a variety of concomitant medications including diuretics, beta blockers, ACE Inhibitors, calcium antagonists, cholesterol lowering medicines, coronary vasodilators, antidiabetic medicines (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Apart from the specific medicine interaction information described above, interaction studies with CLOPIDOGREL ASPIRIN 75/75 mg PD and some medicines commonly administered in patients with atherothrombotic disease have not been performed.

Opioid agonists

Co-administration of opioid agonists has the potential to delay and reduce the absorption of an oral P2Y12 inhibitor such as clopidogrel, presumably because of slowed gastric emptying. The clinical relevance is unknown. Consider the use of a parenteral antiplatelet medicines in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

CLOPIDOGREL ASPIRIN 75/75 mg PD is contraindicated during pregnancy.

Breastfeeding

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether clopidogrel is excreted in human breast milk. ASA is known to be excreted in human breast milk. CLOPIDOGREL ASPIRIN 75/75 mg PD is contraindicated whilst breastfeeding. Fertility There are no fertility data with clopidogrel/acetylsalicylic acid.

4.7. Effects on ability to drive and use machines

CLOPIDOGREL ASPIRIN 75/75 mg PD has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

Bleeding is the most common reaction reported both in clinical studies where frequencies varied from common to very common, as well as in post-marketing experience.

Table: Summary of adverse reactions CLOPIDOGREL ASPIRIN 75/75 mg PD

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia (sometimes severe), increased bleeding time, leucopenia, eosinophilia, neutropenia (sometimes severe), platelets decreased, aplastic anaemia

System Organ Class	Frequency	Side effects
	Frequency unknown	Bleeding*
Nervous system disorders	Less frequent	Intracranial bleeding, headache, dizziness, paraesthesia
Eye disorders	Less frequent	Eye bleeding (mainly conjunctival), ocular, retinal
Ear and labyrinth disorders	Less frequent	Vertigo
Vascular disorders	Frequent	Haematoma
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis
Gastrointestinal disorders	Frequent Less frequent	Dyspepsia, abdominal pain, diarrhoea, gastrointestinal haemorrhage Nausea, gastritis, flatulence, constipation, vomiting, gastric ulcer, duodenal ulcer
Skin and subcutaneous tissue disorders	Frequent Less frequent	Bruising Rash, pruritus, purpura
Renal and urinary disorders	Less frequent	Haematuria
General disorders and administrative site conditions	Frequent	Bleeding at the puncture site

*Post marketing events

Table: Summary of adverse reactions Clopidogrel

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequency unknown	Serious cases of bleeding, mainly skin, musculoskeletal (haemarthrosis), eye (conjunctival, ocular, retinal) and respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), epistaxis, haematuria and haemorrhage of operative wound; cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and

System Organ Class	Frequency	Side effects
		retroperitoneal haemorrhage), acquired haemophilia A, serious haemorrhage in patients taking CLOPIDOGREL ASPIRIN 75/75 mg PD with or without heparin, thrombotic thrombocytopenic purpura (TTP), aplastic anaemia/pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders	Frequency unknown	Anaphylactoid reactions, serum sickness, cross-reactive medicine hypersensitivity among thienopyridines, such as ticlopidine or prasugrel, insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)
Cardiac disorders	Frequency unknown	Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel
Psychiatric disorders	Frequency unknown	Confusion, hallucinations
Nervous system disorders	Frequency unknown	Taste disturbances, ageusia
Vascular disorders	Frequency unknown	Vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders	Frequency unknown	Colitis (including ulcerative or lymphocytic colitis), stomatitis, pancreatitis
Hepatobiliary disorders	Frequency unknown	Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Frequency unknown	Maculopapular, erythematous or exfoliative rash; urticaria; pruritus; angioedema; bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis,

System Organ Class	Frequency	Side effects
		acute generalised exanthematous pustulosis (AGEP)); drug-induced hypersensitivity syndrome (DiHS), drug rash with eosinophilia and systemic symptoms (DRESS), eczema; lichen planus
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthritis, arthralgia, myalgia
Renal and urinary disorders	Frequency unknown	Glomerulonephritis, increased blood creatinine
Reproductive system and breast disorders	Frequency unknown	Gynaecomastia
General disorders and administrative site conditions	Frequency unknown	Fever

Table: Summary of adverse reactions ASA

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequency unknown	Thrombocytopenia, haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, pancytopenia, bicytopenia, aplastic anaemia, bone marrow failure, agranulocytosis, neutropenia, leukopenia
Immune system disorders	Frequency unknown	Anaphylactic shock, aggravation of allergic symptoms of food allergy
Cardiac disorders	Frequency unknown	Kounis syndrome in the context of a hypersensitivity reaction due to ASA
Metabolism and nutrition disorders	Frequency unknown	Hypoglycaemia, gout
Nervous system disorders	Frequency unknown	Intracranial haemorrhage (may be fatal, especially in the elderly)
Ear and labyrinth disorders	Frequency unknown	Hearing loss or tinnitus

System Organ Class	Frequency	Side effects
Vascular disorders	Frequency unknown	Hypertension, cardiac failure, vasculitis including Henoch-Schönlein purpura
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Non-cardiogenic pulmonary oedema with chronic use and in the context of a hypersensitivity reaction due to ASA
Gastrointestinal disorders	Frequent	Gastro-duodenal ulcer/perforations, upper gastrointestinal symptoms such as gastralgia, peptic ulcers, small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, perforation or gastrointestinal bleeding, sometimes fatal, oesophagitis, oesophageal ulceration, perforation, erosive gastritis, erosive duodenitis, colitis, (these reactions may or may not be associated with haemorrhage, and may occur at any dose of ASA and in patients with or without warning symptoms or a previous history of serious gastrointestinal events), nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis
Hepatobiliary disorders	Frequency unknown	acute pancreatitis in the context of a hypersensitivity reaction due to ASA Elevation of hepatic enzymes, liver injury, mainly hepatocellular, chronic hepatitis
Skin and subcutaneous tissue disorders	Frequency unknown	Bullous reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis; fixed eruption
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthritis, arthralgia, myalgia
Renal and urinary disorders	Frequency unknown	Renal failure, acute renal impairment (especially in patients with existing renal impairment, heart decompensation, nephritic syndrome, or concomitant treatment with diuretics)

System Organ Class	Frequency	Side effects
General disorders and administrative site conditions	Frequency unknown	Oedema

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

4.9. Overdose

Signs and symptoms:

There is no information concerning overdosage with CLOPIDOGREL ASPIRIN 75/75 mg PD - the fixed-dose combination tablets, however due to the pharmacological activity of both clopidogrel and ASA individually, overdose may be associated with increased bleeding and subsequent bleeding complications.

Symptoms of the individual active ingredients are as follows:

Clopidogrel:

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications.

Acetylsalicylic acid (ASA):

Moderate overdose:

Dizziness, ringing in the ears, sensation of reduced hearing, headaches, vertigo, and gastrointestinal symptoms (nausea, vomiting and gastric pain).

Severe overdose:

Fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory failure, severe hypoglycaemia, hyperthermia, and perspiration, leading to dehydration. Non-cardiogenic pulmonary oedema can occur with acute and chronic acetylsalicylic acid overdose.

Management of overdose:

Clopidogrel:

Appropriate therapy should be considered if bleedings are observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel. Further treatment is symptomatic and supportive.

Acetylsalicylic acid (ASA):

If a toxic dose has been ingested, admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol sodium bicarbonate for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

5. Pharmacological properties

5.1. Mechanism of Action

Clopidogrel:

Clopidogrel is a specific and potent inhibitor of platelet aggregation. Clopidogrel is a promedicine, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP- mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

Acetylsalicylic acid (ASA):

Acetylsalicylic acid inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

5.2. Pharmacodynamic properties

Clopidogrel:

Due to the irreversible binding, platelets exposed are affected for the remainder of the lifespan (approximately 7 - 10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicines, not all patients will have adequate platelet inhibition.

Dose-dependent inhibition of platelet aggregation was noted 2 hours after single oral doses of clopidogrel.

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40 % and 60 %. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

Acetylsalicylic acid (ASA):

The antiplatelet effect of aspirin is largely unrelated to its systemic bioavailability and its duration of effect does not correlate with the presence of intact salicylic acid in the circulation. The antiplatelet effect is considered to be largely pre-systemic, associated with acetylation of platelet cyclo-oxygenase in the portal circulation.

However, as the endothelial cell is capable of synthesising new cyclo-oxygenase, whereas the platelet is not, the effect on thromboxane is longer lasting.

Due to the low dose enteric-coated formulation of Aspirin 75mg Gastro-Resistant Tablets acetylsalicylic acid is slowly released into the portal circulation and is deacetylated by the liver to inactive salicylate before reaching the systemic circulation. It is postulated that platelets Page 24 of 36 passing through the portal circulation are exposed to acetylsalicylic acid concentrations sufficient to achieve effective thromboxane inhibition, while systemic prostacyclin synthesis remains essentially unaffected.

5.3. Pharmacokinetic properties

Clopidogrel:

Absorption:

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2,2 - 2,5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50 %, based on urinary excretion of clopidogrel metabolites.

Distribution:

Clopidogrel and the main circulating (inactive) metabolite bind reversibly in vitro to human plasma proteins (98 % and 94 % respectively). The binding is non-saturable in vitro over a wide concentration range.

Biotransformation:

Clopidogrel is extensively metabolised by the liver. In vitro and in vivo, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85 % of circulating metabolites), and one mediated by multiple cytochromes P450.

Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

Elimination:

Following an oral dose of 14C-labelled clopidogrel in man, approximately 50 % was excreted in the urine and approximately 46 % in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Pharmacogenetics

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo aggregation assays, differ according to CYP2C19 genotype. The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are non-functional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in white (85 %) and Asian (99 %) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metaboliser genotypes are approximately 2 % for whites, 4 % for blacks and 14 % for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultra-rapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63 - 71 % compared to extensive metabolisers. At steady state, platelet aggregation inhibition (5 µM ADP) was decreased in poor metabolisers with mean IPA of 37 % compared to 58 % in the extensive metabolisers and 60 % in the intermediate metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials. In a meta-analysis including 6 studies of 335 clopidogrel-

treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28 % for intermediate metabolisers, and 72 % for poor metabolisers while platelet aggregation inhibition (5 µM ADP) was decreased with differences in IPA of 5,9 % and 21,4 %, respectively, when compared to extensive metabolisers.

There is some evidence that patients who are either intermediate or poor metabolisers may have a higher rate of cardiovascular events (death, myocardial infarction, stroke or stent thrombosis) compared to extensive metabolisers.

Pharmacokinetics in special patient groups

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Elderly

In elderly (≥ 75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renal impairment

After repeated administration of 75 mg clopidogrel/day in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) ADP-induced platelet aggregation was lower (25 %) than that observed in healthy subjects, however, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg clopidogrel per day.

Ethnicity

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to ethnicity (see section 5.2, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

Acetylsalicylic acid (ASA):

Absorption:

Following absorption, the ASA in the fixed dose combination tablet is hydrolised to salicylic acid with peak plasma levels of salicylic acid occurring within 1 hour of dosing, such that plasma levels of ASA are essentially undetectable 1,5 - 3 hours after dosing.

Distribution:

ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 l). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (< 100 µg/ml), approximately 90 % of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

Biotransformation and Elimination:

The ASA in the fixed dose combination tablet is rapidly hydrolised in plasma to salicylic acid, with a half-life of 0,3 - 0,4 hours for ASA doses from 75 to 100 mg. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid in the fixed dose combination tablet has a plasma half-life of approximately 2 hours.

Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10 - 20 g), the plasma half-life may be increased to over 20 hours. At high ASA doses, the elimination of salicylic acid follows zero-order kinetics (i.e., the rate

of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged medicine depends upon urinary pH. As urinary pH rises above 6,5, the renal clearance of free salicylate increases from < 5 % to > 80 %. Following therapeutic doses, approximately 10 % is found excreted in the urine as salicylic acid, 75 % as salicyluric acid, 10 % phenolic- and 5 % acyl-glucuronides of salicylic acid. Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant PK interactions are unlikely.

6. Nonclinical properties

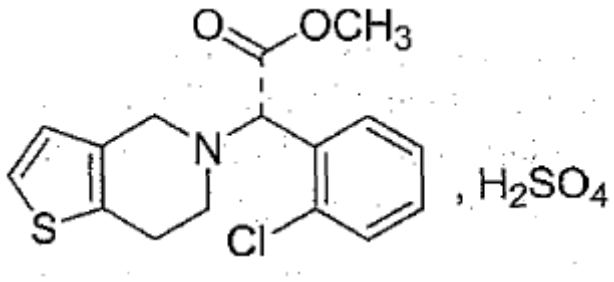
6.1. Animal Toxicology or Pharmacology

Not available

7. Description

Clopidogrel Bisulphate

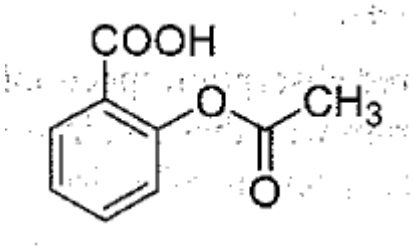
Clopidogrel Bisulphate is methyl (S)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5-(4H)-acetate sulphate. The molecular formula of Clopidogrel Bisulphate is $C_{16}H_{16}ClNO_2S$, H_2SO_4 and the molecular weight is 419.9 g/mol. The chemical structure is as below:



Clopidogrel Bisulphate is a white to off-white powder. It is freely soluble in methanol, practically insoluble in ether.

Aspirin

Aspirin is 2-acetoxybenzoic acid. The molecular formula of Aspirin is $C_9H_8O_4$ and molecular weight is 180.2 g/mol. It is colourless crystals or a white, crystalline powder. It is freely soluble in ethanol (95 per cent), soluble in chloroform and in ether, slightly soluble in water. The chemical structure is as below:



CLODREL PLUS

Bilayered film coated flat tablets with light orange coloured layer having dark orange spots on one side and white coloured layer having white shiny spots on other side of tablets.

The excipients used are Hydroxy Propyl Methyl Cellulose, Ethyl cellulose, PEG – 6000, Iso Propyl Alcohol, Methylene Chloride, Lactose Anhydrous, Microcrystalline Cellulose (AVI.PH-112), Crosspovidone XL-10, Colloidal Silicon Dioxide, Hydrogenated Castor Oil, Colloidal Hydrated Silica, Lake of Sunset Yellow, Stearic Acid, Talc, Citric Acid Anhydrous, Glyceryl Dibehenate, Sodium Starch Glycolate, Methanol.

CLODREL FORTE

Bilayered film coated flat tablets with white coloured layer having white shiny spots on one side and light orange coloured layer having dark orange spots and bisecting line on other side of tablets.

The excipients used are Hydroxy Propyl Methyl Cellulose, Ethyl cellulose, PEG – 6000, Iso Propyl Alcohol, Methylene Chloride, Lactose Anhydrous, Microcrystalline Cellulose (AVI.PH-112), Crosspovidone XL-10, Colloidal Silicon Dioxide, Hydrogenated Castor Oil, Colloidal Hydrated Silica, Lake of Sunset Yellow, Stearic Acid, Talc, Citric Acid Anhydrous, Glyceryl Dibehenate, Sodium Starch Glycolate, Methanol.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

CLODREL PLUS is available in 10 Blister strips of 15 tablets each.

CLODREL FORTE is available in 10 Blister strips of 15 tablets each.

8.4. Storage and handing instructions

STORE BELOW 25°C, IN DRY PLACE.

Keep all tablets out of the reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Torrent Pharmaceuticals Ltd**.**

32 No. Middle Camp, NH - 10,

East District, Gangtok, Sikkim- 737 135

11. Details of permission or licence number with date

M/563/2010 dated on 06.12.2021.

12. Date of revision

NA

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