

COMPOSITION:

FlexiPlus 75/75mg Tablets

Each film coated tablet contains:

Clopidogrel (as bisulfate) U.S.P75mg
Aspirin enteric coated pellets
equivalent to Aspirin (M.S)75mg

Product conforms to the Manufacturer's Specifications.

FlexiPlus 75/150mg Tablets Each film coated tablet contains:

Clopidogrel as bisulfate eq. to
Clopidogrel (U.S.P)75mg
Aspirin enteric coated pellets
equivalent to Aspirin (M.S)75mg

Product conforms to Manufacturer's Specifications.

DESCRIPTION:

Clopidogrel

Clopidogrel bisulfate is a white to off-white powder. Its chemical name is methyl (+)-(5)-a-2-chloro-phenylo-6,7-dihydrothieno[3,2-d] pyridine-5(4H)-acetate sulfate (1:1). Its molecular formula is CHINO SHSO, and its molecular weight is 419.9. Clopidogrel is a specific and potent inhibitor of platelet aggregation. Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of Clopidogrel is necessary to produce inhibition of platelet aggregation.

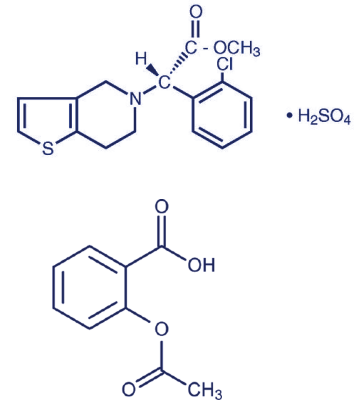
Aspirin

Aspirin is a white crystalline powder or colorless crystals, odorless or almost odorless. Its chemical name is 2-acetoxybenzoic acid. Its molecular formula is HO, and its molecular weight is 180.2. Aspirin inhibits platelet aggregation by irreversible inhibition of platelet Cyclo oxygenase and the production of Thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

PHARMACOKINETICS:

Clopidogrel

Clopidogrel after single and repeated oral doses of 75 mg per day is rapidly absorbed. Clopidogrel mean peak plasma levels (approximately 22-25 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. Clopidogrel is a prodrug which is extensively hydrolyzed in the liver by HCE1 (Human Carboxylesterase1). Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94% respectively). Aspirin is hydrolyzed to Salicylic acid, with peak plasma levels of Salicylic acid occurring within 1 hour of dosing, such as plasma



Aspirin

levels of Aspirin are essentially undetectable 1.5 to 4 hours after dosing. Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10l). Its metabolite, Salicylic acid is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). The Aspirin is rapidly hydrolyzed by HCE2 (Human Carboxylesterase 2) in the intestine and the liver to Salicylic acid, with a half life of 0.3 to 0.4 hours for Aspirin doses from 75 to 100 mg. This Salicylic acid has a plasma half life of approximately 2 hours. Following therapeutic doses, approximately 10% is found excreted in the urine as Salicylic acid, 75% as Salicyluric acid, 10% Phenolic and 5% acylglucuronides of Salicylic acid.

INDICATIONS:

Clopidogrel/Aspirin (FlexiPlus) is indicated for

- Unstable Angina or Non-ST elevation Myocardial Infarction in order to prevent early and long term Atherothrombotic events (Myocardial infarction, Stroke, Vascular death or Refractory ischaemia)
- Acute Coronary Syndrome whether or not patients undergo cardiac revascularization (Surgical or PCI, with or without stent)
- ST-segment elevation Acute Myocardial Infarction in order to prevent Atherothrombotic events

DOSAGE AND ADMINISTRATION:

Adults

Clopidogrel/Aspirin (FlexiPlus) is given as a single tablet (25mg/75mg or 75mg/150mg) once a day with adequate water

Acute Coronary Syndrome

Clopidogrel/Aspirin (FlexiPlus) is used following an initial loading dose of 300 mg of Clopidogrel in combination with Aspirin in patients with acute coronary syndrome

Unstable Angina or Non-ST elevation Myocardial Infarction

Treatment should be initiated with a single 300 mg loading dose of Clopidogrel plus Aspirin (75 to 325mg). Long term daily treatment should be continued with one Clopidogrel/Aspirin (FlexiPlus) tablet (75mg/75mg or 75mg/150mg) once a day with adequate water

ST-segment elevation Acute Myocardial Infarction

Treatment should be initiated with or without a 300 mg loading dose of Clopidogrel in combination with Aspirin and with or without possible after symptoms start. There is no data on the use of a 300 mg loading dose in elderly patients thrombolytics as soon as (aged 75 years or more) with ST segment Acute Myocardial infarction. Daily treatment should continue with one Clopidogrel/Aspirin (FlexiPlus) tablet (75mg/75mg or 75mg/150mg) once a day with adequate water.

CONTRAINDICATIONS:

Clopidogrel/Aspirin (FlexiPlus) is contraindicated in case of:

- Hypersensitivity to Clopidogrel, Salicylates or any of the excipients
- Severe liver impairment
- Active pathological bleeding such as haemophilia, intracranial haemorrhage or gastrointestinal bleeding
- Peptic ulcer or erosive gastritis
- Breast feeding



In addition, due to the presence of Aspirin, its use is also contraindicated in case of

- Known allergy to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and in patients with the syndrome of asthma with rhinitis and/or 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)
- Severe renal impairment
- Third trimester of pregnancy

WARNINGS:

Clopidogrel/Aspirin (FlexiPlus) prolong bleeding time and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions. If a patient is to undergo elective surgery and an anti-platelet effect is not desired, Clopidogrel/Aspirin (FlexiPlus) should be discontinued 7 days prior to surgery.

PRECAUTIONS:

- If the patient is at high risk of ophthalmic bleeding due to intraocular lesions Clopidogrel/Aspirin (FlexiPlus) should be used with extra caution
- Clopidogrel/Aspirin (FlexiPlus) prolongs bleeding time and should be used with caution in patients who have lesions with propensity to bleed (particularly gastrointestinal and intraocular).
- Drugs that might induce such lesions (such as NSAIDs) are not recommended in patients taking Clopidogrel/Aspirin (FlexiPlus).
- Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of Clopidogrel/Aspirin (FlexiPlus), sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment, including plasmapheresis (plasma exchange)
- Clopidogrel/Aspirin (FlexiPlus) should be used with caution in patients with a history of peptic ulcer or gastroduodenal haemorrhage or minor upper gastrointestinal symptoms, as this may be due to gastric ulceration which may lead to gastric bleeding.

PREGNANCY & LACTATION:

Pregnancy:

Pregnancy Category C: No clinical data on exposure to Clopidogrel/Aspirin (FlexiPlus) during pregnancy are available. Clopidogrel/Aspirin (FlexiPlus) should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with Clopidogrel in combination with Aspirin. Due to the presence of Aspirin, Clopidogrel/Aspirin (FlexiPlus) is contraindicated during the third trimester of pregnancy. Clopidogrel/Aspirin (FlexiPlus) should not be used in women during pregnancy unless the potential benefits outweigh the risks

Lactation:

Breast feeding is contraindicated during treatment with Clopidogrel/Aspirin (FlexiPlus), Clopidogrel and/or its metabolites are excreted in breast milk. Salicylates are excreted in breast milk, Chronic high doses of Aspirin can cause adverse effects in the infant. The concomitant administration of Clopidogrel/Aspirin (FlexiPlus) with following drugs, is not recommended:



DRUG- DRUG INTERACTIONS:

Oral Anticoagulants (including Warfarin), Glycoprotein bta Inhibitors, Injectable Anticoagulants, Anti-platelet Agents (such as Eptifibatide, Ticlopidine, Tirufiban), Thrombolytics, Methotrexate, Non-Steroidal Anti-inflammatory Drugs (NSAIDs), Selective Serotonin Reuptake Inhibitors (SSR), Uricosuric Agents (eg. Probenecid), Drugs Metabolised by Cytochrome P450 209

ADVERSE DRUG REACTIONS:

Central and peripheral nervous system disorders Uncommon:

Headache, dizziness and paraesthesia.

Rare: Vertigo

Gastrointestinal system disorders Common:

Dyspepsia, abdominal pain and diarrhea

Uncommon: Nausea, gastritis, flatulence, constipation, vomiting, gastric, peptic or duodenal ulcer

Platelet, Bleeding and Clotting disorders

Uncommon: Bleeding time increased and decreased platelets

Skin and Appendages disorders

Uncommon: Rash and pruritus

White cell and RES disorders

Uncommon: Leucopenia, decreased neutrophils, eosinophilia

OVER DOSAGE:

Clopidogrel

Overdose following Clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleeding is 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. Severe overdosage symptoms: Fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse,

Aspirin

Respiratory failure, severe hypoglycaemia, haemorrhage. In case of severe Aspirin overdose, these actions should be undertaken: Admission to hospital is necessary, control of acid-base balance, possibility of haemodialysis or peritoneal dialysis if necessary. Apart from general measures, treatment of Aspirin overdose consists chiefly of measures to accelerate the excretion (forced alkaline diuresis) and to restore the acid-base and electrolyte balance.

INSTRUCTIONS:

Store in a cool & dry place below 25°C. Protect from light, heat and moisture.

Keep out of reach of children.

PRESENTATION:

FlexiPlus 75/75mg Tablets are available in a blister pack of 10's. FlexiPlus 75/75mg Tablets are available in a blister pack of 20's. FlexiPlus 75/150mg Tablets are available in a blister pack of 10's.

FOR FURTHER INFORMATION PLEASE CONTACT:



Sign of Health & Care