WARNING
DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Clopidogrel at recommended doses 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 . Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

For the use of a Registered Medical Practitioner only

1. Generic Name & Brand Name

Clopidogrel Tablets I.P. 75 mg
STROMIX®

2. Qualitative and Quantitative Composition

Each film coated tablet contains:
Clopidogrel bisulphate I.P.
equivalent to Clopidogrel….75mg
Excipients…….q.s.
Colours: Ferric Oxide (Red) USP - NF & Titanium Dioxide I.P.

3. Dosage Form & Strength

Refer section 1 & 2

4. Clinical Particulars

4.1 Therapeutic Indications

For treatment of atherosclerosis events (myocardial infarction, stroke & vascular disease)

4.2 Posology and Method of Administration

Clopidogrel can be administered with or without food

Acute Coronary Syndrome

- In patients with non-ST-elevation ACS (UA/NSTEMI), Clopidogrel treatment must be initiated with a single 300 mg oral loading dose and then continue at 75 mg once daily. The recommendation is to initiate aspirin (75-325 mg once daily) and continue in combination with Clopidogrel
- In patients with STEMI, the recommended dose of Clopidogrel is 75 mg once daily orally, administered in combination with aspirin (75-325 mg once daily), with or without thrombolytics. Clopidogrel may be initiated with or without a loading dose

Recent MI, Recent Stroke, or Established Peripheral Arterial Disease The recommended daily dose of Clopidogrel is 75 mg once daily orally, with or without food

CYP2C19 Poor Metabolizers
CYP2C19 poor metabolizer status is associated with reduced antiplatelet response to clopidogrel. An appropriate dose regimen for this patient population has not been established.

Use With Proton Pump Inhibitors (PPI)
Avoid using omeprazole or esomeprazole with Clopidogrel as they may significantly reduce the antiplatelet activity of Clopidogrel . If the concomitant administration of a PPI is required, use another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.

4.3 Contraindications
Clopidogrel and aspirin is contraindicated for

- Hypersensitivity to clopidogrel
- Active bleeding

4.4 Special Warning and Precaution for Use

Coronary Artery Bypass Surgery
When coronary artery bypass surgery is to be performed, clopidogrel should be suspended at least 7 days before surgery to reduce the risk of bleeding.
General

- History of peptic ulcer or those prone to dyspepsia and those with gastric mucosal lesion or heavy ethanol consumption
- Tinnitus
- Asthma or allergic disorders
- Pregnancy
- Dehydrated patients
- Impaired renal or hepatic function
- Uncontrolled hypertension
- Children and elderly
- Patients at risk of increased bleeding from trauma
- Other pathological conditions
- Surgery
- Increased risk of Reye's syndrome when used in patients with chicken pox, influenza or flu symptoms.
- Caution should be taken when used in patients with nasal allergies or nasal polyps.
- For patients undergoing elective surgery and an antiplatelet effect is not needed, clopidogrel if used in combination with Aspirin should be discontinued 7-10 days before surgery.

CYP2C19 Metabolism
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain.

Ischaemic Stroke
In view of the lack of data, clopidogrel cannot be recommended in acute ischaemic stroke (less than 7 days).
Acquired Haemophilia
Acquired haemophilia has been reported following use of clopidogrel. 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 should be discontinued.
Hepatic Impairment
Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.
Renal Impairment
Experience with clopidogrel is limited in patients with mild to moderate renal impairment. Therefore, Clopidogrel should be used with caution in this population.
Carcinogenicity
There was no evidence of carcinogenic effects when clopidogrel was given in the diet for 78 weeks to mice and 104 weeks to rats at doses up to 77 mg/kg per day (representing an exposure approx. 18 times the anticipated patient exposure, based on plasma AUC for the main circulating metabolite in elderly subjects).
Effects on Fertility
Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day.
Use in Lactation
Breast-feeding is contraindicated during treatment with Clopidogrel.
Use in Pregnancy (Category C)
No clinical data on exposure to clopidogrel during pregnancy are available. Clopidogrel should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel. Reproduction toxicity data show that aspirin is teratogenic in several laboratory animals.
Clopidogrel should not be used in women during pregnancy unless the potential benefits outweigh the risks.

4.5 Drug Interactions

Clopidogrel	
NSAIDs	Co-administration of clopidogrel with NSAIDs may increase the risk of stomach and intestinal bleeding.
Coumarins, Agatroban, Dasatinib, Heparin, LMWH, Gingko Biloba And Iloprost	There is an increased risk of bleeding with coumarins, agatroban, dasatinib, heparin, LMWH, gingko biloba and iloprost.
Drotrecogin alfa	Increased risk of bleeding if clopidogrel and drotrecogin alfa are given within 7 days. It may increase bupropion level and side effects (light headedness, GI discomfort).

Boosted antiviral human immunodeficiency virus (HIV) therapy	Interaction with boosted antiviral human immunodeficiency virus (HIV) therapy leading to insufficient inhibition of platelet aggregation

4.6 Use in Special Populations

Pregnancy

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Breast-feeding

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel film-coated tablet.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on Ability to Drive and Use Machines

Clopidogrel has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects

- **Nervous system disorders:** Taste disorders, fatal intracranial bleeding, headache
- **Psychiatric disorders:** Confusion, hallucinations
- **Gastrointestinal disorders:** Gastric/duodenal ulcer, diarrhea, gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- **General disorders and administration site condition:** Fever, hemorrhage of operative wound
- **Hepato-biliary disorders:** Acute liver failure, hepatitis, abnormal liver function test
- **Immune system disorders:** Hypersensitivity reactions, serum sickness, anaphylactoid reactions
- **Musculoskeletal, connective tissue and bone disorders:** Arthralgia , Myalgia Musculoskeletal bleeding, myalgia, arthritis
- **Respiratory, thoracic and mediastinal disorders:** Respiratory tract bleeding, eosinophilic pneumonia, bronchospasm, interstitial pneumonitis
- **Renal and urinary disorders:** Increased creatinine levels
- **Blood and lymphatic system disorders:** Thrombotic thrombocytopenic purpura (TTP), agranulocytosis, aplastic anemia/pancytopenia, acquired hemophilia A

- **Eye disorders:** Eye (conjunctival, ocular, retinal) bleeding
- **Skin and subcutaneous tissue disorders:** Urticaria, bullous dermatitis, skin bleeding, lichen planus, generalized pruritus, eczema, maculopapular, erythematous or exfoliative rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme
- **Vascular disorders:** Vasculitis, hypotension

4.9 Overdose

Clopidogrel:

Platelet inhibition by Clopidogrel is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons.

Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.

Based on biological plausibility, platelet transfusion may restore clotting ability.
Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleeding is observed.

5. Pharmacological Properties

5.1 Mechanism of Action

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized 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. Due to the irreversible binding, platelets exposed are affected for the remainder of their 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 medicinal products, not all patients will have adequate platelet inhibition.

5.2 Pharmacodynamic Properties

Clopidogrel is a prodrug and is metabolised an active thiol metabolite. The active metabolite selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GP IIb/IIIa complex, thereby inhibiting platelet aggregation.

5.3 Pharmacokinetic Properties

	Clopidogrel
Absorption	Rapid, incomplete absorption
Distribution	Protein binding: 98% (parent drug).
Metabolism	Extensive hepatic metabolism; converted to inactive carboxylic acid derivative and thiol derivative (active).
Excretion	Via urine (50%) and faeces (46%) as unchanged drug and metabolites. Elimination half-life: Approx 6 hourr.
Half life	Approximately 6 hours

6. Nonclinical Properties

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolizing enzymes. No effect on hepatic metabolizing enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabeled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

7. Description

STROMIX is supplied for oral administration, as a film coated tablet of Clopidogrel bisulphate. Each film coated tablet of STROMIX contains Clopidogrel bisulphate equivalent to Clopidogrel 75mg.

8. Pharmaceutical Particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage and Handling Instruction

Refer Pack

9. Patient Counselling Information

Not available

10. Details of Manufacturer

Manufactured By:
Refer Pack for manufacturer details.

Marketed By:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 6 &
11 to 16 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

11. Details of Permission or Licence Number with Date

Refer Pack for Permission/License details

12. Date of Revision

Version 5.0, dated 14/05/2024

For Product Complaints/Adverse events or Queries please write to **webmasterindia@abbott.com**