

Tablets

# Composition

Each tablet contains: Clopidogrel Bisulfate 75 mg.

## **Action**

## **Pharmacodynamics**

Clopidogrel is a specific and potent inhibitor of platelet aggregation. Platelets have an established role in the pathophysiology of atherosclerotic disease and thrombotic events. Long term use of antiplatelet drugs has shown consistent benefit in the prevention of ischemic stroke, myocardial infarction and vascular death in patients at increased risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis.

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. However, an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover (approximately 7 days).

Statistically significant and 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 7 days after treatment was discontinued.

## **Pharmacokinetics**

After repeated oral doses of 75 mg per day, a single oral dose of Clovix is rapidly absorbed. Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative that represents about 85% of the circulating compound in plasma. Peak plasma levels of this metabolite (approx. 3 mg/L after repeated 75 mg oral doses) occurred approximately 1 hour after dosing.

Following an oral dose of <sup>14</sup>C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

Plasma concentrations of the main circulating metabolite were significantly higher in elderly subjects (≥ 75 years) as compared to young healthy volunteers. However, these higher plasma levels were not associated with differences in platelet aggregation and bleeding time.

Plasma levels of the main circulating metabolite were lower in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal disease (creatinine clearance from 30 to 60 ml/min) and healthy subjects, after repeated doses of 75 mg/day. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day.

## **Special Populations**

Geriatric Patients

Plasma concentrations of the main circulating metabolite are significantly higher in the elderly (≥ 75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

## Renally Impaired Patients

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 ml/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar in healthy volunteers receiving 75 mg of clopidogrel per day. No dosage adjustment is needed in renally impaired patients. However, experience with clopidogrel is limited in patients with severe renal impairment. Therefore clopidogrel should be used with caution in this population.

#### Gender

No significant difference was observed in the plasma levels of the main circulating metabolite between males and females.

#### Race

Pharmacokinetic differences due to race have not been studied.

#### **Indications**

Prevention of vascular ischemia associated with atherothrombotic events (MI, stroke and vascular death) in patients with a history of symptomatic atherosclerotic disease.

## **Acute Coronary Syndrome**

Clovix is indicated in combination with aspirin for patients with:

- Unstable angina or non-ST elevation MI. Indicated for early and long-term reduction of atherothrombotic events (myocardial infarction, stroke, vascular death and refractory ischemia) whether or not patients undergo cardiac revascularization (surgical or PCI, with or without stent).
- ST-segment elevation acute myocardial infarction. Clopidogrel has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke.

## **Contraindications**

- Hypersensitivity to clopidogrel or any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.
- Breast-feeding.

### **Adverse Reactions**

#### Musculoskeletal, connective and bone

• Very rare: Arthralgia, arthritis, myalgia

## Immune system disorders

Very rare: anaphylactoid reactions, serum sickness

## Vascular disorders

Very rare: vasculitis, hypotension

### Blood and lymphatic system disorders

• Very rare: serious cases of bleeding, mainly skin, musculoskeletal, eye (conjunctival, ocular, retinal) and respiratory tract bleeding, epistaxis, haematuria and haemorrhage of operative wound. Fatal haemorrhage, including intracranial, gastrointestinal, and retroperitoneal haemorrhage. Cases of serious haemorrhage have been reported in patients taking clopidogrel concomitantly with aspirin or clopidogrel with aspirin and heparin.

- Very rare cases of thrombotic thrombocytopenic purpura (TTP) have been reported.
- Very rare: Agranulocytosis, aplastic anaemia, neutropenia, pancytopenia
- Uncommon: eosinophilia, leucopenia, decreased neutrophils, decreased platelets, increased bleeding time

#### Skin and subcutaneous tissue disorders

• Very rare: macropapular or erythematous rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) eczema, lichen planus

## **Psychiatric**

Very rare: confusion, hallucinations

#### **Nervous system disorders**

Very rare: taste disturbances

#### **Hepatobiliary disorders**

• Very rare: hepatitis, acute liver failure

#### **Gastrointestinal disorders**

• Very rare: colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomtatitis

## Respiratory, thoracic and mediastinal disorders

Very rare: bronchospasm, interstitial pneumonitis

## **Renal and Urinary disorders**

Very rare: glomerulopathy

## Investigations

• Very rare: blood creatinine increase, abnormal liver function tests

## General disorders and administration site conditions

Very rare: fever, syncope

[Very common  $\geq$ 1/10, common  $\geq$ 1/100 and <1/10, uncommon  $\geq$ 1/1000 and <1/100, rare  $\geq$ 1/10,000 and <1/1000, very rare <1/10,000.]

## **Precautions**

#### General

As with the other anti-platelet agents, clopidogrel prolongs 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, as follows:

- If a patient is to undergo elective surgery and an anti-platelet effect is not desired, clopidogrel should be discontinued at least 5 days prior to surgery.
- If the patient is at high risk of ophthalmic bleeding due to intraocular lesions clopidogrel should be used with extra caution.
- Although clopidogrel has shown a lower incidence of gastrointestinal bleeding compared to aspirin, the drug should be used with caution in patients who have lesions with a propensity to bleed. Drugs that might induce such lesions (such as aspirin and NSAID) should be used with caution in patients taking clopidogrel.
- Patients should be told that it may take longer than usual for bleeding to stop when they take clopidogrel (alone or in combination with aspirin), and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.
- In patients with recent transient ischemic attack or stroke who are at high risk of recurrent ischemic events, the combination of aspirin and clopidogrel has been shown to increase major

bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

Experience with clopidogrel is limited in patients with severe renal impairment. Therefore clopidogrel should be used with caution in this population.

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

In view of the lack of data, clopidogrel cannot be recommended in acute ischemic stroke (less than 7 days).

## **Coronary Artery Bypass Surgery**

When coronary artery bypass surgery is to be performed, clopidogrel should be suspended at least 5 days before surgery to reduce the risk of bleeding.

### Haematological

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterized by thrombocytopenia and microangiopathic haemolytic anaemia associated with neurological findings, renal dysfunction, or fever. TTP is a potentially fatal condition requiring prompt treatment, including plasmapheresis (plasma exchange).

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have also been reported very rarely in patients taking clopidogrel.

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As with other anti-platelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with aspirin, non-steroidal anti-inflammatory drugs, heparin, glycoprotein IIb/IIIa inhibitors, or thrombolytics. Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery.

## **Pregnancy**

#### Category B

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

## **Nursing Mothers**

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in breast milk.

# **Drug Interactions**

## Aspirin

A pharmacodynamic interaction between clopidogrel and aspirin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and aspirin have been administered together for up to one year.

### Injectable Anticoagulants

A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

### Glycoprotein IIb/IIIa inhibitors

As a pharmacological interaction between clopidogrel and glycoprotein IIb/IIIa inhibitors is possible, concomitant use should be undertaken with caution.

## **Thrombolytics**

The safety of the concomitant administration of clopidogrel, rt-PA and heparin was assessed in patients with recent myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when rt-PA and heparin are co-administered with aspirin. The safety of the administration of clopidogrel with other thrombolytic agents has not been established and should be undertaken with caution.

### **Oral Anticoagulants**

Due to the increased risk of bleeding, concomitant administration of warfarin and clopidogrel should be undertaken with caution.

## Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

The concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. Consequently, there is a potential increased risk of gastrointestinal bleeding and NSAID's and clopidogrel should be co-administered with caution.

### Drugs metabolised by Cytochrome P450 2C9

Clopidogrel inhibits cytochrome P450 (2C9). Accordingly, it may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is co-administered with Clopidogrel.

### Other concomitant therapy

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

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

In addition to the above specific interaction studies, a variety of concomitant medications were administered including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), anti-epileptic agents, GPIIb/IIIa antagonists and hormone replacement therapy without evidence of clinically significant adverse interactions.

## **Dosage and Administration**

Clovix should be taken once a day with or without food.

#### **Adults**

Generally, Clovix should be given as a single daily dose of 75 mg.

In patients with acute coronary syndrome (unstable angina or non-ST elevation myocardial infarction), Clovix treatment should be initiated with a single 300 mg loading dose and then continued long-term at 75 mg once a day (with aspirin 75 mg-325 mg daily).

No dosage adjustment is necessary for either elderly patients or patients with renal impairment.

### **Children and Adolescents**

Safety and efficacy in subjects below the age of 18 have not been established.

## **Over Dosage**

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.

## Presentation