CLODREL

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

Abbreviated Prescribing information for **CLODREL**

(Clopidogrel Tablets I.P.) [Please refer the complete prescribing information for details].

PHARMACOLOGICAL PROPERTIES:

Mechanism of Action: Clopidogrel is a prodrug, 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. 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.

INDICATIONS: For the treatment of atherosclerosis events (myocardial infarction, stroke & vascular death)

DOSAGE AND ADMINISTRATION: As directed by the Physician. Tablets should be taken orally.

CONTRAINDICATION: Hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria) active substance and to any of the excipients; Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages; Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia; Patients who are suffering from gout; Severe renal impairment; Severe hepatic impairment Doses >100 mg/day during the third trimester of pregnancy Methotrexate used at doses >15mg/week Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

WARNINGS & PRECAUTIONS: *Bleeding and haematological disorders* As with other antiplatelet 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 ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti- inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or other medicinal products associated with bleeding risk such as pentoxifylline. *Thrombotic Thrombocytopenic Purpura (TTP)* Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, 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. *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 hemophilia should be managed and treated by specialists, and clopidogrel should be discontinued. *Recent ischaemic stroke* In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke. *CYP2C8 substrates* Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products. *Renal impairment*

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in these patients. *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

DRUG INTERACTIONS: *Medicinal products associated with bleeding risk*: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution. *Glycoprotein IIb/IIIa inhibitors:* clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors. *Heparin*: in a clinical study conducted 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. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, 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. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA. *SSRIs*: since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

ADVERSE REACTIONS: Thrombocytopenia, leucopenia, eosinophilia, Neutropenia, including severe neutropenia, Kounis syndrome (vasospastic allergicangina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel, Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel)*, insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population), Hallucinations, confusion, Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness, Taste disturbances, ageusia, Eye bleeding (conjunctival, ocular, retinal), Haematoma, Epistaxis, Vertigo, Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension, Respiratory tract Bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia, Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia, Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence, Retroperitoneal haemorrhage, Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis, Bruising, Rash, pruritus, skin bleeding (purpura), Acute liver failure, hepatitis, abnormal liver function test, Bullous dermatitis (toxic epidermal necrolysis, Stevens, Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, druginduced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus, Gynaecomastia, Bleeding at puncture site, Haematuria, Bleeding time prolonged, neutrophil count decreased, platelet count decreased, Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia, Glomerulonephritis, blood creatinine increased, Fever

MARKETED BY:

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(Additional information is available on request)