SCHEDULING STATUS:

PROPRIETARY NAME (AND DOSAGE FORM):

PLAGROL (TABLET)

COMPOSITION:

PLAGROL: Each film-coated tablet contains,clopidogrel bisulfate 97,875 mg.equivalent to 75 mg clopidogrel base.

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Clopidogrel is a specific and potent inhibitor of platelet aggregation. It acts by irreversibly modifying the platelet ADP-receptors. It inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. 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 tumover (of about 7 days). Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP.

Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation.

Repeated doses of 75 mg per day may produce inhibition of ADP-induced platelet aggregation from the first day; this may increase progressively and reach steady state between day 3 and day 7. At steady state the average inhibition level observed with a dose of 75 mg per day may be between 40 % and 60 %. Platelet aggregation and bleeding time gradually returns to baseline values, generally within 7 days after treatment has been discontinued.

Pharmacokinetics:

After oral doses clopidogrel is rapidly absorbed. Absorption is at least 50 %. Clopidogrel is extensively metabolized by the liver and the main metabolite which is inactive, is the carboxylic acid derivative which represents about 85 % of the circulating compound in the plasma.

Clopidogrel and the main metabolite bind *in vitro* reversibly to human plasma proteins (98 % and 94 % respectively).

The elimination half-life of the main circulating metabolite may reach 8 h9urs after administration. Clopidogrel and the main metabolite are excreted in urine (50 %) and faeces (46 %).

INDICATIONS:

PLAGROL is indicated for:

- Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease

CONTRAINDICATIONS:

PLAGROL is contraindicated in:

- hypersensitivity to the active substance or any component of the product
- active bleeding such as peptic ulcer and intracranial haemorrhage
- safety and efficacy in patients below the age of 18 have not been established
- pregnancy and lactation
- severe liver impairment
- thrombocytopenia
- platelet dysfunction

WARNINGS:

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH PLAGROL DURING POST-MARKETING EXPERIENCE. MOST CASES WERE REPORTED IN THE **FIRST TWO WEEKS** OF **TREATMENT. IN ADDITION PRESCRIBERS SHOULD ALSO WARN PATIENTS ABOUT THE SIGNS AND SYMPTOMS OF THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP).**

The clinical diagnosis of TTP is characterized by the presence of thrombocytopenia, haemolytic anaemia, neurological symptoms, renal dysfunction and fever.

Due to the risk of fatal outcome, in the event of suspected thrombotic thrombocytopenic purpura, **PLAGROL** should be stopped. The management of a patient with thrombotic thrombocytopenic purpura is complex.

Early treatment with plasmapharesis is indicated in TTP.

Risk of increased blood loss during dental and surgical procedures.

Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.

Use with caution in patients receiving other drugs that increase the risk of bleeding (acetylsalicylic acid, NSAIDs and other anticoagulants).

INTERACTIONS:

Acetylsalicylic acid (aspirin):

PLAGROL potentiates the effect of acetylsalicylic acid on collagen-induced platelet aggregation. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid (aspirin) is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. The safety of the chronic concomitant administration of acetylsalicylic acid (aspirin} and **PLAGROL** has not been established (see **"Special precautions"}.**

Heparin:

The safety of this combination has not been established and concomitant se should be undertaken with

caution. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding.

Thrombolytics:

The safety of the concomitant co-administration of **PLAGROL** with other thrombolytic agents has not been established and concomitant administration should be undertaken with caution.

Warfarin:

The safety of the co-administration of **PLAGROL** with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken wit.h caution.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including aspirin:

There is a potential risk of gastrointestinal bleeding and NSAIDs, including aspirin, and **PLAGROL** should be co-administered with caution (see **"Special precautions").**

NSAIDs, including COX-2 inhibitors and clopidogrel should be co-administered with caution.

Glycoprotein IIb/IIIa inhibitors:

PLAGROL should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other conditions/disorders that may require glycoprotein fib/IIIa inhibitors intake.

Other concomitant therapy:

No clinically significant pharmacodynamic interactions were observed when **PLAGROL** was administered with atenolol, nifedipine or both atenolol and nifedipine. The pharmacodynamic activity of **PLAGROL** was not significantly influenced by the co-administration of phenobarbital, cimetidine, or oestrogen. The pharrnacokinetics of digoxin or theophylline were not modified by the co-administration of **PLAGROL.**

PLAGROL inhibits the activity of one of the Cytochrome $\mathbf{P_{450}}$ enzymes: (CYP 2C9). This leads to increased plasma levels of medicines such as phenytoin, tolbutamide, warfarin, tamoxifen, fluvastatin and many NSAIOs which are metabolized by CYP 2C9.

PREGNANCY AND LACTATION:

(See **"CONTRAINDICATIONS")**

The use of **PLAGROL** during pregnancy and lactation is not recommended as safety and efficacy have not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults:

PLAGROL should be given as a single daily dose of 75 mg with or without food.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Very common 1110), Common 1/100 and< 1/10), Uncommon 1/1 000 and< 1/100), Rare 1/10 000 and< 111 000), Very rare{< 1110 000)

Side effects:

Blood and lymphatic system disorders:

Common:	Purpura, bruising, epistaxis, gastrointestinal haemorrhage
Uncommon:	Severe neutropenia including agranulocytosis
Rare:	Intracranial haemorrhage
Very rare:	Aplastic anaemia, pancytopenia, severe thrombocytopenia (including thrombotic thrornbocytopenic purpura)
Incidence unknown:	Haematuria, eye bleeding (conjunctiva!, ocular, retinal). respiratory tract bleeding (including haemothorax), musculoskeletal bleeding (including haemarthrosis), haemorrhagic ulcer, haemorrhage of operative wound, retroperitoneal haemorrhage

Immune system disorders:

Very rare:	Bronchospasm, angioedema, anaphylactoid reactions

Psychiatric disorders:

Very rare:	Confusion, hallucinations
Common:	Anxiety, mental depression

Nervous system disorders:

Common:	Syncope, insomnia, hypoesthesia
Uncommon:	Headache, dizziness, paraesthesia
Rare:	Vertigo, intracranial haemorrhage
Very rare:	Taste disturbances

Cardiac disorders:

Common:	Chest pain, atrial fibrillation, palpitations

Vascular disorders:

Common:	Oedema, hypertension
Very rare:	Hypotension, vasculitis

Respiratory, thoracic and mediastinal disorders:

Common:	Bronchitis, dyspnoea, upper respiratory tract infection, cough, rhinitis
Very rare:	Interstitial pneumonitis

Gastrointestinal disorders:

Common:	Abdominal pain, dyspepsia, gastrointestinal haemorrhage, diarrhoea
Uncommon:	Gastric and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence
Incidence unknown:	Tooth disorder

Hepato-biliary disorders:

Very rare:	Abnormal liver function tests, hepatitis, acute liver failure

Skin and subcutaneous tissue disorders:

Uncommon: Rash, pruritus

Very rare: Severe skin reactions (including bullous eruption}, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus, urticaria, eczema

Renal and urinary disorders:

Common: Urinary tract infection

Very rare: Glomerulonephritis, increased creatinine levels

Musculoskeletal system disorders:

Common: Back pain, gout, leg cramps

Very rare: Arthralgia, myalgia, arthritis

Other:

Common: Generalised pain, flu-like symptoms, fatigue, asthenia

Special precautions:

PLAGROL 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 acetylsalicylic acid (aspirin), NSAIDs (including COX-2 inhibitors}, heparin or glycoprotein IIb/IIIa inhibitors. Patients should be monitored carefully for any signs of bleeding, including occult bleeding, especially during the first week of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleedings. If a patient is to undergo elective surgery and an anti-platelet effect is not desired, **PLAGROL** should be discontinued 7 days prior to surgery. **PLAGROL** prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Medicines that might induce such lesions (such as acetylsalicylic acid and NSAIDs) should be used with caution in patients taking **PLAGROL.**

Patients should be told that it *may* take longer than usual to stop bleeding when they take **PLAGROL** and that they should report any unusual bleeding to their medical practitioner. Patients should inform medical practitioners and dentists that they are taking **PLAGROL** before any surgery is scheduled and before any new medicine is taken.

In view of the possible increased risk of bleeding, the concomitant administration of **PLAGROL** with acetylsalicylic acid (aspirin), heparin, warfarin or thrombolytics should be undertaken with caution (see **"INTERACTIONS").**

In patients with recent transient ischaemic attack (TIA) or stroke, who are at high risk of recurrent ischaemic events, the combination of aspirin and **PLAGROL** has not been shown to be more effective than **PLAGROL** alone, but the combination has been shown to increase major bleeding. It is therefore recommended that such addition should be undertaken with caution. In patients with acute myocardial infarction, **PLAGROL** therapy should not be initiated within the first few days following the myocardial infarction.

In view of the lack of data **PLAGROL** cannot be recommended in coronary artery by-pass graft (CABG) and acute ischaemic stroke (less than 7 days).

Clinical experience is limited in patients with renal impairment and moderate hepatic disease with bleeding diatheses. **PLAGROL** should be used in caution in these patients.

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have been reported in patients taking clopidogrel (see **"Side effects").**

Effects on ability to drive and use machines:

No impairment of driving or psychometric performance was observed following **PLAGROL** administration.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See **"SIDE EFFECTS AND SPECIAL PRECAUTIONS")**

Overdose following **PLAGROL** administration may lead to prolonged bleeding time and subsequent bleeding complications. Treatment is symptomatic and supportive.

IDENTIFICATION:

PLAGROL: White, film-coated, round, biconvex tablets embossed "R" on one side and "196" on other side

PRESENTATION:

PLAGROL: Pack sizes of 30 tablets in white HDPE plastic bottles.

STORAGE INSTRUCTIONS:

Store below 25 °C. Protect from light.

Keep the tablets in the original pack in which it was received until you are ready to take a dose.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

40/8.2/0673

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