**SCHEDULING STATUS: S3**

**PROPRIETARY NAME AND DOSAGE FORM**

**ACTICLOP 75** film coated tablets

**COMPOSITION**

Each film coated tablet contains:

Clopidogrel besylate 112,10 mg the molar equivalent of 75 mg Clopidogrel base.

Contains mannitol.

**PHARMACOLOGICAL CLASSIFICATION**

A 8.2 Anticoagulants

**PHARMACOLOGICAL ACTION**

**i) Pharmacodynamic properties**

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.

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).

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.

**ii) Pharmacokinetics**

After repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50 %, based on urinary excretion of clopidogrel metabolites.

Clopidogrel is extensively metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative, which 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.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxo-clopidogrel and subsequent hydrolysis. The oxidative step is regulated

primarily by Cytochrome P450 isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

The kinetics of the main circulating metabolite were linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.

Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98 % and 94 % respectively). The binding is non-saturable *in vitro* over a wide concentration range.

Following an oral dose of 14C-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.

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal impairment (creatinine clearance from 30 to 60 ml/min) and to levels observed in other studies with healthy subjects. 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.

**INDICATIONS**

ACTICLOP 75 is indicated for the 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.

**CONTRA-INDICATIONS**

- Hypersensitivity to the active substance or to any of the excipients of ACTICLOP 75
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.
- Safety and efficacy in patients below the age of 18 have not been established.

- Safety and efficacy in pregnancy and lactation have not been established.
- Thrombocytopenia
- Platelet dysfunction

**WARNINGS**

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| THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH ACTICLOP 75 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, ACTICLOP 75 should be stopped and a specialist team should be contacted. The management of a patient with thrombotic thrombocytopenic purpura is complex. Early treatment with plasmapharesis is indicated in TTP (*see Side Effects and Special Precautions*).

- Risk of increased blood loss during dental and surgical procedures.
- Active bleeding such as peptic ulcer and intracranial haemorrhage.
- Use with caution in patients receiving other medicines that increase the risk of bleeding (anticoagulants; NSAIDs and other anticoagulants).

If a patient is to undergo elective surgery and antiplatelet effect is not necessary, ACTICLOP 75 should be discontinued 7 days prior to surgery. ACTICLOP 75 prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

**INTERACTIONS**

**Acetylsalicylic acid (ASA)**: Clopidogrel potentiated the effect acetylsalicylic acid collagen-induced platelet aggregation. The safety of the chronic concomitant administration of ASA and ACTICLOP 75 has not been established (*see Special Precautions*).
A pharmacodynamic interaction between ACTICLOP 75 and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

**Glycoprotein IIb/IIIa inhibitors**: ACTICLOP 75 should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors.

**Heparin**: A pharmacodynamic interaction between ACTICLOP 75 and heparin is possible, leading to increased risk of bleeding. The safety of this combination has not been established and concomitant use should be undertaken with caution.

**Warfarin**: The safety of the co-administration of ACTICLOP 75 with warfarin has not been established. The concomitant administration of ACTICLOP 75 with warfarin is not recommended since it may increase the intensity of bleedings.

**Thrombolytics**: The safety of the concomitant administration of ACTICLOP 75 with other thrombolytic agents has not been established and should be undertaken with caution.

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) including aspirin**: There is a potential risk of gastro-intestinal bleeding and NSAIDs including aspirin and Cox-2 inhibitors and ACTICLOP 75 should be co-administered with caution.

**Other concomitant therapy**: No clinically significant pharmacodynamic interactions were observed when ACTICLOP 75 was co-administered with atenolol, nifedipine, or both atenolol and nifedipine.

Furthermore, the pharmacodynamic activity of ACTICLOP 75 was not significantly influenced by the coadministration of phenobarbital, cimetidine, or oestrogen.
The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of ACTICLOP 75. Antacids did not modify the extent of ACTICLOP 75 absorption.
Data from studies with human liver microsomes indicated that the carboxylic acid metabolite of clopidogrel could inhibit the activity of Cytochrome P450 2C9. This could potentially lead to increased plasma levels of drugs such as phenytoin, tolbutamide, warfarin, tamoxifen, fluvastatin and many NSAIDs which are metabolised by Cytochrome P450 2C9.

## PREGNANCY AND LACTATION

The use of ACTICLOP 75 during pregnancy and lactation is not recommended as safety and efficacy in pregnancy and lactation have not been established (*see Contra-Indications*).

## DOSAGE AND DIRECTIONS FOR USE

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

## SIDE EFFECTS AND SPECIAL PRECAUTIONS

### i) Side Effects

Clinically relevant adverse drug reactions pooled from clinical studies, as well as all serious and relevant ADR are listed below according to the World Health Organisation classification. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| System Organ | Frequent | Less Frequent |
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| **Class** | | |
| **Skin and appendages disorders** | | Rash and Pruritus |
| **Central and peripheral nervous system disorders** | - | Headache, Dizziness and Paraesthesia<br>Vertigo |
| **Gastrointestinal system disorders** | Diarrhoea, Abdominal pain, Dyspepsia<br>Gastrointestinal bleeding | Gastric ulcer and Duodenal ulcer, Gastritis, Vomiting, Nausea, Constipation, Flatulence. |
| **Red blood cell disorders** | | Aplastic anaemia |
| **White cell and RES disorders** | | Severe neutropenia,<br>Leucopenia, Neutrophils decreased and Eosinophilia. |
| **Platelet, bleeding and clotting disorders** | Bleeding at puncture sites.<br>Purpura/bruising/haematoma, epistaxis | Bleeding time increased and Platelets decreased<br>Haematuria, Eye bleeding (mainly conjunctival), Intracranial bleeding<br>Severe thrombocytopenia |

***Post-marketing experience*:**

Thrombotic thrombocytopenic purpura (TTP) has been reported to occur with ACTICLOP 75 during post-marketing experience (*see Warnings and Special Precautions*).

*Bleeding* is the most common reaction reported in the post-marketing experience and was mostly reported during the first month of treatment.

Bleeding: some cases were reported with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage); serious cases of skin bleeding (purpura), musculo-skeletal bleeding (haemarthrosis, haematoma), eye bleeding (conjunctival, ocular, retinal), epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), haematuria and haemorrhage of operative wound have been reported; cases of serious haemorrhage have been reported in patients taking ACTICLOP 75 concomitantly with acetylsalicylic acid or ACTICLOP 75 with acetylsalicylic acid and heparin.

In addition to clinical studies experience, the following adverse reactions have been spontaneously reported. Within each system organ class (MedDRA classification) and within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **System Organ Class** | |
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| **Blood and lymphatic system disorders** | Thrombotic Thrombocytopenic Purpura (TTP) (1/200,000 exposed patients) (*see Warnings*), severe Thrombocytopenia (platelet count ≤30 x109/l), Agranulocytosis, Granulocytopenia, Aplastic Anaemia/Pancytopenia, Anaemia, Neutropenia |
| **Immune system disorders** | Anaphylactoid reactions, Serum sickness |
| **Psychiatric disorders** | Confusion, Hallucinations |
| **Nervous system disorders** | Taste disturbances |
| **Vascular disorders** | Vasculitis, Hypotension |
| **Respiratory, thoracic and mediastinal disorders** | Bronchospasm, Interstitial pneumonitis |
| **Gastrointestinal disorders** | Pancreatitis, Colitis (including ulcerative or lymphocytic colitis), Stomatitis |
| **Hepato-biliary disorders** | Acute liver failure, Hepatitis |
| **Skin and subcutaneous tissue disorders** | Angioedema, Bullous dermatitis (erythema multiforme, Stevens Johnson Syndrome, toxic epidermal necrolysis), Rash erythematous, Urticaria, Eczema and Lichen planus |
| **Musculoskeletal, connective tissue and bone disorders** | Arthralgia, Arthritis, Myalgia |
| **Renal and urinary disorders** | Glomerulonephritis |
| **General disorders and administration site conditions** | Fever |
| **Investigations** | Abnormal liver function test, Blood creatinine increase |

| System Organ Class | |
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**ii) Special Precautions**

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.

ACTICLOP 75 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 (ASA), nonsteroidal anti-inflammatory drugs including Cox-2 inhibitors, heparin or glycoprotein IIb/IIIa inhibitors *(see Interactions)*.

Patients should be monitored carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of ACTICLOP 75 with warfarin is not recommended, since it may increase the intensity of bleedings.

If a patient is undergoing a neuro-block procedure, ACTICLOP 75 should be discontinued 7 days prior to surgery.

Patients should be told that it might take longer than usual to stop bleeding when they take ACTICLOP 75 (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their doctor. Patients should inform medical practitioners and dentists that they are taking ACTICLOP 75 before any surgery is scheduled and before any new medicine is taken.

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of ACTICLOP 75, 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.

Due to the risk of fatal outcome, in the event of suspected thrombotic thrombocytopenic purpura, ACTICLOP 75 should be stopped and a specialist team should be contacted. The management of a patient with thrombotic thrombocytopenic purpura is complex. Early treatment with plasmapharesis is indicated in TTP *(see Warnings)*.

In view of the lack of data, ACTICLOP 75 cannot be recommended in coronary artery bypass graft (CABG) and in acute ischaemic stroke (less than 7 days).

In patients with recent transient ischaemic attack (TIA) or stroke, who are at risk of recurrent ischaemic events, the combination of aspirin and ACTICLOP 75 has not been shown to be more effective than ACTICLOP 75 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, ACTICLOP 75 therapy should not be initiated within the first few days following myocardial infarction.
Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have been reported in patients taking ACTICLOP 75 *(see Side Effects).*
Therapeutic experience with ACTICLOP 75 is limited in patients with renal impairment. Therefore ACTICLOP 75 should be used with caution in these patients.
Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. ACTICLOP 75 should therefore be used with caution in this population.

**iii) Effects on ability to drive and use machines**

No impairment of driving or psychometric performance was observed following ACTICLOP 75 administration. ACTICLOP 75 has no or negligible influence on the ability to drive and use machines.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

Overdose following ACTICLOP 75 administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are 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.

**IDENTIFICATION**

ACTICLOP 75 tablets are pink, round, biconvex, film-coated tablets of 9,1 mm diameter and 4,2 mm thickness.

**PRESENTATION**

28 (2 blisters of 14 tablets or 4 blisters of 7 tablets) or 30 (3 blisters of 10 tablets) ACTICLOP 75 film-coated tablets packed in either PVC/PE/PVDC/Aluminium (opaque white on aluminium coloured) blisters or in all aluminium blisters, in cardboard cartons.
Not all pack sizes may be marketed at any one time.

**STORAGE INSTRUCTIONS**

Store at or below 25 °C in the original package.
The blisters must be kept in the outer carton until required for use.
Keep out of the reach of children.

**REGISTRATION NUMBER:**

43/8.2/0725

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**

Activo Health (Pty) Ltd
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**DATE OF PUBLICATION OF THE PACKAGE INSERT:**

30 September 2011