1.0 NAME OF THE MEDICINAL PRODUCT

1.1	**Brand Name**	**:**	LUMEGIL
1.2	**Generic Name**	**:**	**Clopidogrel tablets USP 75 mg**
1.2	**Strength**	**:**	75 mg
1.3	**Pharmaceutical Form**	**:**	Oral solid dosage form of Tablets

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film coated tablet contains:
Clopidogrel Bisulfate USP
Eq. to Clopidogrel ……75 mg
Colours: Iron oxide of red (Ferric oxide USNF) & Titanium Dioxide USP

3.0 PHARMACEUTICAL FORM

Light brown coloured, round biconvex, plain on both sides & film coated tablets.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopidogrel is indicated in adults for the prevention of atherothrombotic events in:

- Patients suffering from myocardial infarction, ischemic stroke.
- Patients suffering from acute coronary syndrome:
  - Non-ST segment elevation acute coronary syndrome, including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults and elderly

Clopidogrel should be given as a single daily dose of 75 mg.

In patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome, clopidogrel treatment should be initiated with a single 300 mg loading dose and then continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily).

- ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg loading dose in combination with ASA and with or without thrombolytics.

• *Paediatric population*

The safety and efficacy of clopidogrel in children and adolescents under 18 years old have not yet been established.

• *Renal impairment*

Therapeutic experience is limited in patients with renal impairment.

• *Hepatic impairment*

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses.

Method of administration

For oral use

It may be given with or without food.

4.3 CONTRAINDICATIONS

• Hypersensitivity to the active substance.

• Severe hepatic impairment.

• Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, 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 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. 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. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings.

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

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 haemophilia 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.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products 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. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.

Allergic cross-reactivity

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since allergic cross-reactivity among thienopyridines has been reported. Patients who have had previous hypersensitivity to other thienopyridines should be carefully monitored for signs of hypersensitivity to clopidogrel during treatment.

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.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

Acetylsalicylic acid (ASA): ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

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.

NSAIDs: in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution.

Proton Pump Inhibitors (PPI):
Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.
Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.
The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

4.6 PREGNANCY AND LACTATION

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.

Lactation

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.

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

Haematoma, Epistaxis, Gastrointestinal haemorrhage, Diarrhoea, Abdominal pain, Dyspepsia, Bruising, Bleeding at puncture site, Bleeding time prolonged, Neutrophil count decreased, Platelet count decreased, Haematuria, Rash, Pruritus, Purpura, Gastric ulcer, Duodenal ulcer, Gastritis, Vomiting, Nausea, Constipation, Flatulence, Intracranial bleeding, Headache, Paraesthesia, Dizziness.

4.9 OVERDOSE

Overdose following clopidogrel 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 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 PHARMACOKINETIC PROPERTIES

Elimination

Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces.

5.3 PRECLINICAL SAFETY DATA

None.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Maize Starch USP
Microcrystalline Cellulose USP
Sodium Starch Glycolate USP
Sodium Lauryl Sulphate USP
Povidone USP
Magnesium Stearate USP
Colloidal Silicon Dioxide USP
Talc USP
Croscarmellose USP
Polyethylene glycol USNF
Titanium dioxide USP
Colour Iron oxide of Red (Ferric oxide) USNF

6.2 INCOMPATIBILITIES

No effect noted to date.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C, Protected from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

10 tablets packed in Alu/Alu Blister and such 3 blister packs in a monocarton with pack insert.

6.6 SPECIAL PRECAUTION FOR DISPOSAL

Not Applicable

7. MARKETING AUTHORIZATION HOLDER:

Name	:	SUPERIOR PHARMACEUTICALS LTD.
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Phone	:	+234 816 621 7019
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NAME AND ADDRESS OF THE MANUFACTURE

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