1.3.1

Summary of Product Characteristics (SmPC)

1. Name of the medicinal Product

Clopidogrel Tablets USP 75 mg (CLOPIBEST TABLETS)

2. Qualitative and Quantitative Composition

2.1 Strength:

Each film coated tablet contains:

Clopidogrel bisulfate USP	
Equivalent to Clopidogrel	75 mg
Excipients	Q.S.

2.2 Quantitative declaration:

Each film-coated tablet contains 75 mg of Clopidogrel**.**

Excipients with known effect:

Each film-coated tablet contains hydrogenated castor oil.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Oral Tablet

Peach coloured, round shaped, deep convex, plain on both the sides of film coated tablets.

4. Clinical Particulars

4.1 Therapeutic Indications

Clopidogrel is indicated for the reduction of thrombotic events in patients with recent MI,recent stroke or established peripheral arterial disease and in acute coronary syndrome.

4.2 Posology and Method of Administration

Method of administration: orally.

Recent MI,recent stroke or established PAD:The recommended dose is 75mg once daily.

Acute coronary syndrome: Clopidogrel should be initiated with a single 300 mg loading dose and then continued with 75 mg once dail. Aspirin (75-325 mg)once daily should be initiated and continued in combination with Clopidogrel.

4.3 Contraindications

Hypersensitivity to the drug.

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

4.4 Special Warnings and Special Precautions for Use

Thrombotic thrombocytopenic purpura (TIP)

TIP has been reported rarely following usc of clopidogrcl, sometimes after a short exposure (<2wccks).

TIP is a serious condition requi ring prompt treatment. It is characterized by thrombocytopenia a, microangiopathic hemolytic anemia, neurological findings, renal dysfunction. and fever. TTP has been reported at a rate of about four cases per million patients exposed, or about I I cases per million patient-years. G/8/ending: Clopidogrel prolongs the bleeding time. Clopidogrel should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions (such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) should be used with caution in patients taking Clopidogrel.

General: 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. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, Clopidogrel should be discontinued 5 days prior to surgery.

Hepatic Impairment: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses Clopidogrel should be used with caution in this population. Renal Impairment: Experience is limited in patients with severe renal impaim1ent. Clopidogrel should be used with caution in this population.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin: Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel and aspirin have been used together up to one year.

Heparin: In a study in healthy volunteers, 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 inhibition of platelet aggregation induced by Clopidogrel. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of Clopidogrel was associated with increased occult gastrointestinal l blood loss. NSAIDs and Clopidogrel should be coadministcred with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin and Clopidogrel should be undertaken with caution Phenytoin. tamoxifen. tolbmamide. torsemide.jluvastatin and many NSA/Ds : At high concentrations in vitro, Clopidogrel inhibits P450 (2C9). Accordingly, Clopidogrel may interfere with the metabolism of phenytoin,tamoxifen, tolbutamide, torsemide and fluvastatin, 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. Clopidogrel is not recommended in combination with alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects.

4.6 Pregnancy and Lactation

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Clopidogrel should be used during pregnancy only if clearly needed.

Lactation: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

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

The drug is generally well tolerated. Side effects that have been reported include abdominal pain, dyspepsia, gastritis, diarrhoea, constipation, gastrointestinal haemorrhage, neutropenia, msh, palpitation, syncope,asthenia, neuralgia, paresthesia and vertigo.

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 Pharmacodynamics Properties

Pharmacotherapeutic group; platelet aggregation inhibitors excluding heparin, ATC CODE; B01AC-04.

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet agreegation. Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabgolites 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 (7-10days) 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.

5.2 Pharmacokinetic Properties

ABSORPTION

Clopidogrel is rapidly but incompletely absorbed following oral administration; absorption appears to be about 50% based on urinary excretion of clopidogrel metabolites.

DISTRIBUTION

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

BIOTRANSFORMATION

Clopidogrel is extensively metabolized in the liver following absorption, mainly to the inactive carboxylic acid derivative. The active metabolite appears to be a thiol derivative but has not been identified in plasma.

ELIMINATION

Clopidogrel carboxylic and its metabolites arc excreted about equally in urine and in faeces.

5.3 Preclinical Safety Data

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolizing enzymes. No effect on hepatic metabolizing enzymes was observed in humans receiving Clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of Clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when Clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, Clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled Clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcelac 100
Low substituted Hydroxypropyl Cellulose
Hydrogentaed castor oil
Instacoat Aqua-III

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 months (proposed)

6.4 Special Precautions for Storage

Do not store above 30°C. Protect from light and moisture

6.5 Nature and Contents of Container

10 tablets are packed in Alu/Alu blister pack, 3 blisters pack is packed in printed carton with packing insert.

6.6 Special precaution for disposal and other handling

No special requirements for disposal.

7. Registrant (Marketing Authorization Holder And Manufacturing Site Addresses)

7.1 Name and Address of Marketing Authorization Holder

Generics And Specialities Ltd.

31b Awoniyi Elemo Street, Off Lateef Salami Street,

Ajao Estate, Lagos

Nigeria.

E-mail: info@gslnigeria.com

7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceutical Ltd.

Trimul Estate, Khatraj, Tal. Kalol,

District: Gandhinagar Gujarat, India.

Telephone no.: +91-7941-078096

Fax: +91-7941-078062

Email: hiren@lincolnpharma.com

Website: www.lincolnpharma.com

7.3 Marketing Authorization Number

To be included after obtaining first registration.

7.4 Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

8. Date of Revision of the Text

9. Dosimetry (If Applicable)

Not Applicable

10. Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable