Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Nugrel (Clopidogrel Tablets USP 75 mg).

2. Qualitative and quantitative composition
Each film- coated tablet contains: Clopidogrel bisulfate USP equivalent to Clopidogrel 75 mg.

For full list of excipients see Section 6.1

3. Pharmaceutical form
Film-coated Tablet.

4. Clinical particulars
4.1 Therapeutic indications
Cardiovascular Risk Reduction Following Recent Myocardial Infarction or Stroke or *in Established Peripheral Arterial Disease.*

Clopidogrel bisulfate is used to reduce the risk of cardiovascular or cerebrovascular events (myocardial infarction [MI], stroke, and vascular death) in patients with atherosclerosis documented by recent ischemic stroke, recent MI, or established peripheral arterial disease (secondary prevention).

Acute Coronary Syndromes

-Unstable Angina or Non-ST-Segment-Elevation Myocardial Infarction

Clopidogrel in combination with aspirin is used for the reduction of cardiovascular and cerebrovascular events in patients with non-ST-segment elevation acute coronary syndromes(ACS), including unstable angina and non-ST-segment-elevation MI (NSTEMI). The drug is used in patients who are to be managed medically and in those who are to be managed with coronary intervention (percutaneous coronary intervention [PCI] with or without coronary artery stenting or coronary artery bypass grafting [CABG]).

-ST-Segment-Elevation Myocardial Infarction

Clopidogrel in combination with aspirin is used to reduce the rate of ischemic cardiovascular events (e.g., death, re infarction, stroke) in patients with ST-segment-elevation MI (STEMI). Current treatment of STEMI in many patients includes the use of thrombolytic therapy for lysis of coronary artery thrombi, and a P2Y12-receptor antagonist (e.g., clopidogrel, ticagrelor) and/or aspirin is used with anticoagulants (e.g., un fractionated heparin, warfarin, low molecular weight heparin) as adjunctive therapy during and after successful coronary artery reperfusion.

-Stent Thrombosis

Compared with bare-metal stents, implantation of drug-eluting stents has been associated with a reduction in the frequency of restenosis and repeat revascularization without evidence of excess MI or death in randomized controlled trials evaluated for US Food and Drug Administration (FDA) approval of these stents (clinically stable patients without other serious medical conditions who had newly diagnosed coronary lesions less than 28–30 mm in length).

Chronic Stable Angina

Clopidogrel may be used as an alternative to aspirin in patients with symptomatic chronic stable angina who cannot tolerate aspirin.

Embolism Associated with Atrial Fibrillation and/or Valvular Heart Disease

Clopidogrel has been used in combination with aspirin as an alternative to warfarin anticoagulation for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Dual antiplatelet therapy with clopidogrel and aspirin was evaluated as a potential alternative to warfarin in a randomized controlled study in patients with atrial fibrillation at high risk of stroke.

4.2 Posology and method of administration

Clopidogrel bisulfate is administered orally. Food does not affect systemic exposure to the active metabolite of clopidogrel, and the drug may be administered without regard to meals. Dosage of Clopidogrel bisulfate is expressed in terms of clopidogrel.

Cardiovascular Risk Reduction Following Recent Myocardial Infarction or Stroke or in established Peripheral Arterial Disease

In patients with established peripheral arterial disease or a history of recent myocardial infarction (MI) or stroke, the recommended dosage of clopidogrel for reducing the risk of fatal or nonfatal MI, stroke, or vascular death in adults is 75 mg once daily.

Acute Coronary Syndromes

-Unstable Angina or Non-ST-Segment-Elevation Myocardial Infarction

In patients with unstable angina or non-ST-segment-elevation MI (NSTEMI) (i.e., non-ST-segment-elevation acute coronary syndromes [NSTE ACS]), an initial loading dose of 300 mg of clopidogrel is recommended by the manufacturer, followed by 75 mg once daily given concomitantly with aspirin.

Although the optimal loading dose of clopidogrel in patients with NSTE ACS undergoing percutaneous coronary intervention (PCI) is uncertain, some experts suggest a loading dose of 600 mg, administered as early as possible prior to or at the time of the procedure in conjunction with aspirin; clopidogrel should then be continued at a maintenance dosage of 75 mg once daily for at least 12 months.

-ST-Segment-Elevation Myocardial Infarction

In patients with acute ST-segment-elevation MI (STEMI), the manufacturer recommends a clopidogrel dosage of 75 mg once daily in conjunction with

aspirin. The manufacturer states that clopidogrel may be initiated with or without a loading dose in patients with STEMI.

In patients with STEMI who will undergo PCI, a clopidogrel loading dose of 600 mg, administered as soon as possible before or at the time of PCI, is recommended. A higher loading dose of 900 mg does not appear to provide additional benefit in patients undergoing PCI.

Managing Antiplatelet Therapy in Patients Requiring Invasive Procedures

Antiplatelet agents generally should be discontinued prior to surgery or other invasive procedures to minimize the risk of peri operative bleeding. The manufacturer states that in patients requiring an invasive procedure in whom an antiplatelet effect is not desired, clopidogrel should be temporarily discontinued 5 days prior to the procedure and resumed as soon as possible.

In patients receiving dual antiplatelet therapy (e.g., aspirin and clopidogrel) who require coronary artery bypass grafting (CABG), interruption of clopidogrel therapy is recommended at least 5 days prior to surgery. However, aspirin generally should be continued around the time of surgery in such patients.

In patients receiving dual antiplatelet therapy (e.g., aspirin and clopidogrel) who require surgery within 6 weeks of bare-metal stent implantation or within 6 months of drug-eluting stent implantation, ACCP suggests continuation of dual antiplatelet therapy in the periprocedural period. If therapy with clopidogrel is interrupted prior to non elective major surgery to reduce the risk of excessive bleeding, the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) recommends that aspirin be continued if at all possible and clopidogrel be restarted as soon as possible after the procedure because of concerns about late stent thrombosis.

Special Populations

No dosage adjustments are necessary in geriatric patients or in those with hepatic impairment.

4.3 Contraindications

Known hypersensitivity to clopidogrel or any ingredient in the formulation. Presence of active pathological bleeding (e.g., peptic ulcer, intracranial hemorrhage).

4.4 Special warnings and precautions for use

Compliance with Therapy in Patients with Drug-eluting Stents

Premature discontinuance of dual-drug antiplatelet therapy with a thienopyridine derivative (i.e., clopidogrel, ticlopidine) and aspirin in patients with coronary artery stents, particularly discontinuance of clopidogrel therapy in patients with drug-eluting stents, has been associatedwith stent thrombosis, often leading to myocardial infarction (MI) and/or death. Before implantation of a drug-eluting stent, patients should be carefully assessed

regarding the likelihood of compliance with prolonged (e.g., at least 12 months) dual-drug antiplatelet therapy (i.e., aspirin and a thienopyridine derivative); strong consideration should be given to avoiding use of a drug-eluting stent in patients who are not expected to comply. In addition, patients should be educated before discharge about the reasons they have been prescribed the drugs and the substantial risks associated with premature discontinuance of dual-drug antiplatelet therapy. Superficial or "nuisance" bleeding is common in patients receiving dual-drug antiplatelet therapy after drug-eluting stent implantation and may be a reason for premature discontinuation of clopidogrel. In a single-center observational study in 2360 patients who underwent drug-eluting stent implantation, 11.1% of patients who were receiving dual-drug antiplatelet therapy discontinued clopidogrel prematurely as a result of superficial bleeding. The American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association (ACCF/ACG/AHA) states that concomitant use of proton-pump inhibitors may reduce GI symptoms (e.g., dyspepsia) associated with antiplatelet agents and thereby prevent patients from discontinuing their antiplatelet treatment. Patients should be advised to *never* stop taking dual-drug antiplatelet therapy without first consulting with their cardiologist, even if instructed to do so by another health-care professional (e.g., dentist). In patients who are likely to require invasive or surgical procedures within 12 months of drug-eluting stent implantation, implantation of a bare-metal stent or balloon angioplasty with provisional stent placement should be considered instead.

Reduced Efficacy Associated with Impaired CYP2C19 Function

Clopidogrel is a prodrug that requires activation by the cytochrome P-450 (CYP) enzyme system to produce its pharmacologically active metabolite. Production of the active metabolite and response to clopidogrel may be reduced by genetic polymorphism of CYP2C19, one of the key enzymes involved in the metabolic activation of clopidogrel, or concurrent use of drugs (e.g., omeprazole, esomeprazole) that inhibit CYP2C19. Use of alternative clopidogrel dosing strategies or other antiplatelet therapy options (e.g., prasugrel, ticagrelor) should be considered in patients who are identified as potential poor metabolizers of CYP2C19.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) has been reported rarely with clopidogrel, sometimes after short exposure (less than 2 weeks) to the drug.TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes on peripheral blood smear), neurologic findings, renal dysfunction, and fever. TTP is a potentially fatal condition that requires urgent referral to a hematologist for prompt treatment (e.g., plasmapheresis).

Risks of Discontinuance of Therapy

In general, treatment with a thienopyridine derivative should not be discontinued prematurely because of the increased risk of cardiovascular events. If clopidogrel must be temporarily discontinued (e.g., prior to surgery), therapy should be re initated as soon as possible. Patients should be advised

to *never* stop clopidogrel therapy without first consulting the prescribing clinician. Prior to scheduling an invasive procedure, patients should inform their clinicians (including dentists) that they are currently taking clopidogrel, and clinicians performing the invasive procedure should consult with the prescribing clinician before advising patients to discontinue therapy.

General Precautions

Bleeding

Clopidogrel increases the risk of bleeding. The drug should be discontinued 5–10 days prior to surgery or coronary artery bypass grafting (CABG), if antiplatelet effect is undesirable. If bleeding occurs, hemostasis may be restored with exogenous administration of platelets; however, platelet transfusions within 4 hours of a loading dose of clopidogrel or within 2 hours of a maintenance dose may have reduced effectiveness. With holding a dose is unlikely to resolve a bleeding episode or prevent bleeding associated with an invasive procedure because of clopidogrel's prolonged effects on platelet inhibition.

In patients with transient ischemic attacks (TIAs) or stroke that are at high risk for recurrent ischemic events, the combination of clopidogrel and aspirin has *not* been shown to be more effective than clopidogrel alone but has been associated with an increase in major bleeding.

Hepatic Impairment

Inhibition of ADP-induced platelet aggregation in patients with severe hepatic impairment appears to be similar to that observed in healthy individuals.

Renal Impairment

Experience is limited in patients with moderate (creatinine clearance of 30–60 mL/minute) or severe (creatinine clearance of 5–15 mL/minute) renal impairment. Inhibition of ADP-induced platelet aggregation may be decreased by 25% in such patients.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes

Potential pharmacokinetic interaction (clopidogrel-induced inhibition of the cytochrome P-450 [CYP] 2C9 isoenzyme [CYP2C9] at high drug concentrations in vitro). Drugs that inhibit CYP2C19 decrease plasma concentrations of the active metabolite of clopidogrel and reduce its antiplatelet effects. Concomitant use of drugs that are known to be potent inhibitors of CYP2C19 activity (e.g., omeprazole, esomeprazole) should be avoided in patients receiving clopidogrel.

Cilostazol

Potential additive inhibition of platelet aggregation. Caution is advised; bleeding times should be monitored during concurrent administration.

Pharmacokinetic interaction unlikely.

Nonsteroidal Anti-inflammatory Agents

Potential pharmacodynamic interaction (increased risk of bleeding).

Warfarin

Potential pharmacodynamic interaction (increased risk of bleeding).Caution is advised.

Proton-Pump Inhibitors

Potential pharmacokinetic interaction (decreased plasma concentrations of the active metabolite of clopidogrel) and pharmacodynamic interaction (reduced antiplatelet effects) with certain proton-pump inhibitors. Because the antiplatelet activity of clopidogrel (a prodrug) is dependent on biotransformation, principally by CYP2C19, of the prodrug to an active metabolite, concurrent use of drugs such as omeprazole or esomeprazole that inhibit CYP2C19 reduces plasma concentrations of the active metabolite and potentially could reduce clinical efficacy.

4.6 Pregnancy and Lactation

Pregnancy

Either animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than on fertility) but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester and there is no evidence of risk in later trimesters. In either case, the drug should be used during pregnancy only when clearly needed.

Lactation

Clopidogrel is distributed into milk in rats; not known whether the drug is distributed into milk in humans. Discontinue nursing or the drug because of potential for severe adverse effects in infants.

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

Adverse effects occurring in at least 2.5% of patients with recent MI, stroke, or established peripheral arterial occlusive disease receiving clopidogrel in the CAPRIE study included chest pain, accidental injury, influenza-like symptoms, pain, fatigue, edema, hypertension, headache, dizziness, abdominal pain, dyspepsia, diarrhea, nausea, hypercholesterolemia, arthralgia, back pain, purpura (bruising), epistaxis, depression, upper respiratory tract infection, dyspnea, rhinitis, bronchitis, coughing, rash,

pruritus, and urinary tract infection. In this study, rash and diarrhea were reported more frequently with clopidogrel therapy while patients receiving aspirin experienced indigestion/nausea/vomiting, GI hemorrhage, or abnormal liver function more

frequently. Rash classified as severe was more common with clopidogrel therapy, while GI hemorrhage classified as severe was more common in patients receiving aspirin.

Adverse effects occurring in at least 2% of patients with non-ST-segment-elevation acute coronary syndromes (NSTE ACS) receiving clopidogrel and aspirin in the CURE study included chest pain, headache, dizziness, abdominal pain, dyspepsia, or diarrhea.[1] In this study, the incidence of major bleeding (principally GI hemorrhage and bleeding at puncture sites), including life-threatening bleeding, was substantially greater in patients receiving clopidogrel and aspirin than in those receiving placebo and aspirin (3.7 and 2.7%, respectively); the incidence of life-threatening bleeding (2.2 and 1.8%, respectively) was similar.

Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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 an ADP-receptor antagonist; the active metabolite of clopidogrel binds selectively and noncompetitively to a low-affinity, P2Y12 ADP-receptor binding site on the surface of platelets, thereby inhibiting ADP binding to the receptor and subsequent activation of the platelet glycoprotein (GP IIb/IIIa) complex necessary for fibrinogen-platelet binding. Clopidogrel also inhibits ADP-mediated release of platelet dense granule (e.g., ADP, calcium, and serotonin) and alpha granule (e.g., fibrinogen and thrombospondin) contents that augment platelet aggregation. The low-affinity ADP receptor is irreversibly modified by the drug, so platelets exposed to clopidogrel remain affected for the remainder of their lifespan (about 7–10 days).Unlike aspirin, thienopyridine platelet-aggregation inhibitors such as clopidogrel and

ticlopidine do not inactivate platelet cyclooxygenase to prevent synthesis of prostaglandin endoperoxides and thromboxane A.

5.2 Pharmacokinetic properties

Absorption:

Clopidogrel is rapidly absorbed after oral administration; at least 50% of an oral dose is absorbed. Peak plasma concentrations of the active metabolite occur approximately 30–60 minutes following an oral dose. When clopidogrel 75 mg is administered daily, inhibition of platelet aggregation is apparent on the first day of therapy, with 40–60% inhibition being achieved at steady state between days 3–7.Following discontinuance of the drug, platelet aggregation and bleeding time generally return to baseline values within about 5 days.

Distribution & Plasma Protein Binding:

Clopidogrel and the main circulating (inactive) 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.

Metabolism:

Biotransformation occurs through a 2-step process where clopidogrel is initially oxidized to a 2-oxo-clopidogrel intermediate metabolite, then subsequently metabolized to the active thiol metabolite.[1] This metabolic pathway has been shown to be mediated by several cytochrome P-450 isoenzymes (e.g., CYP2C19, CYP3A, CYP2B6, CYP1A2) In particular, the CYP2C19 isoenzyme is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate.

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 in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half- life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.

Renal impairment

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP- induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP- induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

Race

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events

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 metabolising enzymes. No effect on hepatic metabolising 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

Lactose anhydrous (DCL 21)
Microcrystalline cellulose (AVICEL PH 112)
Pregelatinized starch (Starch 1500)
Hydrogenated castor oil (Boricin Pharma)
Polyethylene glycol (PEG 6000)
Colloidal silicon dioxide (AEROSIL - 200)
Talc

Lactose anhydrous (DCL 21)
Crospovidone Type – A (POLYPLASDONE - XL)
Hypromellose (HPMC 15 CPS)
Titanium dioxide
Propylene glycol
Isopropyl alcohol
Methylene chloride
Ferric oxide (Red)

6.2 Incompatibilities
Not applicable

6.3 Shelf-Life
36 months from the date of manufacturing.

6.4 Special Precautions for storage
Store below 30 °C. Protect from light. Keep out from the reach of children.

6.5 Nature and Content of container
Alu - Alu Blister pack of 10 tablets, 3 such blisters in a laminated outer carton along with pack Insert.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing Authorization Holder
Micro Labs Limited
#31,Race course Road,Bangalore-560001
India
Manufactured by:
Micro Labs Limited
92,Sipcot Industrial Complex Hosur,Tamil Nadu-635126,India

8. Marketing Authorization Number
H2009/20325/190

9. Date of first authorization/renewal of the authorization
12/08/2026

10. Date of revision of the text
12/08/2026