

1. NAME OF THE MEDICINAL PRODUCT

Nugrel

1.1 Invented Name of the Medicinal Product

Clopidogrel Tablets USP 75 mg

1.2 Strength

75 mg

1.3 Pharmaceutical Form

Tablets. Light Pink coloured, circular, biconvex film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Clopidogrel Bisulfate USP

equivalent to Clopidogrel 75 mg

3. PHARMACEUTICAL FORM

Film coated Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clopidogrel is indicated in adults for the *Prevention of atherothrombotic events* in:

- patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.
- patients suffering from acute coronary syndrome:
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), 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.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, Clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

4.2 Posology and method of administration

Posology

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 (unstable angina or non-Q-wave myocardial infarction): 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). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.
 - 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 thrombolytic. For patients over 75 years of age Clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of Clopidogrel with ASA beyond four weeks has not been studied in this setting.
- In patients with atrial fibrillation, Clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with Clopidogrel.

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
- For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

Paediatric population

Clopidogrel should not be used in children because of efficacy concerns.

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 or to any of the excipients
- Severe liver 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).

Patients should be told that it might take longer than usual to stop bleeding when they take Clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

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 neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

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)

Pharmacokinetics: 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 thienopyridine has been reported. Patients who have had previous hypersensitivity to other thienopyridine 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.

Excipients

Clopidogrel Tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

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 haemostasis.

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. However, Clopidogrel and ASA have been administered together for up to one year.

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.

Thrombolytic: 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.

Other concomitant therapy: 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.

Medicinal products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

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 of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with Clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/Pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged.

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.

There is no evidence that other medicinal products that reduce stomach acid such as H₂ blockers (except cimetidine which is a CYP2C19 inhibitor) or antacids interfere with antiplatelet activity of Clopidogrel.

Other medicinal products: A number of other clinical studies have been conducted with Clopidogrel and other concomitant medicinal products to investigate the potential for Pharmacodynamic and pharmacokinetic interactions. No clinically significant Pharmacodynamic interactions were observed when Clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the Pharmacodynamic activity of Clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

The pharmacokinetics of digoxin or theophylline was not modified by the co-administration of Clopidogrel. Antacids did not modify the extent of Clopidogrel absorption.

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with Clopidogrel.

Apart from the specific medicinal product interaction information described above, interaction studies with Clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with Clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, Antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

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 film-coated tablet.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

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 reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below. Their frequency is defined using the following conventions: common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Blood and the lymphatic system disorders		Thrombocytopenia, leukopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions, cross reactive drug hypersensitivity among

				thienopyridine (such as ticlopidine, prasugrel)
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation,	Retroperitoneal haemorrhage	Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including

	pain, dyspepsia	flatulence		ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorders				Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, Skin bleeding (purpura)		Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiform), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS),rash erythematous, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders				Musculo-skeletal bleeding (haemarthroses), arthritis, arthralgia, myalgia
Renal and urinary disorders		Haematuria		Glomerulonephritis, blood creatinine increased
General disorders and administration site conditions	Bleeding at puncture site			Fever
Investigations		Bleeding time prolonged, neutrophil count		

		decreased, platelet count decreased		
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4.9 Overdose

(i) Symptoms

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

(ii) Treatments

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 (approximately 7-10 days) 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.

Pharmacodynamic effects

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 5 days after treatment was discontinued.

5.2 Pharmacokinetic properties

Absorption

After single and repeated oral doses of 75 mg per day, Clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged Clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of Clopidogrel metabolites.

Distribution

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.

Biotransformation

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, Clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of Clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. The C_{max} of the active metabolite is twice as high following a single 300-mg Clopidogrel loading dose as it is after four days of 75-mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing.

Elimination

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. 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 pharmacokinetics). 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

Sl. No	Ingredients	Specification
1	Mannitol (Pearlitol SD-200)	USP
2	Microcrystalline Cellulose – Avicel PH102	USP
3	Crospovidone Type-B (Polyplasdone)	USP
4	Butylated Hydroxytoluene	BP
6	Hydrogenated Castor oil (Boricin Pharma)	USP
6	Hypromellose (HPMC 15 CPS)	USP
7	Titanium Dioxide	USP
8	Propylene Glycol	USP
9	Isopropyl alcohol	USP
10	Methylene chloride	USP
11	Ferric oxide (Red)	USP

6.2 Incompatibility

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

Alu/Alu Blister pack of 10's Tablets. Such 3 blisters are packed in a carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements

7. REGISTRANT

Micro Labs Limited

27, Race Course Road,

Bangalore-560 001,

INDIA

8. MANUFACTURER

Name and Address of the Manufacturer

Micro Labs Limited

92, Sipcot,

Hosur-635 126.

India.

9 DATE OF REVISION OF THR TEXT

Applicable once the registration is obtained.

10. DOSIMETRY

Not applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable