[Instructions in this font/colour are from the World Health Organization Public Assessment Report WHOPAR guidelines.]

1. NAME OF THE MEDICINAL PRODUCT

Clopidogrel and Aspirin Capsules

Plagerine-A

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clopidogrel bisulfate USP equivalent to clopidogrel……. 75 mg

Aspirin BP ……..75 mg

(as enteric coated tablet)

3. PHARMACEUTICAL FORM

Capsules

4. Clinical particulars

4.1 Therapeutic indications

Clopidogrel and Aspirin is a fixed-dose combination product intended as continuation of therapy in patients with acute coronary syndrome already initiated with separate clopidogrel and aspirin products:

Unstable angina or non-ST elevation myocardial infarction in order to prevent early and long-term atherothrombotic events (myocardial infarction, stroke, vascular death and refractory ischaemia). Clopidogrel and Aspirin is indicated for the treatment of acute coronary syndrome whether or not patients undergo cardiac revascularization (surgical or PCI, with or without stent).

ST-segment elevation acute myocardial infarction in order to prevent atherothrombotic events. In this population, Clopidogrel and Aspirin has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke in medically treated patients eligible for thrombolytic therapy.

4.2 Posology and method of administration

Adults

Clopidogrel and Aspirin is given as single capsules (75mg/75mg or 75mg/100mg) once a day taken with adequate water.

Acute Coronary Syndrome

It is used following an initial loading dose of 300 mg clopidogrel in combination with aspirin in patients with acute coronary syndrome:

- Unstable angina or non-ST-elevation myocardial infarction:

- Treatment should be initiated with a single 300 mg loading dose of clopidogrel plus aspirin (75 mg to 325 mg).

- Long-term daily treatment should be continued with one Clopidogrel and Aspirin capsules (75mg/75mg or 75mg/100mg) once a day taken with adequate water.

- ST-segment elevation acute myocardial infarction:

- Treatment should be initiated with or without a 300 mg loading dose of clopidogrel in combination with aspirin and with or without thrombolytic as soon as possible after symptoms start.

- Daily treatment should continue with one Clopidogrel and Aspirin Capsules (75mg/75mg or 75mg/100mg) once a day with adequate water. The benefit of the combination of clopidogrel with aspirin beyond four weeks has not been studied in this setting.

In patients who have had percutaneous coronary intervention with stent insertion, clopidogrel and aspirin should be continued for as long as is currently recommended in evidence based guidelines for the type of stent and circumstances of implantation or for as long as otherwise indicated, taking into account the overall atherothrombotic risk profile of the patient. Should doses of aspirin greater than 100 mg is required for daily maintenance therapy, clopidogrel and aspirin products should be administered separately

Renal Impairment

Experience is limited in patients with mild to moderate renal impairment Clopidogrel and Aspirin should not be used in patients with severe renal impairment

Hepatic Impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel and Aspirin should not be used in patients with severe hepatic impairment

No dosage adjustment is necessary for elderly patients

Children and Adolescents

Safety and efficacy in subjects below the age of 18 have not been established.

There is a possible association between aspirin and Reye's syndrome when aspirin is given to children. Reye's syndrome is a very rare disease which can be fatal.

4.3 Contraindications

Due to the presence of both components of the product, It is contraindicated in case of:

- Hypersensitivity to clopidogrel, salicylates or any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as Haemophilia, intracranial haemorrhage or gastrointestinal bleeding.
- Peptic ulcer or erosive gastritis
- Breast-feeding.

In addition, due to the presence of aspirin, its use is also contraindicated in case of:

Known allergy to Non-Steroidal Anti-inflammatory Drugs (NSAIDs) products and in patients with the syndrome of asthma with rhinitis and/or nasal polyps

- Severe renal impairment.
- Third trimester of pregnancy

4.4 Special warnings and precautions for use

General

Clopidogrel and aspirin prolong bleeding time, and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions, as follows:

- If a patient is to undergo elective surgery and an anti-platelet effect is not desired,

Clopidogrel and Aspirin should be discontinued 7 days prior to surgery.

- If the patient is at high risk of ophthalmic bleeding due to intraocular lesions clopidogrel should be used with extra caution.
- Clopidogrel and Aspirin prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). Drugs that might induce such lesions (such as NSAIDs) are not recommended in patients taking Clopidogrel and Aspirin.
- Clopidogrel and Aspirin should be used with caution in patients with a history of peptic ulcer or gastro duodenal haemorrhage or minor upper gastrointestinal symptoms, as this may be due to gastric ulceration which may lead to gastric bleeding.
- Gastrointestinal side effects, including stomach pain, heartburn, nausea, vomiting and gastrointestinal bleeding, may occur. Minor gastrointestinal symptoms, such as dyspepsia, are common and can occur anytime during therapy. Physicians should remain alert for signs of GI ulceration and bleeding, even in the absence of previous gastrointestinal symptoms.
- Patients should be told about the signs and symptoms of gastrointestinal side effects and what steps to take if they occur. Patients should be told that it may take longer than usual for bleeding to stop when they take Clopidogrel and Aspirin , and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking Clopidogrel and Aspirin before any surgery is scheduled and before any new drug is taken.
- In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of aspirin and clopidogrel has been shown to increase major bleeding. Therefore, use of the combination of clopidogrel and aspirin should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.
- To prevent gastric irritation due to aspirin, Clopidogrel and Aspirin should be taken with or after food. Due to the presence of aspirin, caution is required in patients

with a history of asthma or allergic disorders (as they are at increased risk of hypersensitivity reactions) or with gout (as low doses of aspirin increase urate concentrations).

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- The hypoglycemic effect of chlorpropamide may be enhanced by the concurrent administration of aspirin. Large doses of aspirin may have intrinsic hypoglycemic activity when given to diabetic patients, but the effects on carbohydrate metabolism are complex and it may cause hyperglycemia
- Tinnitus is a premonitory sign of salicylic but may not be detected in patients with hearing loss
- This medicinal product also contains hydrogenated castor oil which may cause stomach upset and diarrhoea.
- Clopidogrel and Aspirin is to be used under medical supervision only.

Coronary Artery Bypass Surgery

- When coronary artery bypass surgery is to be performed, clopidogrel and aspirin should be suspended at least 7 days before surgery to reduce the risk of bleeding.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are CYP2C19 poor metabolizers clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function (see Pharmacokinetics, Pharmacogenetics). Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider the alternative treatment strategies in patients identified as CYP2C19 poor metabolisers.

Ischaemic Stroke

In view of the lack of data, clopidogrel cannot be recommended in acute ischaemic stroke (less than 7 days).

Haematological

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterized 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 (plasma exchange).

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have also been reported very rarely in patients taking clopidogrel.

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. With chronic administration, occult blood loss may lead to iron deficiency anaemia. As a dual anti-platelet agent, it 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 other NSAIDs including Cox-2 inhibitors, heparin, glycoprotein IIb/IIIa inhibitors or thrombolytics. 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.

4.4Interaction with other medicinal products and other forms of interaction.

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4.5Interaction with other medicinal products and other forms of interaction

Interactions with other medicines

Oral Anticoagulants (including warfarin)

The concomitant administration of Clopidogrel and Aspirin with warfarin is not recommended since it may increase the intensity of bleeding.

Injectable Anticoagulants

A Pharmacodynamic interaction between Clopidogrel and Aspirin and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Glycoprotein IIb/IIIa inhibitors

It should be used with caution in patients who may be at risk of increased bleedingfrom trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIa/IIb inhibitors.

Anti-platelet agents (such as eptifibatide, ticlopidine, tirofiban)

The effects of Clopidogrel and Aspirin and other drugs which inhibit platelet aggregation may be additive, leading to an increased risk of bleeding.

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 aspirin. The safety of concomitant administration of Clopidogrel and Aspirin with other thrombolytic agents has not been formally established and should be undertaken with caution.

Methotrexate

Due to the presence of aspirin, methotrexate and Clopidogrel and Aspirin should only be used together with caution, as aspirin can inhibit renal clearance of methotrexate, which may lead to bone marrow toxicity.

Non Steroidal Anti-inflammatory Drugs (NSAIDs)

Aspirin may increase the risk of gastrointestinal side effects, including bleeding, when administered with NSAIDs. Aspirin displaces diclofenac from its binding sites, reducing diclofenac effectiveness.

The concomitant administration of ibuprofen with aspirin may limit the beneficial cardiovascular effects of aspirin in patients with increased cardiovascular risk.

Uricosuric agents (e.g. Probenecid)

Caution is required because aspirin may inhibit the effect of uricosuric agents through competitive elimination of uric acid.

Drugs metabolised by Cytochrome P450 2C9

At high concentrations in vitro, the carboxylic acid metabolite of clopidogrel inhibits cytochrome P450 (2C9). Accordingly, Clopidogrel and Aspirin may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, fluvastatin, and many non-steroidal anti-inflammatory agents, 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 and Aspirin .

Other concomitant therapy

A number of other clinical studies have been conducted with clopidogrel and other concomitant medications 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, cimetidine, or oestrogen. The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics:
Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including aspirin or COX-2 inhibitors) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with preexisting renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy and periodically thereafter.

Interactions with higher dose aspirin
Interactions with the following medicines with higher (anti-inflammatory) doses of aspirin have been reported: alendronate, angiotensin converting enzyme (ACE) inhibitors, anticonvulsants (phenytoin and valproic acid), beta blockers, systemic corticosteroids, diuretics, selective serotonin reuptake inhibitors (SSRIs), spironolactone, verapamil, hypoglycemic agents and zafirlukast. However, more than 30 000 patients entered into clinical trials with clopidogrel plus aspirin at maintenance doses lower than or equal to 325mg, received a variety of concomitant medications, including diuretics, beta blockers, ACE inhibitors, calcium channel antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), anti-epileptic agents, hormone replacement therapy and

GPIIb/IIIa antagonists, without evidence of clinically significant adverse interactions.

4.6 Pregnancy and Lactation

Pregnancy:

No clinical data on exposure to clopidogrel plus aspirin during pregnancy are available. Clopidogrel plus aspirin should not be used during the first two trimesters of pregnancy unless the clinical condition of the woman requires treatment with clopidogrel in combination with aspirin. Due to the present of aspirin clopidogrel plus aspirin is contraindicated during the third trimester of pregnancy.

Clopidogrel and/or its metabolites are known to cross the placenta in pregnant rats and rabbits. However, teratology studies in rats and rabbits at doses up to 500 mg and 300 mg/kg/day PO, respectively, revealed no evidence of embryotoxicity or teratogenicity.

Reproduction toxicity data show that aspirin is teratogenic in several laboratory animals.

Aspirin inhibits prostaglandin synthesis. When given late in pregnancy, it may cause premature closure of the foetal ductus arteriosus, prolong labour and delay birth. Aspirin increases bleeding time both in the newborn infant and in the mother because of its anti-platelet effects.

Clopidogrel and Aspirin should not be used in women during pregnancy unless the potential benefits outweigh the risks.

Lactation:

Breast-feeding is contraindicated during treatment with Clopidogrel and Aspirin . Studies in rats have shown that clopidogrel and/or its metabolites are excreted in breast milk. Salicylates are excreted in breast milk. Chronic high doses of aspirin can cause adverse effects in the infant.

4.7 Effects on ability to drive and use machines

Clopidogrel and Aspirin has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Clopidogrel

The following have been reported spontaneously from worldwide post-marketing experience with clopidogrel:

-Musculoskeletal, connective and bone: Arthralgia, arthritis, myalgia.

-Immune system disorders: anaphylactoid reactions, serum sickness

-Vascular disorders vasculitis, hypotension

-Blood and lymphatic system disorders: serious cases of bleeding, mainly skin, Musculo-skeletal (haemarthrosis, haematoma), eye (conjunctival, ocular, retinal) and respiratory tract bleeding (hemoptysis, pulmonary haemorrhage), epistaxis, hematuria and haemorrhage of operative wound. Fatal haemorrhage, including intracranial, gastrointestinal and retroperitoneal haemorrhage**.**

-Skin and subcutaneous tissue disorders: macropapular or erythematous rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) eczema, lichen planus.

-Psychiatric: confusion, hallucinations

-Nervous system disorders: taste disturbances

-Hepatobiliary disorders: hepatitis, acute liver failure

-Gastrointestinal disorders: colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis.

-Respiratory, thoracic and mediastinal disorders: bronchospasm, interstitial pneumonitis.

-Renal and Urinary disorders: glomerulopathy

-General disorders and administration site conditions: fever, syncope.

Aspirin

In addition to some of the adverse reactions listed above, aspirin is associated with the following adverse effects.

Aspirin produces a prolongation of the bleeding time and may produce epigastric distress, nausea and vomiting, gastric or duodenal ulcers and erosive gastritis which may lead to serious gastrointestinal bleeding. These side effects are more likely to occur when higher doses are administered, although they may also occur

when low doses are used.

Iron deficiency anaemia may develop as a result of occult gastrointestinal bleeding when aspirin is used for long periods of time. Aspirin may cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

Aspirin may cause tinnitus or hearing loss.

4.9 Overdose

There is no information concerning over dosage with Clopidogrel and Aspirin .

In animals, clopidogrel at single oral doses ³ 1500 mg/kg caused necrotic-haemorrhage gastritis, esophagitis and enteritis in mice, rats and baboons. Necrotic tubulopathy and tubulo-interstitial nephritis were also noted in mice.

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleeding is 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.

Aspirin over dosage is manifested by the following symptoms:

Moderate over dosage: tinnitus, hearing loss, dizziness, headaches, vertigo, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).

Severe over dosage: fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory failure, severe hypoglycaemia, haemorrhage

In case of severe aspirin overdose, the following actions should be undertaken: admission to hospital is necessary, control of acid-base balance, possibility of hemodialysis or peritoneal dialysis if necessary.

Apart from general measures, treatment of aspirin over dosage consists chiefly of measures to accelerate the excretion (forced alkaline diuresis) and to restore the acid-base and electrolyte balance. Infusions of sodium bicarbonate and potassium chloride solutions may be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Clopidogrel

Clopidogrel is a specific and potent inhibitor of platelet aggregation. Platelets have an established role in the pathophysiology of atherosclerotic disease and thrombotic events. Long term use of anti-platelet drugs has shown consistent benefit in the prevention of ischaemic stroke, myocardial infarction and vascular death in patients at increased risk of such outcomes, including those with established atherosclerosis or a history of atherothrombosis. 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. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis. The active thiol metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet ADP receptors, P2Y12, thus inhibiting platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP. 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 (approximately 7 days).

-Statistically significant and dose-dependent inhibition of platelet aggregation was noted 2 hours after single oral doses of clopidogrel.

-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.

Aspirin

Aspirin inhibits platelet aggregation by irreversible inhibition of prostaglandin cyclo-oxygenase and thus inhibits the generation of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet.

5.2 Pharmacokinetic properties

Absorption

Clopidogrel

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

Aspirin

Following absorption, the aspirin in Nugrel – A is hydrolysed to salicylic acid, with peak plasma levels of salicylic acid occurring within 1-1.5 hours of dosing, such that plasma levels of aspirin are essentially undetectable 1.5-4 hours after dosing.

Distribution and Plasma Protein Binding

Clopidogrel

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.

Aspirin

Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). Its metabolite, salicylic acid, is highly bound to plasma proteins, but its binding is concentration dependent (nonlinear). At low concentrations (<100 µg/mL), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and foetal tissues.

Metabolism

Clopidogrel

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 the formation of the active metabolite, a thiol derivative of clopidogrel. In vitro, the metabolic pathway is mediated by CYP3A4, CYP2C19, CYP 1A2 and CYP2B6. The active thiol metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The Cmax 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. Cmax occurs approximately 30 to 60 minutes after dosing.

Aspirin

The aspirin in Nugrel – A is rapidly hydrolysed in plasma to salicylic acid, with a half-life of 0.3 to 0.4 hours for aspirin doses from 75 to 325 mg. This salicylic acid has a plasma half-life of approximately 2 hours. Salicylic acid is primarily conjugated in the liver to form salicylic acid, a phenolic glucuronide, an acyl glucuronide and a number of minor metabolites. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations, due to the limited ability of the liver to form both salicylic acid and phenolic glucuronide. Following toxic aspirin doses (10−20 g), the plasma half-life may be increased to over 20 hours.

Elimination

Clopidogrel

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 75mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

Aspirin

At high aspirin doses, the elimination of salicylic acid follows zero-order kinetics (i.e. the rate of elimination is constant in relation to plasma concentration), with an apparent half-life of 6 hours or higher. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from <5% to >80%. Following therapeutic doses, approximately 10% is found excreted in the urine as salicylic acid, 75% as salicylic acid, 10% phenolic- and 5% acyl-glucuronides of salicylic acid. Based on the pharmacokinetic and metabolic characteristics of both compounds, clinically significant pharmacokinetic interactions are unlikely.

Special Population

Geriatric Patients:

Plasma concentrations of the main circulating metabolite of clopidogrel are significantly higher in the elderly (≥ 75years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients:

After repeated doses of 75 mg clopidogrel per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar in healthy volunteers receiving 75 mg of clopidogrel per day. Experience with clopidogrel plus aspirin is limited in patients with mild to moderate renal impairment.

Therefore Clopidogrel and Aspirin should be used with caution in this population. Clopidogrel and Aspirin is contraindicated in severe renal impairment.

Patients with Hepatic Impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. It should therefore be used with caution in this population. It is contraindicated in severe liver impairment.

Gender:

No significant difference was observed in the plasma levels of the main circulating metabolite of clopidogrel between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race:

Clopidogrel pharmacokinetic differences due to race have not been studied.

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

Sugar Spheres

Sugar powder

Poly Vinyl Pyridone K-30 (PVPK-30)

Iron Oxide Yellow

Iron Oxide Red

Hydroxy PropylMethyl Cellulose (HPMC-E_5)

Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months from the date of Manufacturing.

6.4 Special precautions for storage

Store below 30°C. Keep medicine away from the reach of children

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Strip pack of 3x10's ,such 3 strips are packed in a carton along with a pack insert.

6.6 Special Precautions for disposal < and other handling>

Not Applicable.

7. APPLICANT/MANUFACTURER

Micro Labs Limited

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