Fixed Dose Combination (FDC) of Rosuvastatin 10 mg, Aspirin 75 mg & Clopidogrel 75 mg Capsule
Rosukem GOLD

1. NAME OF THE MEDICINAL PRODUCT

Rosukem GOLD

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:

Rosuvastatin Calcium IP

Equivalent to Rosuvastatin	10 mg
(As pellets)	
Aspirin IP	75 mg
(As enteric coated pellets)	
Clopidogrel Bisulphate IP	
Equivalent to Clopidogrel	75 mg
(As pellets)	
Excipients	q.s.

3. PHARMACEUTICAL FORM

Capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secondary Prevention of Cardiovascular and cerebrovascular Events

Secondary prevention of major cardiovascular and cerebrovascular events in patients who are estimated to have a high risk for Acute coronary syndrome, myocardial infarction, angina and stroke (see Section 5.1), as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Route of administration is oral and the capsules must not be chewed or crushed. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines. This FDC is administered once daily dose but the dosage should not be increased than maximum allowed dose for individual agents. The maximum dose Rosuvastatin is 40mg once daily and Clopidogrel dose should be initiated with a 75 mg once a day. Rosuvastatin may be given at any time of day, with or without food. Clopidogrel may be given with or without food.

Paediatric population

The safety and efficacy of rosuvastatin use in children younger than 6 years has not been studied. Therefore, Rosuvastatin is not recommended for use in children younger than 6 years. Clopidogrel should not be used in children because of efficacy concerns (see section 5.1).

Dosage in patients with renal insufficiency

No dose adjustment for rosuvastatin is necessary in patients with mild to moderate renal impairment. The use of rosuvastatin in patients with severe renal impairment is contraindicated for all doses. Therapeutic experience with Clopidogrel is limited in patients with renal impairment

Dosage in patients with hepatic impairment

Rosuvastatin is contraindicated in patients with active liver disease. Therapeutic experience with Clopidogrel is limited in patients with moderate hepatic disease who may have bleeding diatheses.

4.3 Contraindications

- Hypersensitivity to rosuvastatin, aspirin, other salicylates or any other NSAIDs, clopidogrel or any of the excipients of this medicinal product.
- A history of, or active peptic ulceration, haemophilia or other clotting disorders, gout, asthma, urticarial, rhinitis or other evidence of hyper sensitivity to aspirin or non-steroidal anti-inflammatory drugs.
- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- In patients with severe renal impairment (creatinine clearance < 30 ml/min).
- In patients with myopathy
- In patients receiving concomitant cyclosporine
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- In children under 12 years

4.4 Special warnings and precautions for use

Rosuvastatin

Skeletal Muscle Effects: Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. These risks can occur at any dose level, but are increased at the highest dose (40 mg). Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g., age ≥ 65 years, inadequately treated hypothyroidism, renal impairment).

Rosuvastatin therapy should be discontinued if markedly elevated creatine kinase levels occur or myopathy is diagnosed or suspected. Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure

secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use.

Liver Enzyme Abnormalities: It is recommended that liver enzyme tests be performed before the initiation of rosuvastatin, and if signs or symptoms of liver injury occur. Increases in serum transaminases [AST (SGOT) or ALT (SGPT)] have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease.

Concomitant Coumarin Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with rosuvastatin because of its potentiation of the effect of coumarin-type anticoagulants in prolonging the prothrombin time/INR. In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs

Proteinuria and Hematuria: In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were reported among rosuvastatin treated patients. These findings were more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator HMG-CoA reductase inhibitors, though it was generally transient and was not associated with worsening renal function.

Endocrine Effects: Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Clopidogrel

Bleeding and haematological disorders: Due to the risk of bleeding and haematological adverse events, 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, or selective serotonin reuptake inhibitors (SSRIs), or other medicinal products associated with bleeding risk such as pentoxifyllin. 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.

Thrombotic Thrombocytopenic Purpura (TTP): TTP has been reported very rarely following the use of clopidogrel, sometimes after a short exposure.

Acquired haemophilia: Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered.

Recent ischaemic stroke: In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

Cytochrome P450 2C19 (CYP2C19): Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function.

CYP2C8 substrates: Caution is required in patients treated concomitantly with Clopidogrel and CYP2C8 substrate medicinal products.

Cross reactions among thienopyridines: Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported

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.

Aspirin

There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children aged less than 12 years unless specifically indicated (e.g. Kawasaki's disease). Aspirin and other NSAIDs may cause salt and water retention and renal failure especially in patients with pre-existing renal impairment. Caution should be exercised in patients with asthma and other allergic conditions, bleeding tendencies, significant anaemia, hypoprothrombinemia, impairment of hepatic or renal function and dehydration.

4.5 Interaction with other medicinal products and other forms of interaction

Rosuvastatin

Cyclosporine: Cyclosporine increased rosuvastatin exposure (AUC) 7 fold. Therefore, in patients taking cyclosporine, the dose of Rosuvastatin should not exceed 5 mg once daily.

Gemfibrozil: Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with Rosuvastatin and gemfibrozil should be avoided. If used together, the dose of Rosuvastatin should not exceed 10 mg once daily.

Protease Inhibitors: Coadministration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to threefold. For these combinations the dose of Rosuvastatin should not exceed 10 mg once daily. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is coadministered with protease inhibitors given in combination with ritonavir.

Coumarin Anticoagulants: Rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with Rosuvastatin. In patients taking coumarin anticoagulants and Rosuvastatin concomitantly, INR should be determined before starting Rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs.

Niacin: The risk of skeletal muscle effects may be enhanced when Rosuvastatin is used in combination with lipid-modifying doses (≥1 g/day) of niacin; caution should be used when prescribing with Rosuvastatin.

Fenofibrate: When Rosuvastatin was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concomitant use of fenofibrates, caution should be used when prescribing fenofibrates with Rosuvastatin.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, coadministered with colchicine, and caution should be exercised when prescribing Rosuvastatin with colchicine.

Clopidogrel:

Medicinal products associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution.

Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings.

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. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Heparin: A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Thrombolytics: The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA.

NSAIDs: NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution.

SSRIs: Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Other concomitant therapy: Since clopidogrel is metabolized 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.

Proton Pump Inhibitors (PPI): Inconsistent data on the clinical implications of 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. There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers 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.

CYP2C8 substrate medicinal products: clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

Aspirin

Alcohol and corticosteroids may enhance the effects of aspirin on the gastrointestinal tract. Aspirin may enhance the effects of Coumarin anticoagulant, oral hypoglycaemics (of the sulphonylurea type), Phenytoin and sodium valproate. Aspirin may increase the risk of bleeding with other antiplatlet drugs such as clopidogrel and ticlopidine. The toxicity of methotrexate may be enhanced by concomitant use of aspirin. Aspirin 75mg may antagonise the diuretic effect of spironolactone and may reduce acetazolamide excretion (risk of toxicity). Aspirin increases plasma concentration of zafirlukast. Metoclopramide and domperidone enhance the effect of aspirin (increased rate of absorption). Avoid concomitant administration with mifepristone (theoretical interaction). Aspirin diminishes the action of uricosurics. Aspirin may reduce the efficacy of antihypertensive drugs. Aspirin is pharmaceutically incompatible with iron salts and alkalis. Avoid concomitant administration of antacids and absorbents (excretion of aspirin is increased in alkaline urine whilst kaolin may reduce absorption). This product should be administered cautiously for such conditions.

4.6 Fertility, pregnancy and lactation

Rosuvastatin

Pregnancy Teratogenic effects: Pregnancy Category X: Rosuvastatin is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. If the patient becomes pregnant while taking Rosuvastatin, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

Nursing Mothers: It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Women who require Rosuvastatin treatment should be advised not to nurse their infants.

Clopidogrel

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.

Breast-feeding: It is unknown whether clopidogrel is excreted in human breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel.

Aspirin

Pregnancy:

Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arterlosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

Labor and Delivery: Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers: Nursing mothers should avoid using aspirin because Salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

4.7 Effects on ability to drive and use machines

Studies to determine the effect of rosuvastatin on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, rosuvastatin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment. Clopidogrel has no or negligible influence on the ability to drive and use machines. Aspirin: None stated.

4.8 Undesirable effects

Rosuvastatin:

Rosuvastatin is generally well tolerated. The most commonly reported adverse reactions with the rosuvastatin were headache, myalgia, abdominal pain, asthenia, nausea, muscle cramp, myositis, anorexia,

vomiting, pruritus, rash, constipation, dizziness. Reported evidence suggests that, 1.4% of patients on rosuvastatin discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were myalgia, abdominal pain, and nausea.

The following serious adverse reactions were reported with rosuvastatin:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis)
- Liver enzyme abnormalities

Clopidogrel:

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment. In CAPRIE, in patients treated with either clopidogrel or ASA, the overall incidence of any bleeding was 9.3%. The incidence of severe cases was similar for clopidogrel and ASA.

Blood and the lymphatic system disorders: Thrombocytopenia, leucopenia, eosinophilia, Neutropenia, aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia

Immune system disorders: Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel)

Psychiatric disorders: Hallucinations, confusion

Nervous system disorders: Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness

Eye disorders: Eye bleeding (conjunctiva, 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, eosinophilic pneumonia

Gastrointestinal disorders: Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia, Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence, Retroperitoneal haemorrhage, Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including 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 multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus

Reproductive systems and breast disorders: Gynaecomastia

Musculoskeletal, connective tissue and bone disorders: Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia

Renal and urinary disorders: Haematuria, Glomerulonephritis, blood creatinine increased

General disorders and administration site conditions: Bleeding at puncture site, Fever

Aspirin

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature Body as a whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central nervous stystem: Agitation, Cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures. Fluid and Electrolyte: Dehydration, hyperkalemia, membolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, heartburn, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia, anaemia, purpura, leucopenia

Dermatologic and hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, , pruritus, skin eruptions, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reroductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, vertigo, tinnitus. Patients with higher frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

4.9 Overdose

Rosuvastatin: There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

Clopidogrel: 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.

Aspirin: Common features of overdose include dizziness, tinnitus, deafness, vasodilation and sweating, nausea and vomiting, headache and mental confusion. If more severe, hyperventilation, fever, restlessness,

ketosis, respiratory alkalosis and metabolic acidosis. Coma, if severe, with cardiovascular collapse and respiratory failure. Hypoglycaemia may be severe in children. Overdosage should be treated initially by aspiration and lavage and a saline purgative such as sodium sulphate, 30g in 250ml of water should be given to promote peristalsis. Otherwise treat as for aspirin poisoning and observe for at least 72 hours to allow for possible delayed reaction from gastro-resistant system. Restoration of acid-base balance may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Rosuvastatin

Rosuvastatin is a 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase inhibitor indicated for the treatment of hyperlipidemia. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase is a rate-limiting enzyme that converts 3-hydroxy-3-methyl glutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering. It differs structurally from other statins, containing a polar methane sulphonamide group which confers relative hydrophilicity. The relative hydrophilicity of rosuvastatin imparts greater selectivity for uptake into hepatic versus nonhepatic cells. Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles. In preclinical studies, the potency of rosuvastatin has been found to be greater than that of other statins (i.e. atorvastatin, simvastatin, pravastatin, lovastatin, cerivastatin, and fluvastatin). Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I. It also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios. A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clopidogrel

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.

Aspirin:

Acetylsalicylic acid (ASA) interferes with the production of prostaglandins in various organs and tissues through acetylation of the enzyme cyclooxygenase. The inhibition of platelet aggregation by ASA is due to its abilityto interfering with the production of thromboxane A2 within the platelet. Thromboxane A2 is, largely, responsible for the aggregating properties of platelets. Platelets play an important role in normal hemostasis and clinical pathologic and experimental evidence indicates that their aggregation may play an equally important role in the evolution of a variety of disease states including cerebrovascular disease, ischemic heart disease and myocardial infarction. Aspirin inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin endoperoxides PGG2 and PGH2 which are precursors of the major platelet-aggregating material, thromboxane A2, which is also a powerful vasoconstrictor. However, aspirin does not prevent the adherence of platelets to damaged vessel walls or the release of granule contents from these adherent platelets. As the anuclear platelets are unable to synthesize new enzyme molecules to replace those that have been inactivated, inhibition of platelet aggregation by aspirin thus persists for the life of the platelets.

Besides inhibiting the biosynthesis of thromboxane A2 by platelets, aspirin also interferes with the production of prostacyclin (PGI2) by vascular endothelial cells, the above-mentioned prostaglandin endoperoxides being common precursors of both thromboxane A2 and prostacyclin. This latter compound is one of the most powerfully acting platelet deaggregators and vasodilators and thus it would appear that the interference with the hemostatic processes by aspirin depends on the thromboxane-prostacyclin balance. In fact, it has been suggested that under some conditions, high doses of aspirin may be thrombogenic. However, in contrast to platelets, the vascular endothelial cells are able to regenerate cyclo-oxygenase in a relatively short time and therefore therapeutic doses of aspirin are likely to produce a lesser inhibition of the vascular prostacyclin system than of the platelet thromboxane-forming mechanism.

In fact, there is no clinical evidence to indicate that high doses of aspirin would result in an increased risk of thromboembolism. Absorption of non-ionised aspirin occurs in the stomach and intestine. Some aspirin is hydrolysed to salicylate in the gut wall. After absorption aspirin is rapidly converted to salicylate but during the first 20 minutes following oral administration, aspirin is the predominant form of the drug in the plasma. Aspirin is bound to plasma proteins and is widely distributed. Plasma aspirin concentrations decline rapidly (half-life 15-20 minutes) as plasma salicylate concentrations increase. Salicylate is mainly eliminated by hepatic metabolism - the metabolites including salicylic acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid.

As a result of zero order kinetics, plasma steady state salicylate concentrations increase disproportionately with dose. Salicylate is also excreted unchanged in the urine to an extent which depends on the dosage and

urinary pH. Renal excretion involves glomerular filtration, active renal tubular secretion and passive tubular reabsorption.

5.2 Pharmacokinetic properties

Rosuvastatin

Absorption: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution: The reported mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism: Rosuvastatin is not extensively metabolized; the major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9. *In vitro* studies have reported that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound.

Excretion: Following oral administration, rosuvastatin and its metabolites are primarily reported to be excreted in the feces (90%). The reported elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours.

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with a higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes.

Clopidogrel

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. 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.

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.

Pharmacogenetics: CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype.

Aspirin:

Absorption:

Aspirin is well and completely absorbed from the gastrointestinal (GI) tract and is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid seen within 1-2 hours of dosing. The rate of absorption is dependent upon the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. The gastric mucosa is permeable to the non-ionized form of acetylsalicylic acid, which passes through the stomach wall by a passive diffusion process. Optimum absorption of salicylate in the human stomach occurs in the pH range of 2.15 to 4.10. Absorption in the small intestine occurs at a significantly faster rate than in the stomach.

Distribution:

Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk, and fetal tissues, with highest concentrations seen in plasma, liver, renal cortex, heart, and lungs. The protein binding of salicylate is non-linear; at low concentrations (< 100 mcg/mL), approximately 90% is bound to albumin while at higher concentrations (> 400 mcg/mL), only about 75% is bound.

Metabolism:

Aspirin is hydrolyzed rapidly by esterases in the gastrointestinal mucosa and the liver to salicylic acid. The half-life of aspirin in the circulation is from 13 to 19 minutes so that the blood level drops quickly after absorption is complete. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites (gentisic acid and other hydroxybenzoic acids).

Excretion:

Excretion of salicylates occurs principally via the kidney, through a combination of glomerular filtration and tubular excretion. Following therapeutic doses, excretion is in the form of free salicylic acid, salicyluric acid, as well as phenolic and acyl glucuronides. Salicylate can be detected in the urine shortly after its ingestion

but the full dose requires up to 48 hours for complete elimination. The rate of excretion of free salicylate is extremely variable, reported recovery rates in human urine ranging from 10% to 85%, depending largely on urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5% to > 80%. The half-life of salicylic acid is approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 gm), the plasma half-life may be increased to over 20 hours. The elimination of salicylic acid follows zero order pharmacokinetics.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

18 Months.

6.2 Special Precautions for Storage

Store in dry well ventilated place at a temperature not exceeding 30 °C .

Protect from light and moisture

Keep out of reach of children.

6.3 Nature and Contents of Container

10 x 10's Capsules

7. MARKETED BY

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8. DATE OF PREPARATION/REVISION OF THE TEXT

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