Fixed Dose Combination (FDC) of Rosuvastatin 10 mg & Clopidogrel 75 mg Capsules
ROSUKEM CV 10

1. NAME OF THE MEDICINAL PRODUCT

ROSUKEM CV 10

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROSUKEM CV 10

Each hard gelatin capsule contains:

Rosuvastatin Calcium IP

Equivalent to Rosuvastatin……10 mg

(As 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

Prevention of Cardiovascular and cerebrovascular Events

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 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, urticaria, 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.

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.

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.

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.

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 (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, 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, 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

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.

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.

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.

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

Alkem Laboratories Ltd.

ALKEM HOUSE,

S. B. Road, Lower Parel (West),

Mumbai - 400 013. INDIA.

8. DATE OF PREPARATION/REVISION OF THE TEXT

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