For the use of Registered Medical Practitioner only

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms.
- Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events

1. Generic Name & Brand Name

Rosuvastatin, Aspirin & Clopidogrel Capsules
Fortius® Gold 10

Rosuvastatin, Aspirin & Clopidogrel Capsules
Fortius® Gold 20

2. Qualitative and Quantitative Composition:

Fortius® Gold 10
Each Hard Gelatin Capsule Contains:
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin……10 mg
Excipients……...q.s.
(As Film Coated Rosuvastatin Tablets I.P.)
Colours: Titanium Dioxide I.P.
Aspirin I.P……..75 mg
Excipients……q.s.
(As Aspirin Gasto-Resistant Tablet I.P.)
Colours: Red Oxide of Iron & Titanium Dioxide I.P.
Clopidogrel Bisulphate I.P.
Equivalent to Clopidogrel……75 mg
Excipients…….q.s.
(As Film Coated Clopidogrel Tablets I.P.)
Colours: Red Oxide of Iron & Titanium Dioxide I.P.
Colours used in Capsule Shell: Ponceau 4R, Sunset Yellow FCF, Tartrazine, Carmoisine and Titanium Dioxide I.P.

Fortius® Gold 20

Version No.2.0, dated 7-Jan-26
Replaces Version No. 1.0, dated 25-Oct-24

Each Hard Gelatin Capsule Contains:
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin……20 mg
Excipients……...q.s.
(As Film Coated Rosuvastatin Tablets I.P.)
Colours: Indigo Carmine & Titanium Dioxide I.P.
Aspirin I.P……..75 mg
Excipients……q.s.
(As Aspirin Gasto-Resistant Tablet I.P.)
Colours: Red Oxide of Iron & Titanium Dioxide I.P.
Clopidogrel Bisulphate I.P.
Equivalent to Clopidogrel……75 mg
Excipients…….q.s.
(As Film Coated Clopidogrel Tablets I.P.)
Colours: Red Oxide of Iron & Titanium Dioxide I.P.
Colours used in Capsule Shell: Brilliant Blue FCF, Erythrosine, Tartrazine, Carmoisine and Titanium Dioxide I.P.

3. Dosage Form & strength
Refer section 1 & 2

4. Clinical particulars
4.1 Therapeutic indication
For the treatment of dyslipidemia associated with artherscleroticarterial disease with risk of Myocardial infarction, stroke or peripheral vascular disease.

4.2 Posology and method of administration
Posology
The recommended dose is 1 Capsule, to be given once daily or as directed by the Physician.

Method of Administration:
For oral use only.
Patients should be advised to swallow the Capsule as whole and must not be chewed or crushed.

4.3 Contraindications
It is contraindicated in patients with a known hypersensitivity to any of the active substance(s) or any other component of the formulation.

Rosuvastatin is contraindicated:
- In patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
- In patients with severe renal impairment (creatinine clearance <30ml/min).
- In patients with myopathy.
- In patients receiving concomitant ciclosporin.

- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

The 40 mg dose of Rosuvastatin is contraindicated in patients with pre-disposing factors for myopathy/ rhabdomyolysis.
Such factors include moderate renal impairment (creatinine clearance < 60 ml/min); hypothyroidism; personal or family history of hereditary muscular disorders; previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate; alcohol abuse; situations where an increase in plasma levels may occur; Asian patients; and concomitant use of fibrates.

Aspirin should not be taken by patients with the following conditions:
Known hypersensitivity to aspirin, other ingredients in the product, other salicylates or non-steroidal anti inflammatory drugs (a patient may have developed anaphylaxis, angioedema, asthma, rhinitis or urticaria induced by aspirin or other NSAIDs).
History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
Active or history of recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding).
Severe heart failure.

Clopidogrel is contraindicated in patients with:
- Severe hepatic impairment.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage

4.4 Special warnings and precautions for use
Warning: Diminished Effectiveness in Poor Metabolizers
The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Rosuvastatin

- Renal Effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.
- Skeletal Muscle Effects: Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin -treated patients with all doses and in particular with doses > 20 mg. Very rare cases of rhabdomyolysis have been reported with

the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use.

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

- Creatine Kinase Measurement: Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5-7 days. If the repeat test confirms a baseline CK>5xULN, treatment should not be started.
- Before Treatment: Rosuvastatin, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include: renal impairment, hypothyroidism, personal or family history of hereditary muscular disorders, previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate, alcohol abuse, age >70 years, situations where an increase in plasma levels may occur, concomitant use of fibrates. In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.
- Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination.
- Liver Effects: As with other HMG-CoA reductase inhibitors, rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.
- In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.
- Race: Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians.
- Protease inhibitors: Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of rosuvastatin is adjusted.

- Interstitial lung disease: Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
- Diabetes Mellitus**:** Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/L.
- Paediatric population: The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 6 to 17 years of age taking rosuvastatin is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations>10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults.

Aspirin

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- Before commencing long-term aspirin therapy for the management of cardiovascular or cerebrovascular disease, patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.
- 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 and adolescents aged under 16 years unless specifically indicated.
- Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration necessary to control symptoms. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.
- The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.
- In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function.
- Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter. As NSAIDs can interfere with platelet function, they should be used with caution in patients with intercranial haemorrhage and bleeding diathesis.
- The use of aspirin with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided. Gastrointestinal bleeding, ulceration and perforation: GI

bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available.

- Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.
- Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin.
- When GI bleeding or ulceration occurs in patients receiving aspirin, the treatment should be withdrawn.
- NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.
- Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Aspirin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Cardiovascular and cerebrovascular effects: Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
- Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
- There are insufficient data to exclude such a risk for aspirin.
- Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with aspirin after careful consideration.
- Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
- Aspirin should be used with caution in patients with:
- allergic disease
- anaemia (may be exacerbated by GI blood loss)
- asthma (increased risk of bronchospastic sensitivity reactions)

- cardiac failure (conditions which predispose to fluid retention as NSAIDs may exacerbate this)
- dehydration
- dyspepsia
- glucose-6-phosphate dehydrogenase deficiency (aspirin rarely causes haemolytic anaemia)
- gout (serum urate may be increased)
- haemophilia or other haemorrhagic disorder (including thrombocytopenia) as there is an increased risk of bleeding
- nasal polyps associated with asthma (high risk of severe sensitivity reactions)
- surgery. Aspirin should be discontinued several days before scheduled surgery (including dental extractions)
- systemic lupus erythematosus and other connective tissue disorders (hepatic and renal function may be impaired in these conditions) In patients with strokes, aspirin should not be given until the possibility of cerebral haemorrhage has been excluded.

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.
  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.
  Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).
- Thrombotic Thrombocytopenic Purpura (TTP): TTP has been reported very rarely following the use of clopidogrel, sometimes after a short exposure.
  It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever.
  TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.
- 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.
  Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.
- 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): 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.
- 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.
- Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia.
- Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.
- 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 Drug Interactions

Rosuvastatin

Effect of co-administered medicinal products on Rosuvastatin:

Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

Ciclosporin: During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin. Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products: Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C max and AUC. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because

they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Antacid: The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminum and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from in vitro and in vivo studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. Therefore, drug interactions resulting from cytochrome P450mediated metabolism are not expected. In addition, rosuvastatin is a poor substrate for these isoenzymes. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

Effect of rosuvastatin on co-administered medicinal products
Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses.

Other medicinal products:
Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving combined drugs. If treatment with systemic fusidic acid is necessary, Rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

Aspirin
The following drug interactions should be considered when prescribing aspirin:

- It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.
- Alcohol - may enhance gastro-intestinal side effect of aspirin.
- Analgesics - avoid concomitant administration of other salicylates or other NSAIDs (including topical formulations eg ibuprofen) as increased risk of side effects.
- Alkalizers of urine (eg carbonic anhydrase inhibitors such as acetazolamide, antacids, citrates eg sodium citrate) - increased excretion of aspirin.
- Anticoagulants - NSAIDs may enhance the effects of anti-coagulants, such as warfarin.
- Antiepileptic drugs (eg phenytoin, sodium valproate) - increased effect.
- Antihypertensives - reduced anti-hypertensive effect.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.
- Corticosteroids eg hydrocortisone, prednisone - increased risk of gastro-intestinal bleeding or ulceration.
- Diuretics: furosemide and acetazolamide (risk of toxic effects), spironolactone (antagonized diuretic action). All diuretics can cause nephrotoxicity.
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels. o Lithium: decreased elimination of lithium
- Oral hypoglycaemics eg glibenclamide, gliclazide - enhanced activity. Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia
- Methotrexate: decreased elimination of methotrexate, increased toxicity.
- Ciclosporin: increased risk of nephrotoxicity with NSAIDs.
- Other NSAIDs: avoid concomitant use of two or more NSAIDs.
- Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.
- Probenecid: reduction in metabolism and elimination of NSAID and metabolites.
- Mifepristone - avoid aspirin until 8-12 days after mifepristone.
- Metoclopramide and domperidone - increased rate of absorption of aspirin.
- Ototoxic medicine (eg vancomycin) - potential for ototoxicity increased. Hearing loss may occur and may progress to deafness even after discontinuation of the medication. Effects may be reversible but are usually permanent.
- Uricosurics (eg sulfinpyrazone) - effects of uricosurics reduced.
- Laboratory investigations - aspirin may interfere with some laboratory tests such as urine 5-hydroxyundoleacetic acid determinations and copper sulphate urine sugar tests. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

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.
Heparin: a pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.
NSAIDs: in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs.
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.
CYP2C8 substrate medicinal products: clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel.
Proton Pump Inhibitors (PPI): Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.
Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged.
Other medicinal products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions.
No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen. The pharmacokinetics of digoxin or theophylline was not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy
Rosuvastatin is contraindicated in women who are or may become pregnant.
Rosuvastatin may cause fetal harm when administered to a pregnant woman.
Women of child bearing potential should use appropriate contraceptive measures.
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy.
Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.
As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Lactation
Rosuvastatin is contraindicated in pregnancy and lactation. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.
It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel.

Paediatric Use
Safety and effectiveness in children and adolescents under 18 years old have not been established. Paediatric use should only be carried out by specialists. Clopidogrel should not be used in children because of efficacy concern.

Geriatric Use
Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Elderly patients are at higher risk of myopathy and, hence, it should be prescribed with caution in the elderly.

Renal Impairment
No dose adjustment of Rosuvastatin is necessary in patients with mild to moderate renal impairment.
The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance of <60 ml/min).
Experience with clopidogrel is limited in patients with severe and moderate renal impairment.

Hepatic Impairment
Rosuvastatin is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is

known to increase rosuvastatin exposure; rosuvastatin should be used with caution in these patients.
Experience of clopidogrel is limited in patients with moderate hepatic disease who may have bleeding diatheses.

Aspirin

Salicylates readily cross the placenta and have been shown to be teratogenic in animals.
Although some studies and anecdotal reports have implicated aspirin in the formation of congenital abnormalities, largest studies have failed to find any significant risk or evidence of teratogenicity.
Ingestion of aspirin during the last two weeks of pregnancy may increase the risk of foetal or neonatal haemorrhage.
Regular or high dose use of salicylates late in pregnancy may result in constriction or premature closing of the foetal ductus arteriosus, increased risk of still birth or neonatal death, decreased birth weight, prolonged labour, complicated deliveries and increased risk of maternal or foetal haemorrhage and possibly persistent pulmonary hypertension of newborn or kernicterus in jaundiced neonates.
Pregnant women should be advised not to take aspirin in the last three months of pregnancy unless under medical supervision. Aspirin is distributed in breast milk. Aspirin should be avoided while breastfeeding.

Clopidogrel

Pregnancy: Category B
Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day, respectively (65 and 78 times the recommended daily human dose, respectively, on a mg/m2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.

Nursing Mothers:

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use:

Safety and effectiveness in pediatric populations have not been established. A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

Geriatric Use:
Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with Clopidogrel were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with Clopidogrel were 60 years and older, 26% of whom were 70 years and older. The observed risk of bleeding events with Clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Table 1 and Table 2 for the CURE and COMMIT trials, respectively. No dosage adjustment is necessary in elderly patients.

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
The following serious adverse reactions are discussed in greater detail in other sections:
• Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy (including myositis).
• Liver enzymes abnormalities.
In the rosuvastatin controlled clinical trials database (placebo or active-controlled) of 5,394 patients with a mean treatment duration of 15 weeks, 1.4% of patients discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: Myalgia, abdominal pain, and nausea.
The most commonly reported adverse reactions (incidence >2%) in the rosuvastatin controlled clinical trial database of 5,394 patients were: Headache, myalgia, abdominal pain, asthenia, and nausea.
Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis. The following laboratory abnormalities have also been reported: dipstick-positive proteinuria and microscopic hematuria; elevated creatine kinase (CK), transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.
The following adverse events have been reported with some statins: Sexual dysfunction; Exceptional cases of interstitial lung disease, especially with long term therapy.
The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

Paediatric population: Creatine kinase elevations>10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

Post-marketing Experience:

The following adverse reactions have been identified during post-approval use of rosuvastatin: arthralgia, fatal and non-fatal hepatic failure, hepatitis, jaundice, thrombocytopenia, depression, sleep disorders (including insomnia and nightmares), peripheral neuropathy and gynecomastia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
There have been rare reports of immune-mediated necrotizing myopathy associated with statin use.
There has been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Aspirin
Adverse effects of aspirin treatment which have been reported include:

- Allergic reactions - rhinitis, urticaria, angioneurotic oedema and worsening of asthma. Aspirin may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions in susceptible individuals.
- Effects on GI system - the most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.
- Effects on blood - anaemia, haemolytic anaemia, hypoprothrombinaemia, thrombocytopenia, aplastic anaemia, pancytopenia.
- Effects on sensory system - tinnitus.
- Effects on heart – oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. o Effects on the skin – bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).
- Salicylism - mild chronic salicylate intoxication may occur after repeated administration of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea, vomiting, headache and mental confusion, and may be controlled by reducing the dose. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke)

Clopidogrel
Blood and lymphatic system disorders: Increased bleeding tendencies, agranulocytosis, thrombocytopenia, leucopenia, eosinophilia, neutropenia, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A, granulocytopenia, and anemia.
Eye disorders: Eye (conjunctival, ocular, retinal) bleeding.

Ear and labyrinth disorders: Vertigo.
Gastrointestinal disorders: Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea, abdominal pain, dyspepsia, gastritis, vomiting, nausea, constipation, flatulence.
General disorders and administration site condition: Fever, hemorrhage of operative wound, bleeding at puncture site.
Hepato-biliary disorders: Acute liver failure, hepatitis (non-infectious), abnormal liver function test.
Immune system disorders: Hypersensitivity reactions (including cross reactive drug hypersensitivity among thienopyridines), anaphylactoid reactions, serum sickness.
Musculoskeletal, connective tissue and bone disorders: Musculoskeletal bleeding (hemarthrosis), myalgia, arthralgia, arthritis.
Nervous system disorders: Taste disorders, fatal intracranial bleeding, headache, ageusia, paraesthesia, dizziness.
Psychiatric disorders: Confusion, hallucinations.
Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, respiratory tract bleeding, eosinophilic pneumonia, epistaxis, hemoptysis, pulmonary hemorrhage.
Renal and urinary disorders: Increased creatinine levels, hematuria, and glomerulonephritis.
Skin and subcutaneous tissue disorders: Maculopapular, erythematous or exfoliative rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, skin bleeding (purpura), lichen planus, generalized pruritus, bruising.
Reproductive systems and breast disorders: Gynecomastia.
Vascular disorders: Vasculitis, hypotension, hematoma.
Investigations: Bleeding time prolonged, neutrophil count decreased, and platelet count decreased.
Cardiac disorders: Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to Clopidogrel.

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. Hemodialysis does not significantly enhance clearance of rosuvastatin.

Aspirin
Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (95.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning
Symptoms
Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases. A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic

acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier

Uncommon features

include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Management

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

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 Mechanism of action

Rosuvastatin

Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of cholesterol. In vivo studies in animals and in vitro studies in cultured animal and human cells have shown rosuvastatin to have a high uptake into, and selectivity for, action in the liver, the target organ for cholesterol lowering. In in vivo and in vitro studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic low-density lipoprotein (LDL) receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of very-low-density lipoprotein (VLDL), which reduces the total number of VLDL and LDL particles.

Clopidogrel

Clopidogrel is a thienopyridine class inhibitor of P2Y12 adenosine diphosphate (ADP) platelet receptors. It is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. Clopidogrel must be metabolized by cytochrome P (CYP) 450 enzymes to produce the active metabolite that inhibits

platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of ADP to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein (GP) IIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel's active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). 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:
Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and the production of thromboxane A2, an inducer of platelet aggregation and vasoconstriction. This effect lasts for the life of the platelet

5.2 Pharmacodynamic Properties
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 (see Table 3).
Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 3. Dose response in patients with primary hypercholesterolaemia (type IIa and IIb)
(adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

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.

Aspirin
Aspirin is an anti-inflammatory analgesic and antipyretic. It inhibits prostaglandin synthetase and platelet aggregation. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred.

However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusion can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Clopidogrel

Repeated doses of clopidogrel 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued. Acetylsalicylic acid 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. Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.3 Pharmacokinetic properties

Rosuvastatin

In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing.

Both peak concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose.

The absolute bioavailability of rosuvastatin is approximately 20%.

Administration of rosuvastatin with food did not affect the AUC of rosuvastatin.

The AUC of rosuvastatin does not differ following evening or morning drug administration. Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 (CYP450) 2C9, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound. Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses.

Aspirin

Absorption
Acetylsalicylic acid is rapidly absorbed from the gastrointestinal tract. Following oral administration, the absorption of non-ionised acetylsalicylic acid will occur in the stomach and the intestine. Absorption is delayed by the presence of food and reduced in patients suffering from migraine. The rate of absorption is increased in patients who suffer from achlorhydria or in patients undergoing treatment with polysorbates or antacids. Peak serum concentration for acetylsalicylic acid is achieved within half an hour and within 1-2 hours for salicylic acid.
Distribution
Acetylsalicylic acid has a plasma protein binding of 80-90%. The distribution volume has been reported at 170 ml/kg bodyweight in adults. When the plasma concentration increases, the proteins' binding sites become saturated resulting in increased distribution volume. The salicylates are largely bound to plasma proteins and are rapidly distributed throughout the body. Salicylates are found in mother's milk and can cross the placenta barrier.
Metabolism
Some acetylsalicylic acid is hydrolysed to salicylate in the gut wall. After absorption aspirin is rapidly converted to salicylate but during the first 20 minutes 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. Both aspirin and salicylate have pharmacological activity; only aspirin has an antiplatelet effect.
Elimination
Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, gentisic acid, and gentisuric acid. The steady state plasma salicylate concentration will therefore increase disproportionally with dose level. At a dose level of 325 mg acetylsalicylic acid, elimination follows the first order kinetics and the half-life for plasma salicylate is 2-3 hours. At high doses of acetylsalicylic acid, the half-life increases to 15-30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption.

<u>Clopidogrel</u>
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. 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. It 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-oxoclopidogrel intermediate metabolite.
Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been

isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Rosuvastatin

Preclinical data reveals no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

Clopidogrel

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.

7. Description

Fortius Gold 10 is supplied for oral administration as hard gelatin capsules of Rosuvastatin Calcium equivalent to Rosuvastatin (As film coated Rosuvastatin Tablets I.P.), Aspirin (As Aspirin Gastro-resistant Tablets I.P.) & Clopidogrel Bisulphate equivalent to Clopidogrel (As film coated Clopidogrel Tablets I.P.). Each hard gelatin capsule of Fortius Gold 10 contains Rosuvastatin

Calcium equivalent to Rosuvastatin 10 mg (As film coated Rosuvastatin Tablets I.P.), Aspirin 75 mg (As Aspirin Gastro-resistant Tablets I.P.) & Clopidogrel Bisulphate equivalent to Clopidogrel 75 mg (As film coated Clopidogrel Tablets I.P.).

Fortius Gold 20 is supplied for oral administration as hard gelatin capsules of Rosuvastatin Calcium equivalent to Rosuvastatin (As film coated Rosuvastatin Tablets I.P.), Aspirin (As Aspirin Gastro-resistant Tablets I.P.) & Clopidogrel Bisulphate equivalent to Clopidogrel (As film coated Clopidogrel Tablets I.P.). Each hard gelatin capsule of Fortius Gold 20 contains Rosuvastatin Calcium equivalent to Rosuvastatin 20 mg (As film coated Rosuvastatin Tablets I.P.), Aspirin 75 mg (As Aspirin Gastro-resistant Tablets I.P.) & Clopidogrel Bisulphate equivalent to Clopidogrel 75 mg (As film coated Clopidogrel Tablets I.P.).

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage condition & handling instructions

Refer Pack

9. Patient Counseling Information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

10. Details of manufacturer

Refer Pack for manufacturer details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 &
111 to 116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.

Version No.2.0, dated 7-Jan-26
Replaces Version No. 1.0, dated 25-Oct-24

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12. Date of revision
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webmasterindia@abbott.com