

**Size: 320 (L) x 480 (H) mm**  
**Folding size: 80 x 120 mm**  
**Carton size: 88 x 30 x 142**

Bible paper 40 gsm



## ROUVASTATIN + CLOPIDOGREL

### TURBOVAS-CP

5 mg/75 mg Capsule

Lipid Modifying Agent-Antithrombotic Agent

#### PRODUCT NAME:

Turbovas-CP

#### DOSAGE FORM AND STRENGTH:

Rosuvastatin and Clopidogrel Capsules 5 mg/75 mg

#### PHARMACOLOGIC CATEGORY:

Lipid Modifying Agent-Antithrombotic Agent

#### PRODUCT DESCRIPTION

Pink cap/Pink body, size "1" hard gelatin capsules containing white to off white powder and one yellow colored circular film coated tablet.

#### FORMULATION/COMPOSITION

Each capsule contains:

Rosuvastatin (as calcium)  
(as a film coated tablet) ..... 5 mg  
Clopidogrel (as bisulfate) USP ..... 75 mg

#### PHARMACODYNAMICS/PHARMACOKINETICS

##### Pharmacodynamics

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A 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 LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, Rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

##### Clopidogrel

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized 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 P2Y<sub>2</sub> receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

##### Pharmacodynamic effects

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

##### Pharmacokinetics

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

**Distribution & Plasma Protein Binding:** 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.

**Metabolism:** Rosuvastatin undergoes limited metabolism (approximately 10%). *In vitro* metabolism studies using human hepatocytes indicate that Rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzymes involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than Rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

**Elimination:** 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. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of Rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of Rosuvastatin.

##### 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 metabolized by the liver. *In vitro* and *in vivo*, clopidogrel is metabolized according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its active carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolized to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. *In vitro*, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The C<sub>max</sub> of the active metabolite is twice as high following a single 300-mg clopidogrel loading dose as it is after four days of 75-mg maintenance dose. C<sub>max</sub> occurs approximately 30 to 60 minutes after dosing.

**Elimination:** Following an oral dose of <sup>14</sup>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.

#### INDICATIONS:

It is used for the treatment for acute coronary syndrome, myocardial infarction, stroke and angina

#### DOSAGE AND MODEL ROUTE OF ADMINISTRATION:

Rosuvastatin and Clopidogrel should be taken once a day or as directed by physician

It may be given at any time of day, with or without food.

#### CONTRAINDICATIONS & PRECAUTION(S), WARNING(S):

It is contraindicated:

- In patients with hypersensitivity to Rosuvastatin or to any of the excipients, 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 cyclosporin.
- During pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.
- The 40 mg dose 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; concomitant use of fibrates.

Known hypersensitivity to clopidogrel or any ingredient in the formulation. Presence of active pathological bleeding (e.g., peptic ulcer, intracranial hemorrhage)

#### PRECAUTIONS & WARNINGS:

##### 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

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.

**Whilst on Treatment:** Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted. There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including Rosuvastatin. IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with Rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including Gemfibrozil, ciclosporin, nicotinic acid, azole antifungals,

protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of Rosuvastatin and Gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of a fibrate.

Combination with Rosuvastatin and fusidic acid is not recommended. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

Rosuvastatin should not be used 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, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

**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 hypercholesterolemia 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.

**Lactose intolerance:** Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

##### Clopidogrel

##### Compliance with Therapy in Patients with Drug-eluting Stents

Premature discontinuance of dual-drug antiplatelet therapy with a thienopyridine derivative (i.e., clopidogrel, ticlopidine) and aspirin in patients with coronary artery stents, particularly discontinuance of clopidogrel therapy in patients with drug-eluting stents, has been associated with stent thrombosis, often leading to myocardial infarction (MI) and/or death. Before implantation of a drug-eluting stent, patients should be carefully assessed regarding the likelihood of compliance with prolonged (e.g., at least 12 months) dual-drug antiplatelet therapy (i.e., aspirin and a thienopyridine derivative); strong consideration should be given to avoiding use of a drug-eluting stent in patients who are not expected to comply. In addition, patients should be educated before discharge about the reasons they have been prescribed the drugs and the substantial risks associated with premature discontinuance of dual-drug antiplatelet therapy. Superficial or "nuisance" bleeding is common in patients receiving dual-drug antiplatelet therapy after drug-eluting stent implantation and may be a reason for premature discontinuation of clopidogrel. In a single-center observational study in 2360 patients who underwent drug-eluting stent implantation, 11.1% of patients who were receiving dual-drug antiplatelet therapy discontinued clopidogrel prematurely as a result of superficial bleeding. The American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association (ACC/F/ACG/AHA) states that concomitant use of proton-pump inhibitors may reduce GI symptoms (e.g., dyspepsia) associated with antiplatelet agents and thereby prevent patients from discontinuing their antiplatelet treatment. Patients should be advised to never stop taking dual-drug antiplatelet therapy without first consulting with their cardiologist, even if instructed to do so by another health-care professional (e.g., dentist). In patients who are likely to require invasive or surgical procedures within 12 months of drug-eluting stent implantation, implantation of a bare-metal stent or balloon angioplasty with provisional stent placement should be considered instead.

##### Reduced Efficacy Associated with Impaired CYP2C19 Function

Clopidogrel is a prodrug that requires activation by the cytochrome P-450 (CYP) enzyme system to produce its pharmacologically active metabolite. Production of the active metabolite and response to clopidogrel may be reduced by genetic polymorphism of CYP2C19, one of the key enzymes involved in the metabolic activation of clopidogrel, or concurrent use of drugs (e.g., omeprazole, esomeprazole) that inhibit CYP2C19. Use of alternative clopidogrel dosing strategies or other antiplatelet therapy options (e.g., prasugrel, ticagrelor) should be considered in patients who are identified as potential poor metabolizers of CYP2C19.

##### Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) has been reported rarely with clopidogrel, sometimes after short exposure (less than 2 weeks) to the drug. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes on peripheral blood smear), neurologic findings, renal dysfunction, and fever. TTP is a potentially fatal condition that requires urgent referral to a hematologist for prompt treatment (e.g., plasmapheresis).

##### Risks of Discontinuation of Therapy

In general, treatment with a thienopyridine derivative should not be discontinued prematurely because of the increased risk of cardiovascular events. If clopidogrel must be temporarily discontinued (e.g., prior to surgery), therapy should be re-initiated as soon as possible. Patients should be advised to never stop clopidogrel therapy without first consulting the prescribing clinician. Prior to scheduling an invasive procedure, patients should inform their clinicians (including dentists) that they are currently taking clopidogrel, and clinicians performing the invasive procedure should consult with the prescribing clinician before advising patients to discontinue therapy.

##### General Precautions

**Bleeding:** Clopidogrel increases the risk of bleeding. The drug should be discontinued 5–10 days prior to surgery or coronary artery bypass grafting (CABG), if antiplatelet effect is undesirable. If bleeding occurs, hemostasis may be restored with exogenous administration of platelets; however, platelet transfusions within 4 hours of a loading dose of clopidogrel or within 2 hours of a maintenance dose may have reduced effectiveness. Withholding a dose is unlikely to resolve a bleeding episode or prevent bleeding associated with an invasive procedure because of clopidogrel's prolonged effects on platelet inhibition.

**In patients with transient ischemic attacks (TIAs) or stroke that are at high risk for recurrent ischemic events, the combination of clopidogrel and aspirin has not been shown to be more effective than clopidogrel alone but has been associated with an increase in major bleeding.**

**Hepatic Impairment:** Inhibition of ADP-induced platelet aggregation in patients with severe hepatic impairment appears to be similar to that observed in healthy individuals.

**Renal Impairment:** Experience is limited in patients with moderate (creatinine clearance of 30–60 mL/min) or severe (creatinine clearance of 5–15 mL/min) renal impairment. Inhibition of ADP-induced platelet aggregation may be decreased by 25% in such patients.

#### PREGNANCY AND LACTATION:

##### Rosuvastatin

Rosuvastatin is contraindicated in pregnancy and lactation.

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.

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.</

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**Acetylsalicylic acid (ASA):** ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A Pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, clopidogrel and ASA have been administered together for up to one year.

**Heparin:** in a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A Pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

**Thrombolytic:** the safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA.

**NSAIDs:** in a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution.

**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.

Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, flucloxacillin, carbamazepine, and efavirenz.

**Proton Pump Inhibitors (PPI):**

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

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

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.

The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H<sub>2</sub> 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. Furthermore, the Pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

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

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

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

#### ADVERSE EFFECTS:

##### Rosuvastatin

The adverse reactions seen with Rosuvastatin are generally mild and transient. In controlled clinical trials, less than 4% of Rosuvastatin-treated patients were withdrawn due to adverse reactions.

##### Tabulated list of adverse reactions

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for Rosuvastatin. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

The frequencies of adverse reactions are ranked according to the following convention: Common ( $\geq 1/100$  to  $<1/10$ ); Uncommon ( $\geq 1/1,000$  to  $<1/100$ ); Rare ( $\geq 1/10,000$  to  $<1/1,000$ ); Very rare ( $<1/10,000$ ); Not known (cannot be estimated from the available data).

Table 2. Adverse reactions based on data from clinical studies and post-marketing experience

System organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Thrombocytopenia		
Immune system disorders			Hypersensitivity reactions including angioedema		
Endocrine disorders	Diabetes mellitus <sup>1</sup>				
Psychiatric disorders				Depression	
Nervous system disorders	Headache Dizziness		Polyneuropathy Memory loss	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)	
Respiratory, thoracic and mediastinal disorders				Cough Dyspnoea	
Gastro-intestinal disorders	Constipation Nausea Abdominal pain		Pancreatitis		Diarrhoea
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice Hepatitis	
Skin and subcutaneous tissue disorders		Puritis Rash Urticaria			Stevens-Johnson syndrome
Musculo-skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathy
Renal and urinary disorders				Haematuria	
Reproductive system and breast disorders				Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema

<sup>1</sup> Frequency will depend on the presence or absence of risk factors (fasting blood glucose  $\geq 5.6$  mmol/L, BMI  $>30$  kg/m<sup>2</sup>, raised triglycerides, history of hypertension).

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

**Renal effects:** Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with Rosuvastatin and clinical trial data show that the occurrence is low.

**Skeletal muscle effects:** Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in Rosuvastatin-treated patients with all doses and in particular with doses  $> 20$  mg.

A dose-related increase in CK levels has been observed in patients taking Rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated ( $>5\times ULN$ ), treatment should be discontinued.

**Liver effects:** As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking Rosuvastatin; the majority of cases were mild, asymptomatic and transient.

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  $>10\times ULN$  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.

#### Clopidogrel

##### Summary of the safety profile

Clopidogrel has been evaluated for safety in more than 44,000 patients who have participated in clinical studies, including over 12,000 patients treated for 1 year or more. Overall, clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the CAPRIE, CURE, CLARITY, COMMIT and ACTIVE-A studies are discussed below. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

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.

In CURE, there was no excess in major bleeds with clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In CLARITY, there was an overall increase in bleeding in the clopidogrel plus ASA group vs. the placebo plus ASA group. The incidence of major bleeding was similar between groups. This was consistent across subgroups of patients defined by baseline characteristics,

and type of fibrinolytic or heparin therapy.

In COMMIT, the overall rate of non-cerebral major bleeding or cerebral bleeding was low and similar in both groups. In ACTIVE-A, the rate of major bleeding was greater in the clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extracranial origin in both groups (5.3% in the clopidogrel + ASA group, 3.5% in the placebo + ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the clopidogrel + ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the clopidogrel + ASA group and 0.7% in the placebo + ASA group) and haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

##### Tabulated list of adverse reactions

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

System Organ Class	Common	Uncommon	Rare	Very rare, not known*
Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia
Immune system disorders				Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thiopyridines (such as ticlopidine, prasugrel)
Psychiatric disorders				Hallucinations, confusion
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Haematoma			Serious haemorrhage, haemorrhage of operative wound, vacuities, 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	Retropertitoneal haemorrhage	Gastrointestinal and retropertitoneal 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 exanthematosus 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
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased		

\* Information related to clopidogrel with frequency "not known".

#### OVERDOSE AND TREATMENT

##### 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. Hemodialysis 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.

#### STORAGE CONDITION

Store at temperature not exceeding 30°C.

#### DOSAGE FORMS AND PACKAGING AVAILABLE

Dosage Form: Capsules  
Packaging: Aluminium/Aluminium Blister pack of 3 x 10 capsules

#### INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):

Not Applicable

#### NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder  
Brown & Burk Philippines Inc  
U-501, 5/F, SEDCCO 1 Bldg., 120 Rada cor.  
Legaspi Sts., Legaspi Village, Makati City, Philippines

#### NAME AND ADDRESS OF MANUFACTURER

MICRO LABS LIMITED  
92, Sipcot Industrial Complex,  
Hosur-635 126 (T.N), India

<b>MICRO LABS LIMITED, BANGALORE, INDIA</b>						
1	Product Name	Turbovas-CP			<u>Colours Used</u>	
2	Strength	5 mg and 75 mg			 BLACK	
3	Component	Leaflet				
4	Category	Export - Philippines				
5	Dimension	320 (L) x 480 (H) mm				
6	Artwork Code	EXG-ML01I-1750				
7	Pharma Code	N/A				
8	Reason for Change	New Artwork			 Keylines	
		<b>Prepared by (DTP)</b>	<b>Checked by (PD)</b>	<b>Approved by</b>		
Sign	Date			Head CQA	Head Production/ Packing (Site)	Head QC (Site)
Kantharaju L.	31-01-2022					