Vasoclin 10 Tablet

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1. Name of the medicinal product

Vasoclin 10 mg film-coated tablets.

2. Qualitative and quantitative composition

10 mg: Each tablet contains 10 mg rosuvastatin (as rosuvastatin calcium). Each tablet contains 91.3 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

10 mg: Film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of hypercholesterolaemia

Adults, adolescents and children aged 6 years or older with primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Adults, adolescents and children aged 6 years or older with homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis) or if such treatments are not appropriate.

Prevention of Cardiovascular Events

Prevention of major cardiovascular events in patients who are estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualised according to the goal of therapy and patient response, using current consensus guidelines.

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

Treatment of hypercholesterolaemia

The recommended start dose is 5 or 10 mg orally once daily in both statin naïve or patients switched from another HMG CoA reductase inhibitor. The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see section 5.1). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see section 4.8), a final titration to the

maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see section 4.4). Specialist supervision is recommended when the 40 mg dose is initiated.

Prevention of cardiovascular events

In the cardiovascular events risk reduction study, the dose used was 20 mg daily (see section 5.1).

Paediatric population

Paediatric use should only be carried out by specialists.

Children and adolescents 6 to 17 years of age (Tanner Stage <II-V)

Heterozygous familial hypercholesterolaemia

In children and adolescents with heterozygous familial hypercholesterolaemia the usual start dose is 5 mg daily.

• In children 6 to 9 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-10 mg orally once daily. Safety and efficacy of doses greater than 10 mg have not been studied in this population.

• In children 10 to 17 years of age with heterozygous familial hypercholesterolaemia, the usual dose range is 5-20 mg orally once daily. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

Titration should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations (see section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment.

Homozygous familial hypercholesterolaemia

In children 6 to 17 years of age with homozygous familial hypercholesterolaemia, the recommended maximum dose is 20 mg once daily.

A starting dose of 5 to 10 mg once daily depending on age, weight and prior statin use is advised. Titration to the maximum dose of 20 mg once daily should be conducted according to the individual response and tolerability in paediatric patients, as recommended by the paediatric treatment recommendations (see section 4.4). Children and adolescents should be placed on standard cholesterol-lowering diet before rosuvastatin treatment initiation; this diet should be continued during rosuvastatin treatment.

There is limited experience with doses other than 20 mg in this population.

The 40 mg tablet is not suitable for use in paediatric patients.

Children younger than 6 years

The safety and efficacy of use in children younger than 6 years has not been studied. Therefore, Vasoclin is not recommended for use in children younger than 6 years.

Use in the elderly

A start dose of 5 mg is recommended in patients >70 years (see section 4.4). No other dose adjustment is necessary in relation to age.

Dosage in patients with renal insufficiency

No dose adjustment 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 <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of Vasoclin in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Dosage in patients with hepatic impairment

There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see section 5.2). In these patients an assessment of renal function should be considered (see section 4.4). There is no experience in subjects with Child-Pugh scores above 9. Vasoclin is contraindicated in patients with active liver disease (see section 4.3).

Race

Increased systemic exposure has been seen in Asian subjects (see sections 4.3, 4.4 and 5.2). The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.

Genetic polymorphisms

Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure (see section 5.2). For patients who are known to have such specific types of polymorphisms, a lower daily dose of Vasoclin is recommended.

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is 5 mg in patients with predisposing factors to myopathy (see section 4.4).

The 40 mg dose is contraindicated in some of these patients (see section 4.3).

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Vasoclin is administered concomitantly

with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir and/or tipranavir; see sections 4.4 and 4.5). Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Vasoclin therapy. In situations where co-administration of these medicinal products with Vasoclin is unavoidable, the benefit and the risk of concurrent treatment and Vasoclin dosing adjustments should be carefully considered (see section 4.5).

4.3 Contraindications

Vasoclin 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 times 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 combination of sofosbuvir/velpatasvir/voxilaprevir (see section 4.5)

- in patients receiving concomitant ciclosporin.

- 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.

(See sections 4.4, 4.5 and 5.2)

4.4 Special warnings and precautions for use

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Vasoclin, 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 (see section 4.8). 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 Vasoclin-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 (see section 4.5) and caution should be exercised with their combined use. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with Vasoclin 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

Vasoclin, 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 (see sections 4.2, 4.5 and 5.2)

• 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.

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 ≤5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing Vasoclin 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 characterised 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 Vasoclin 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 Vasoclin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of Vasoclin 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 (see sections 4.5 and 4.8).

Vasoclin 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 (see section 4.5). Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of Vasoclin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Vasoclin 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).

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appear, Vasoclin should be discontinued immediately and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of Vasoclin, treatment with Vasoclin must not be restarted in this patient at any time.

Liver Effects

As with other HMG-CoA reductase inhibitors, Vasoclin 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. Vasoclin 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 Vasoclin.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see sections 4.2, 4.3 and 5.2).

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 Vasoclin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating Vasoclin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of Vasoclin is adjusted. (See sections 4.2 and 4.5).

Lactose Intolerance

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

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy (see section 4.8). 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 >30 kg/m^2, 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 (see section 5.1).

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 (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

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 Vasoclin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see sections 4.2, 4.4 and 4.5 Table 1).

Ciclosporin: During concomitant treatment with Vasoclin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). Vasoclin is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). 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 (see Table 1). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and C_{max} respectively. The concomitant use of Vasoclin and some protease inhibitor combinations may be considered after careful consideration of Vasoclin dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4 and 4.5 Table 1).

Gemfibrozil and other lipid-lowering products: Concomitant use of Vasoclin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see section 4.4).

Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/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 (see sections 4.3 and 4.4). These patients should also start with the 5 mg dose.

Ezetimibe: Concomitant use of 10 mg Vasoclin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between Vasoclin and ezetimibe cannot be ruled out (see section 4.4).

Antacid: The simultaneous dosing of Vasoclin with an antacid suspension containing aluminium 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 Vasoclin. The clinical relevance of this interaction has not been studied.

Erythromycin: Concomitant use of Vasoclin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in C_{max} 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. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. 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).

Interactions requiring rosuvastatin dose adjustments (see also Table 1): When it is necessary to co-administer Vasoclin with other medicinal products known to increase exposure to rosuvastatin, doses of Vasoclin should be adjusted. Start with a 5 mg once daily dose of Vasoclin

if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose of Vasoclin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of Vasoclin taken without interacting medicinal products, for example a 20 mg dose of Vasoclin with gemfibrozil (1.9-fold increase), and a 10 mg dose of Vasoclin with combination ritonavir/atazanavir (3.1-fold increase).

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the Vasoclin dose above 20mg.

Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials		
2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Sofosbuvir/velpatasvir/voxilaprevir (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10mg single dose	7.4 -fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5mg, single dose	5.2-fold ↑
Regorafenib 160 mg, OD, 14 days	5 mg, single dose	3.8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		

Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓
*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as "↑", decrease as "↓". **Several interaction studies have been performed at different Vasoclin dosages, the table shows the most significant ratio AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily		

The following medical product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at coadministration:

Aleglitazar 0.3 mg 7 days dosing; Fenofibrate 67 mg 7 days TID dosing; Fluconazole 200mg 11 days OD dosing; Fosamprenavir 700 mg/ritonavir 100 mg 8 days BID dosing; Ketoconazole 200 mg 7 days BID dosing; Rifampin 450 mg 7 days OD dosing; Silymarin 140 mg 5 days TID dosing.

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 Vasoclin 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 Vasoclin 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 Vasoclin 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. There are no pharmacokinetic data available in subjects taking concomitant Vasoclin and HRT, therefore, a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Other medicinal products:

Digoxin: Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

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. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, Vasoclin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Also see section 4.4.**

Paediatric population: Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

4.6 Fertility, pregnancy and lactation

Vasoclin 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 (see section 5.3). 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 (see section 4.3).

4.7 Effects on ability to drive and use machines

Studies to determine the effect of Vasoclin on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, Vasoclin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

The adverse reactions seen with Vasoclin are generally mild and transient. In controlled clinical trials, less than 4% of Vasoclin-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 (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); 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[1]				
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		Pruritus Rash Urticaria			Stevens-Johnson syndrome Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculo-skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis Lupus-like syndrome Muscle rupture	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

[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m^2, 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 Vasoclin. 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 Vasoclin 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 Vasoclin-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 (>5xULN), treatment should be discontinued (see section 4.4).

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 (see section 4.4).

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 (see section 4.4). In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitors

Mechanism of action

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 for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects

Vasoclin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 3). Vasoclin also lowers the LDL-C/HDL-C, total C/HDL-C and non-HDL-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.

Clinical efficacy and safety

Vasoclin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

From pooled phase III data, Vasoclin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/L) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/L).

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given Vasoclin from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. Thirty-three percent (33%) of patients reached EAS guidelines for LDL-C levels (<3 mmol/L).

In a force-titration, open label trial, 42 patients (including 8 paediatric patients) with homozygous familial hypercholesterolaemia were evaluated for their response to Vasoclin 20 – 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, Vasoclin has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin (see section 4.4).

In a multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/L (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Vasoclin 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk (see section 4.2).

In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events was assessed in 17,802 men (≥50 years) and women (≥60 years).

Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.

LDL-cholesterol concentration was reduced by 45% (p<0.001) in the rosuvastatin group compared to the placebo group.

In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score >20% (1558 subjects) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.028) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high-risk group (p=0.193). In a post-hoc analysis of a high-risk

subgroup of subjects (9302 subjects total) with a baseline SCORE risk ≥5% (extrapolated to include subjects above 65 yrs) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high-risk group (p=0.076).

In the JUPITER trial, there were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.6% placebo).

Paediatric population

In a double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n=176, 97 male and 79 female) followed by a 40-week (n=173, 96 male and 77 female), open-label, rosuvastatin dose-titration phase, patients 10 to 17 years of age (Tanner stage II-V, females at least 1-year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 to 13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/L.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected (see section 4.4). This trial (n=176) was not suited for comparison of rare adverse drug events.

Rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolaemia aged 6 to 17 years (88 male and 110 female, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.

After 24 months of treatment with rosuvastatin, the LS mean percent reduction from the baseline value in LDL-C was -43% (Baseline: 236 mg/dL, Month 24: 133 mg/dL). For each age group, the LS mean percent reductions from baseline values in LDL-C were -43% (Baseline: 234 mg/dL, Month 24: 124 mg/dL), -45% (Baseline: 234 mg/dL, Month 24: 124 mg/dL) and -35% (Baseline:

241 mg/dL, Month 24: 153 mg/dL) in the 6 to <10, 10 to <14, and 14 to <18 age groups, respectively.

Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL C/HDL-C, ApoB, ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.

No effect on growth, weight, BMI or sexual maturation was detected after 24 months of treatment (see section 4.4).

Rosuvastatin was studied in a randomised, double-blind, placebo-controlled, multi-centre, cross-over study with 20 mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with homozygous familial hypercholesterolaemia. The study included an active 4-week dietary lead-in phase during which patients were treated with rosuvastatin 10 mg, a cross-over phase that consisted of a 6-week treatment period with rosuvastatin 20 mg preceded or followed by a 6-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20 mg. Patients who entered the study on ezetimibe or apheresis therapy continued the treatment throughout the entire study.

A statistically significant (p=0.005) reduction in LDL-C (22.3%, 85.4 mg/dL or 2.2 mmol/L) was observed following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. Statistically significant reductions in Total-C (20.1%, p=0.003), non-HDL-C (22.9%, p=0.003) and ApoB (17.1%, p=0.024) were observed. Reductions were also seen in TG, LDL-C/HDL-C, Total-C/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-1 following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. The reduction in LDL-C after 6 weeks of treatment with rosuvastatin 20 mg following 6 weeks of treatment with placebo was maintained over 12 weeks of continuous therapy. One patient had a further reduction in LDL-C (8.0%), Total-C (6.7%) and non-HDL-C (7.4%) following 6 weeks of treatment with 40 mg after up-titration.

During an extended open-label treatment in 9 of these patients with 20 mg rosuvastatin for up to 90 weeks, the LDL-C reduction was maintained in the range of -12.1% to -21.3%.

In the 7 evaluable children and adolescent patients (aged from 8 to 17 years) from the force-titration open label study with homozygous familial hypercholesterolaemia (see above), the percent reduction in LDL-C (21.0%), Total-C (19.2%) and non-HDL-C (21.0%) from baseline following 6 weeks of treatment with rosuvastatin 20 mg was consistent with that observed in the aforementioned study in children and adolescents with homozygous familial hypercholesterolaemia.

The European Medicines Agency has waived the obligation to submit the results of studies with rosuvastatin in all subsets of the paediatric population in the treatment of homozygous familial hypercholesterolaemia, primary combined (mixed) dyslipidaemia and in the prevention of cardiovascular events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Distribution: 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 isoenzyme 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.

Excretion: 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.

Linearity: Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations:

Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The exposure in children and adolescents with heterozygous familial hypercholesterolemia appears to be similar to or lower than that in adult patients with dyslipidaemia (see “Paediatric population” below).

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and Cmax. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency: In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration

compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic insufficiency: In a study with subjects with varying degrees of hepatic impairment, there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with a higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of Vasoclin is recommended.

Paediatric population: Two pharmacokinetic studies with rosuvastatin (given as tablets) in paediatric patients with heterozygous familial hypercholesterolaemia 10 to 17 or 6 to 17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

5.3 Preclinical safety data

Preclinical data reveal 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.

6. Pharmaceutical particulars

6.1 List of excipients

Ludipress
Microcrystalline Cellulose (Type-1 0 1)
Dibasic Calcium Phosphate Anhydrous
Pregelatinized Starch
Crospovidone

Magnesium Stearate
Colloidal Silicon Dioxide (Aerosil-200)
Opadry II OY -LS-34950 (Pink)
Carnauba Wax (Powder)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Keep out of the reach of children. Keep in a dry place, below 300C. Protect from light.

6.5 Nature and contents of container
10 mg

Blisters of aluminium laminate/aluminium foil of 30 tablets

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Beximco Pharmaceuticals Ltd.

19 Dhanmondi R/A, Road #7, Dhaka 1205

Dhaka

Bangladesh

Applicant: STANDARD GENERICS LIMITED, 373, AGEGE MOTOR ROAD, MUSHIN

8. Marketing authorization number(s): 186-678-061

9. Date of first authorization/renewal of the authorization: 06-07-2010

10. Category for distribution: POM