Version 2.0, 08/2011
Rev. 1, 10/2011

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALVOSTAT 10 mg film-coated tablets
ALVOSTAT 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).
Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).

Excipient with known effect:
Each 10 mg film-coated tablet contains 91.440 mg lactose monohydrate.
Each 20 mg film-coated tablet contains 182.880 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

ALVOSTAT 10 mg
Round, biconvex, light pink coloured tablets, 7.0 mm in diameter, debossed with “10” on one side.

ALVOSTAT 20 mg
Round, biconvex, dark pink coloured tablets, 9.0 mm in diameter, debossed with “20” on one side.

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, as an adjunct to correction of other risk factors."

4.2 Posology and method of administration

General: The patients should be placed on a standard cholesterol-lowering diet before receiving rosuvastatin and should continue on this diet during treatment. The National Cholesterol Education Program (NCEP) treatment guidelines should be consulted for recommendations on dietary and other non-drug therapies.

Dosage: Dosage of rosuvastatin calcium is expressed in terms of rosuvastatin.

When initiating rosuvastatin therapy or switching from another statin, the appropriate initial dosage of rosuvastatin should be used; dosage may then be carefully adjusted according to individual requirements (i.e., target LDL-cholesterol goal) and response.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients.
The usual dosage range of rosuvastatin for the management of heterozygous familial hypercholesterolemia in boys and girls (who are at least 1 year postmenarchal) 10-17 years of age is 5-20 mg once daily. Dosage adjustments should be made at intervals of 4 weeks or longer. The maximum recommended dosage of rosuvastatin in pediatric patients is 20 mg daily. Safety and efficacy of rosuvastatin dosages exceeding 20 mg daily have not evaluated in controlled trials in this patient population.

Homozygous Familial Hypercholesterolemia. The recommended initial dosage of rosuvastatin in adults with homozygous familial hypercholesterolemia is 20 mg once daily. Response to therapy should be estimated based on preapheresis LDL-cholesterol concentrations.

Prevention of Cardiovascular Events or Management of Dyslipidemias
General Dosage. The usual initial dosage of rosuvastatin in adults is 10-20 mg once daily. The usual dosage range of rosuvastatin in adults is 5-40 mg once daily. The 40 mg daily dosage of rosuvastatin should be used only for those patients who have not achieved their LDL-cholesterol goal with the 20 mg daily dosage.

Rosuvastatin is administered orally as a single dose at any time of day, with or without food.

Special populations

Renal Impairment

In patients with severe renal impairment (creatinine clearance less than 30 mL/minute per 1.73 m^2) who are not undergoing hemodialysis, rosuvastatin should be initiated at a dosage of 5 mg once daily, and dosage should not exceed 10 mg once daily.
Hepatic Impairment
The manufacturer makes no specific dosage recommendations at this time for patients with hepatic impairment.
Geriatric Patients
Although there are no specific dosage recommendations for geriatric patients, caution is recommended when rosuvastatin is used in these patients.

Dose in patients with renal insufficiency
Exposure to rosuvastatin (i.e. plasma concentrations) does not appear to be influenced by mild or moderate renal impairment (creatinine clearance of 30 mL/minute per 1.73 m2 or greater).
Dosage adjustments are required in patients with severe renal impairment who are not undergoing hemodialysis.

Dose in patients with hepatic impairment
Plasma concentrations of rosuvastatin are modestly increased in patients with chronic alcoholic liver disease. Peak plasma concentrations and AUC of rosuvastatin are increased by 60 and 5%, respectively, in patients with Child-Pugh class A disease and by 100 and 21% respectively, in patients with children-Pugh class B disease compared with individuals with normal liver function.
Rosuvastatin should be used with caution in patients with a history of liver disease (e.g. chronic alcoholic liver disease) and/or in patients who consume substantial amounts of alcohol. Rosuvastatin is contraindicated in patients with active liver disease, including unexplained, persistent elevations in hepatic aminotransferase concentrations.

Method of administration
ALVOSTAT is intended for oral use.

4.3 Contraindications

Rosuvastatin is contraindicated:

- In patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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.

4.4 Special warnings and precautions for use

Musculoskeletal Effects

Myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported in patients receiving stains, including rosuvastatin. These adverse effects can occur at any dosage, but the risk is increased with the highest dosage of rosuvastatin (40 mg daily).

Rosuvastatin should be used with caution in patients with predisposing factors for myopathy (e.g., advanced age 65 years or older, renal impairment, inadequately treated hypothyroidism). The risk of myopathy may be increased when rosuvastatin is used concomitantly with some other antilipemic agents (niacin or certain fibric-acid derivatives i.e. gemfibrozil, cyclosporine, ritonavir-boosted atazanavir, or the fixed combination of lopinavir and ritonavir (lopinavir/ritonavir).

Rosuvastatin should be discontinued if creatine kinase (CK, creatine phosphokinase, CPK) concentration become markedly elevated or if myopathy is diagnosed or suspected. Rosuvastatin therapy should be temporarily withheld in any patient experiencing an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension; dehydration; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; uncontrolled seizures.

Hepatic Effects

Increases in serum aminotransferase (i.e. AST (SGOT), ALT (SGPT) concentrations have been reported in patients receiving statins, including rosuvastatin. These increases usually were transient and resolved or improved with continued therapy or after temporary interruption of therapy. In a pooled analysis of placebo-controlled studies, increases in serum aminotransferase concentrations exceeding 3 times the upper limit of normal (ULN) occurred in 1.1% of patients receiving rosuvastatin compared with 0.5% of those receiving placebo. Jaundice has been reported in at least 2 patients but resolved following discontinuance of rosuvastatin therapy; a causal relationship to rosuvastatin has not been established. Although liver failure and irreversible liver disease have not been reported in clinical studies evaluating rosuvastatin, cases of fatal and nonfatal hepatic failure have been reported rarely in patients receiving stains, including rosuvastatin, during post-marketing surveillance.

If serious liver injury with clinical manifestations and/or hyperbilirubinemia or jaundice occurs, rosuvastatin therapy should be promptly interrupted. If an alternate etiology is not found, rosuvastatin therapy should not be restarted.

Rosuvastatin should be used with caution in patients who consume substantial amounts of alcohol and/or have a history of chronic liver disease. The drug is contraindicated in patients with active liver disease, including unexplained, persistent elevations in serum aminotransferase concentrations.

Paediatric Use

Safety and efficacy of rosuvastatin have not been evaluated in prepubertal children or in children younger than 10 years of age with heterozygous familial hypercholesterolemia. In a randomized, double-blind, placebo-controlled study in boys and postmenarchal girls 10-17 years of age, the adverse effect profile of rosuvastatin (5-20 mg daily for 12 weeks) generally was similar to that of placebo.

Dosages exceeding 20 mg daily have not been evaluated in this pediatric population. There were no detectable adverse effects on growth, weight, body mass index (BMI), or sexual maturation in children 10-17 years of age. In a pharmacokinetic study in 18 children (9 boys and 9 girls) 10-17 years of age with heterozygous familial hypercholesterolemia, peak plasma concentrations and area under the plasma concentration-time curve (AUC) of rosuvastatin were similar to those observed in adults receiving the same dosages of rosuvastatin.
The manufacturer states that experience with rosuvastatin in children and adolescents 8 years of age or older with homozygous familial hypercholesterolemia is limited to 8 patients.

4.5 Interaction with other medicinal products and other forms of interaction

Rosuvastatin is minimally (approximately 10%) metabolized by cytochrome P-450 (CYP) isoenzyme 2C9. Clearance of rosuvastatin is not dependent on metabolism by CYP3A4 to a clinically important extent.

Antacids: In a pharmacokinetic study, *simultaneous* administration of rosuvastatin (40 mg as a single dose) and an antacid containing aluminium hydroxide and magnesium hydroxide decreased rosuvastatin peak plasma concentration and area under the plasma concentration-time curve (AUC) by 50 and 54%, respectively. Therefore, if rosuvastatin and an aluminium-magnesium hydroxide antacid are used concomitantly, the antacid should be administered at least 2 hours after rosuvastatin.

Cyclosporine: Concomitant use of rosuvastatin and cyclosporine may increase the risk of myopathy. Following concomitant use of rosuvastatin (10 mg once daily for 10 days) and cyclosporine, rosuvastatin peak plasma concentration and AUC were increased by 11 and 7 fold, respectively; such effects were considered clinically important. If used concomitantly with cyclosporine, dosage of rosuvastatin should be limited to 5 mg once daily.

Erythromycin: Concomitant use of rosuvastatin (80 mg as a single dose) and erythromycin (500 mg 4 times daily for 7 days) decreased rosuvastatin peak plasma concentration and AUC by 31 and 20%, respectively.

Gemfibrozil: Concomitant use of rosuvastatin and gemfibrozil may increase the risk of myopathy. Following concomitant use of rosuvastatin (80 mg as a single dose) and gemfibrozil (600 mg twice daily for 7 days), rosuvastatin peak plasma concentration and AUC were increased by 21 and 7%, respectively; such effects were not considered clinically important. Concomitant use of rosuvastatin and gemfibrozil should be avoided.

HIV Protease Inhibitors: Concomitant use of rosuvastatin with certain ritonavir-boosted HIV protease inhibitors has differing effects on exposure to rosuvastatin; caution is advised if rosuvastatin is used concomitantly with ritonavir-boosted HIV protease inhibitors.

Atazanavir: Concomitant use of rosuvastatin and ritonavir-boosted atazanavir may increase the risk of myopathy. Following concomitant use of rosuvastatin (10 mg as a single dose) and ritonavir-boosted atazanavir (atazanavirb300 mg with ritonavir100 mg once daily for 7 days), rosuvastatin peak plasma concentration and AUC were increased by sevenfold and threefold, respectively; such effects were considered clinically important. If used concomitantly with ritonavir-boosted atazanavir, caution is advised and dosage of rosuvastatin should be limited to 10 mg once daily.

Oral contraceptive Concomitant use of rosuvastatin (40 mg once daily for 28 days) and an oral contraceptive (ethinyl estradiol 0.035 mg with norgestrel 0.18, 0.215, and 0.25 mg once daily for 21 days) resulted in a 25 or 26% increase in ethinyl estradiol peak plasma concentration or AUC, respectively, and a 23 or 34% increase in norgestrel peak plasma concentration or AUC, respectively.

Protease inhibitors:
Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by the 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.

4.6 Fertility, pregnancy and lactation

ALVOSTAT is contraindicated in pregnancy and lactation.
Important of advising women and adolescent girls to avoid pregnancy (i.e. using appropriate contraceptive methods) during therapy; if the patient becomes pregnant, importance of discontinuing rosuvastatin and contacting a clinician.

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 distributed into milk in rats. It is not known whether rosuvastatin is distributed into human; however a small amount of another statin is distributed into human milk. Because of the potential for serious adverse reactions from rosuvastatin in nursing infants, the drug is contraindicated in nursing women. Women who require rosuvastatin therapy should not breast-feed their infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Common Adverse Effects
Adverse effects reported in at least 2% of patients received rosuvastatin in clinical studies include headache, nausea, myalgia, asthenia, constipation and abdominal pain.

Sensitivity Reactions Hypersensitivity reactions, including rash, pruritus, urticarial, and angioedema, have been reported in patients receiving rosuvastatin.

Cognitive Impairment
Cognitive impairment (e.g. memory loss, for getfulness, amnesia, memory impairment, confusion) has been reported rarely with all statins during post-marketing surveillance. This adverse CNS effect generally was nonserious and reversible, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks following discontinuance of statin therapy). Following review of available data (i.e., from the Adverse Event Reporting System (AERS) database, randomized clinical trial, observational studies, case reports), FDA concluded that cases of cognitive impairment did not appear to be associated with fixed or progressive dementia (e.g. Alzheimer's disease) or result in clinically important cognitive decline. Development of cognitive impairment did not appear to be associated with any specific statin, age of the patient, statin dosage, or concomitant drug therapy. Therefore, FDA continues to believe that the cardiovascular benefits of statins outweigh this small increased risk of cognitive impairment.

Risk of myopathy and/or rhabdomyolysis. Importance of promptly reporting any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, brown urine, and flu-like symptoms.

Risk of adverse hepatic effects. Importance of promptly reporting any symptoms suggestive of liver injury (e.g. fatigue, anorexia, right upper abdominal discomfort, dark urine, jaundice).

Risk of nonserious, reversible cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion).

Risk of increased glucose concentrations and development of type 2 diabetes mellitus; may need to monitor glucose concentrations following initiation of statin therapy.

Proteinuria and Hematuria

Transient dipstick-positive proteinuria and microscopic hematuria (not associated with worsening renal function) have been reported in patients receiving rosuvastatin. These findings occurred more frequently in patients receiving rosuvastatin 40 mg compared with lower doses of rosuvastatin or comparator statins in clinical trials. Although the clinical importance of this finding is not known, dosage reduction should be considered in patients receiving rosuvastatin who have unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Post marketing experience

In addition to the above, the following adverse events have been reported during post marketing experience for rosuvastatin:

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, ATC code: C10A A07

Rosuvastatin calcium is a synthetic heptenoic acid-derivative antilipemic agent. The drug is a selective, competitive inhibitor of 3-hydroxymethylglutrayl-CoA (HMG-CoA) reductase (i.e., statin) an enzyme that catalyzes the conversion of HMG-CoA to mevalonate (an early and rate-limiting step in cholesterol biosynthesis). Rosuvastatin reduces total and low-density lipoprotein (LDL) cholesterol, apolipoprotein B (apo B), non-high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations, and increases HDL-cholesterol concentrations in patients with primary hyperlipidemia or mixed dyslipidemia. Rosuvastatin also reduces triglyceride concentrations in patients with primary hypertriglyceridemia.

Rosuvastatin is not extensively metabolized 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P-450 (CYP) isoenzyme 2C9. Clearance of rosuvastatin is not dependent on metabolism by CYP3A4 to a clinically important extent. Based on in vitro studies, N-desmethyl rosuvastatin has approximately 17-50% of the HMG-CoA reductase inhibitory activity of the parent drug. The parent drug accounts for greater than 90% of the active plasma HMG-CoA reductase inhibiyory activity. Rosuvastatin and its metabolites are mainly eliminated in feces (90%) following oral administration. The elimination half-life of rosuvastatin is approximately 19 hours. Following an IV dose, approzimately 28% of total body clearance was via the renal route and 72% by the hepatic route.

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.

Biotransformation
Rosuvastatin undergoes limited metabolism (approximately 10%). *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P_{450}-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.

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.

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

Tablet core:
Cellulose, microcrystalline, type 102
Lactose monohydrate
Crospovidone, type A
Magnesium stearate

Film-coating:
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)
Triacetin
Allura red aluminum lake (E129) for 10 mg
Carmine (E120) for 20 mg

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please find the expiry date on the outer carton.

6.4 Special precautions for storage

Store below 30ºC in the original package in order to protect from light.

6.5 Nature and contents of container

Blisters of PA/Aluminum/PVC//Aluminum foil contained in a cardboard box.
Pack size: 28 (4x7), 56 (8x7), 98 (14x7) film-coated tablets

Not all pack sizes may be marketed.

7. Manufacturer

Manufactured by Adamed Pharma S.A., ul. Szkolna 33, 95-054 Ksawerow, Poland.

Repacked and released by Adamed Pharma S.A., ul. Marszalka Jozefa Pilsudskirgo 5, 95-200 Pabianice, Poland

8. Importer

Alvogen (Thailand) Limited, Bangkok, Thailand

9. Marketing Authorization Number

Reg. No. 1C 15016/63 (NG) for 10 mg
Reg. No. 1C 15017/63 (NG) for 20 mg

10. Date of revision of the text