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INSTRUCTION
for medical use

OZALEX®

Composition:
active substance: rosuvastatin;
1 film-coated tablet contains 10 mg, or 20 mg, or 40 mg of rosuvastatin calcium, equivalent to rosuvastatin;
excipients: lactose monohydrate, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, colloidal silicon dioxide anhydrous, magnesium stearate, Opadry pink 03F84827*;
*Opadry pink 03F84827: hypromellose, titanium dioxide (E 171), iron oxide red (E 172), polyethylene glycol, talcum powder.

Pharmaceutical form. Film-coated tablets.
Main physico-chemical properties: round, biconvex, film-coated tablets of pink color smooth on both sides.

Pharmacotherapeutic group. Hypolipidemic agents. HMG-CoA reductase inhibitors.
ATC code C10A A07.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the enzyme that limits the reaction rate and 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 low-density lipoprotein (LDL) receptors on the cell-surface of the liver, enhancing the uptake and catabolism of LDL and inhibits the hepatic synthesis of very-low-density lipoproteins (VLDL), thereby reducing the total number of VLDL and LDL particles.
Pharmacodynamic action
Rosuvastatin reduces elevated LDL cholesterol, total cholesterol and triglycerides and increases high-density lipoprotein cholesterol (HDL-C). It also lowers ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I.
Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios.
The therapeutic effect is obtained within 1 week following the initiation of the medicinal product, and 90% of the maximum response is achieved in 2 weeks. The maximum response is usually achieved after 4 weeks and is maintained after that.
Pharmacokinetics.
Absorption
Maximum rosuvastatin plasma concentrations (C_{max}) 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 identified metabolites are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50 % less active than rosuvastatin whereas the lactone metabolite is considered clinically inactive. Rosuvastatin accounts for more than 90 % of the circulating HMG-CoA reductase inhibitor activity.

Excretion

Approximately 90 % of the rosuvastatin dose is excreted unchanged in the feces (consisting of absorbed and non-absorbed active substance), the rest is excreted in urine. Approximately 5 % is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours and does not increase at higher doses. The geometric mean plasma clearance of the medicinal product is approximately 50 l/hour (coefficient of variation is 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C, which is important in the hepatic elimination of rosuvastatin.

Linearity

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

Special patient groups

Age and sex

There was no clinically significant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolemia was similar to that of adult volunteers (see section “Children”).

Race

Pharmacokinetic studies have shown that median values for the area under the pharmacokinetic curve “concentration-time” (AUC) and C_{max} in subjects of the Mongolian race (Japanese, Chinese, Filipino, Vietnamese, and Korean) are approximately twice as high as that in Europeans; in Indians, the median values of AUC and C_{max} are increased by about 1.3-fold. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Negroid races.

Renal impairment

In a study in patients with varying degrees of renal impairment, no changes in plasma concentrations of rosuvastatin or N-desmethyl metabolite were observed in subjects with mild to moderate insufficiency. Plasma concentrations of rosuvastatin were 3 times higher in patients with severe renal impairment (creatinine clearance < 30 ml/min), and N-desmethyl metabolites were 9 times higher than in healthy volunteers. Steady-state plasma concentrations of rosuvastatin in patients undergoing hemodialysis were approximately 50 % higher compared to healthy volunteers.

Hepatic impairment

In a study in patients 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 patients with lower Child-Pugh scores. There is no experience of the use of rosuvastatin in subjects with Child-Pugh scores above 9.

Genetic polymorphism

Distribution of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphism there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with a higher rosuvastatin 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 the medicinal product Ozalex® is recommended.
Children
Two studies of the pharmacokinetics of rosuvastatin (given as tablets) in children with heterozygous familial hypercholesterolemia aged 10 to 17 years or 6 to 17 years (total of 214 patients) demonstrated that exposure of the drug in children appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to the dose and time over more than 2 years of observation.

Clinical characteristics.
Indications.
Treatment of hypercholesterolemia
Adults, adolescents and children aged 6 years or older with primary hypercholesterolemia (type IIa , including heterozygous familial hypercholesterolemia) or mixed dyslipidemia (type IIb) as an adjunct to the diet when the response to the diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is insufficient.
Adults, adolescents and children aged 6 years or older with homozygous familial hypercholesterolemia as an adjunct to the 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 “Pharmacodynamics”), as an adjunct to correction of other risk factors.

Contraindications.
The medicinal product Ozalex® is contraindicated:
– in patients with hypersensitivity to rosuvastatin or to any of the excipients of the medicinal product;
– in patients with active liver disease including persistent elevations of serum transaminases of unknown etiology and any elevation of serum transaminases 3 times higher than 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 “Interaction with other medical products and other forms of interaction”);
– in patients receiving concomitant cyclosporine;
– during pregnancy and breastfeeding and in women of reproductive age who do not use appropriate contraceptive measures.
The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis.
Such risk 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 that can lead to an increase in the concentration of the medicinal product in the plasma;
– belonging to the Mongoloid race;
– concomitant use of fibrates.
(See sections “Pharmacokinetics”, “Interaction with other medical products and other forms of interaction” and “Administration details”).

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 rosuvastatin 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 "Interaction with other medicinal products and other forms of interaction", "Administration details" and "Dosage and administration", table).

Cyclosporine

During concomitant treatment with rosuvastatin and cyclosporine, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see table). Rosuvastatin is contraindicated in patients receiving concomitant cyclosporine (see section "Contraindications").

Concomitant administration did not affect plasma concentrations of cyclosporine.

Protease inhibitors

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see table). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combined medicinal product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy volunteers was associated with an approximately 3-fold and 7-fold increase in rosuvastatin AUC and C_{max} respectively. Concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of dose adjustments of the medicinal product Ozalex® based on the expected increase in rosuvastatin exposure (see sections "Interaction with other medical products and other forms of interaction", "Administration details" and "Dosage and administration", table).

Gemfibrozil and other lipid-lowering products

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see section "Administration details").

Based on data from specific studies, no pharmacokinetically 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 cause myopathy when used separately. The 40 mg dose is contraindicated with concomitant use of fibrates (see sections "Contraindications" and "Administration details"). Such patients should also start the therapy with the 5 mg dose.

Ezetimibe

Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in the AUC of rosuvastatin in hypercholesterolemic patients (see table). A pharmacodynamic interaction, in terms of adverse reactions, between rosuvastatin and ezetimibe cannot be ruled out (see section "Administration details").

Antacids

Simultaneous administration of rosuvastatin with antacid suspensions containing aluminium or magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentrations of approximately 50%. This effect was mitigated when the antacids were dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

Erythromycin

Concomitant use of rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in C_{max}. This interaction may be caused by the increase in gut motility caused by erythromycin.

Ticagrelor

Ticagrelor may cause renal insufficiency and may affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. In some cases, concomitant use of ticagrelor and rosuvastatin led to a decrease of renal function, increased creatine phosphokinase (CPK) levels and rhabdomyolysis. Renal function and CPK level control is recommended upon concomitant use of ticagrelor and rosuvastatin.

Cytochrome P450 enzymes

Results from *in vitro* and *in vivo* studies show that rosuvastatin neither inhibits nor induces 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 the table)
When it is necessary to co-administer rosuvastatin with other medicinal products known to increase its exposure, doses of rosuvastatin should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the AUC of the medicinal product is expected to increase approximately 2-fold or higher. The maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure does not exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products; for example, when administered with gemfibrozil, the dosage of rosuvastatin would be 20 mg (1.9-fold increase of exposure), when used with the combination of ritonavir/atazanavir – 10 mg (3.1-fold increase).
If the medicinal product increases rosuvastatin AUC less than 2-fold, the starting dose does not need to be decreased but caution should be taken if increasing the dose of the medicinal product Ozalex® above 20 mg.

Table
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	10 mg, single dose	↑ 7,4-fold
Cyclosporine from 75 mg twice a day to 200 mg twice a day, 6 months	10 mg once a day, 10 days	↑ 7,1-fold
Darolutamide 600 mg twice a day, 5 days	5 mg, single dose	↑ 5,2-fold
Regorafenib 160 mg once daily, 14 days	5 mg, single dose	↑ 3,8-fold
Atazanavir 300 mg/ritonavir 100 mg once a day, 8 days	10 mg, single dose	↑ 3,1-fold
Velpatasvir 100 mg once a day	10 mg, single dose	↑ 2,7-fold
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg once a day/dasabuvir 400 mg twice a day, 14 days	5 mg, single dose	↑ 2,6-fold
Grazoprevir 200 mg/elbasvir 50 mg once a day, 11 days	10 mg, single dose	↑ 2,3-fold
Glecaprevir 400 mg/pibrentasvir 120 mg once a day, 7 days	5 mg once a day, 7 days	↑ 2,2-fold
Lopinavir 400 mg/ritonavir 100 mg twice a day, 17 days	20 mg once a day, 7 days	↑ 2,1-fold
Clopidogrel 300 mg, followed by 75 mg in 24 hours	20 mg, single dose	↑ 2-fold
Gemfibrozil 600 mg twice a day, 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 once a day, 5 days	10 mg, single dose	↑ 1,6-fold
Darunavir 600 mg/ritonavir 100 mg twice a day, 7 days	10 mg once a day,	↑ 1,5-fold

	7 days	
Tipranavir 500 mg/ritonavir 200 mg twice a day, 11 days	10 mg, single dose	↑ 1,4-fold
Dronedarone 400 mg twice a day	Not available	↑ 1,4-fold
Itraconazole 200 mg once a day, 5 days	10 mg, single dose	↑ 1,4-fold **
Ezetimibe 10 mg once a day, 14 days	10 mg once a day, 14 days	↑ 1,2-fold **
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Erythromycin 500 mg four times a day, 7 days	80 mg, single dose	↓ 20 %
Baicalin 50 mg three times a day, 14 days	20 mg, single dose	↓ 47 %

* Data given as an x-fold change represent a ratio between co-administration and rosuvastatin alone. Data given as a % change represent % difference relative to rosuvastatin alone.
Increase is indicated as "↑", decrease as "↓".
** Several interaction studies have been performed at different rosuvastatin doses; the table shows the most significant ratio.

Medicinal products/combinations that did not have a clinically significant effect on the AUC ratio of rosuvastatin upon coadministration: aleglitazar 0.3 mg 7 days; fenofibrate 67 mg 7 days three times a day; fluconazole 200 mg 11 days once a day; fosamprenavir 700 mg/ritonavir 100 mg 8 days twice a day; ketoconazole 200 mg 7 days twice a day; rifampin 450 mg 7 days once a day; silymarin 140 mg 5 days twice a day.

Effect of rosuvastatin on co-administered medicinal products

Vitamin K antagonists

As with other HMG-CoA-reductase inhibitors, the initiation of treatment or dosage increase of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in the International Normalised Ratio (INR). Discontinuation of rosuvastatin or reduction of its dosage may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/hormone replacement therapy (HRT)

Concomitant use of rosuvastatin and an oral contraceptives resulted in an increase in AUC of ethinyl estradiol and norgestrel of 26 % and 34 %, respectively. Such increased plasma levels should be considered when selecting oral contraceptive doses. There are no data available on the pharmacokinetics of medicinal products in patients taking concomitant rosuvastatin 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 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 (pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

In patients for whom treatment with systemic fusidic acid is deemed necessary, rosuvastatin treatment should be discontinued throughout the entire duration of treatment with fusidic acid. See also section "Administration details".

Children

Interaction studies have only been performed in adults. The extent of interactions in the children is not known.

Administration details.

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 (see section "Adverse reactions"). The reporting rate for serious renal events in post-marketing studies is higher at a dose of 40 mg. In patients taking the medicinal product at a dose of 40 mg, kidney function should be monitored regularly.

Skeletal muscle effects

Disturbances of skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with rosuvastatin with all doses and in particular with doses over 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 "Interaction with other medicinal products and other forms of interaction") and caution should be exercised with this combination.

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

Creatine kinase measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of plausible alternative causes of CK increase which may confound the interpretation of the results. If CK levels are significantly elevated at baseline (> 5 times higher than ULN) a confirmatory test should be carried out within 5–7 days. If the repeat test confirms that the baseline CK is 5 times higher than ULN, the use of the medicinal product should not be initiated.

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;
– history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate;
– alcohol abuse;
– age > 70 years;
– situations where an increase in plasma levels of the medicinal product may occur (see sections "Pharmacokinetics", "Interaction with other medicinal products and other forms of interaction" and "Dosage and administration");
– concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to the expected benefit; clinical monitoring is also recommended. If CK levels are significantly elevated at baseline (>5 times higher than ULN), the treatment should not be initiated.

During treatment

Patients should be asked to report about muscle pain, weakness or inexplicable cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in such patients. The use of the medicinal product should be discontinued if CK levels are markedly elevated (> 5 × ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ × ULN). If symptoms disappear 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.

Regular monitoring of CK levels in asymptomatic patients is not required. There have been very rare reports of an immune-mediated necrotizing 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 even following 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 medicinal products. 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, cyclosporine, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when used concomitantly with some HMG-CoA 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 upon concomitant use of fibrates (see sections “Interaction with other medical products and other forms of interaction” and “Adverse reactions”).

Rosuvastatin must not be co-administered with systemic medicinal products of fusidic acid or within 7 days of discontinuing treatment with fusidic acid. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued for the entire duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including several fatalities) in patients receiving a combination of fusidic acid and statins (see section “Interaction with other medical products and other forms interactions”).

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 rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Rosuvastatin should not be used in patients with an acute, serious conditions suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders or uncontrolled seizures).

Severe cutaneous adverse reactions

The use of rosuvastation was associated with 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. If rosuvastation is prescribed, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, rosuvastation should be discontinued immediately and alternative treatment should be considered.

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

Liver effects

As with other HMG-CoA reductase inhibitors, rosuvastatin should be used with caution in patients who abuse 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 ULN. The reporting rate for serious hepatic events (mainly for increased hepatic transaminases) in post-marketing use was 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 indicate an almost 2-fold increase in exposure in patients of the Mongoloid race compared with Caucasians (see sections “Pharmacokinetics”, “Contraindications” and “Dosage and administration”).

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 the use of rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating therapy and increasing rosuvastatin doses in patients treated with protease inhibitors. Concomitant use of the medicinal product with certain protease inhibitors is not recommended unless the dose of rosuvastatin

is adjusted (see sections “Interaction with other medical products and other forms of interaction” and “Dosage and administration”).

Interstitial lung disease

When using some statins, especially with long-term treatment, isolated cases of interstitial lung disease were reported (see section "Adverse reactions"). The manifestations of this disease include shortness of breath, unproductive cough and general deterioration of the condition (fatigue, weight loss and fever). In case of suspicion of interstitial pulmonary disease, the use of statins 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 mellitus, may produce a level of hyperglycemia where appropriate diabetes mellitus treatment is necessary. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for discontinuation of statin treatment. Patients at risk (fasting glucose 5.6–6.0 mmol/l, BMI > 30 kg/m^2, raised triglycerides, arterial 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.

Children

The evaluation of linear growth (height), bodyweight, BMI (body mass index), and secondary sex characteristics by Tanner staging in children 6 to 17 years of age taking rosuvastatin is limited to a two-year period. After 2 years of study treatment, no effect on growth, bodyweight, BMI or sexual maturation was detected (see section “Pharmacodynamics”). In a clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations > 10 times greater than ULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults (see section “Adverse reactions”).

Myasthenia gravis/ocular myasthenia

The use of statins was associated with several reports of *de novo* onset or exacerbation of myasthenia gravis or ocular myasthenia (see section “Adverse reactions”). The medicinal product Ozalex® should be discontinued in case of aggravation of symptoms. Relapses of the disease have been reported with repeated use of the same or different statin.

Excipients

The product contains lactose. Patients with intolerance to some sugars should consult their doctor before taking this medicinal product.

Use during pregnancy and breastfeeding.

Rosuvastatin is contraindicated during pregnancy and breastfeeding.

Women of childbearing potential should use appropriate contraceptive measures.

Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the fetus, the potential risk from inhibition of HMG-CoA-reductase outweighs the advantage of using the medicinal product during pregnancy. Data of animal studies on reproductive toxicity are limited. If a patient becomes pregnant during the 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 of rosuvastatin in milk in humans (see section “Contraindications”).

Effect on reaction rate when driving motor transport or using other mechanisms.

Studies of the effect of rosuvastatin on the ability to drive motor transport and use other mechanisms have not been conducted. However, based on the pharmacodynamic properties of the medicinal product, rosuvastatin is unlikely to affect this ability. When driving motor transport or using other mechanisms, it should be taken into account that dizziness may occur during treatment.

Dosage and administration.

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

The medicinal product Ozalex® may be given at any time of day, with or without food.
Treatment of hypercholesterolemia
The recommended starting dose is 5* or 10 mg orally once daily for patients who had not previously taken statins as well as those who transferred to a medicinal product with another HMG-CoA-reductase inhibitor.
* Since the tablet is not divided, if the dosage is less than 10 mg, rosuvastatin preparations with the possibility of such dosage should be used.

The choice of the starting dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. A dose adjustment to the next dose level can be made after 4 weeks, if necessary (see section "Pharmacodynamics"). In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see section "Adverse reactions"), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolemia), who did not achieve their treatment goal on 20 mg, and who will be under close supervision (see section "Administration details"). Specialist supervision is recommended when initiating the administration of the medicinal product at a dose of 40 mg.
Prevention of cardiovascular events
In a study of the reduction of cardiovascular risk, the medicinal product was used at a dose of 20 mg per day (see section "Pharmacodynamics").
Elderly patients
The recommended starting dose for patients aged > 70 years is 5* mg (see section "Administration details"). No other dose adjustment is required in relation to age.
* Since the tablet is not divided, if the dosage is less than 10 mg, rosuvastatin preparations with the possibility of such dosage should be used.

Patients with renal insufficiency
No dose adjustment is necessary in patients with mild to moderate renal impairment.
The recommended starting dose is 5* mg in patients with moderate renal impairment (creatinine clearance < 60 ml/min).
* Since the tablet is not divided, if the dosage is less than 10 mg, rosuvastatin preparations with the possibility of such dosage should be used.

The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of the medicinal product Ozalex® in patients with severe renal impairment is contraindicated at any doses (see sections "Pharmacokinetics" and "Contraindications").
Patients with hepatic impairment
There was no increase in systemic exposure to rosuvastatin in patients with hepatic impairment with Child-Pugh scores of 7 or below. However, increased systemic exposure was observed in subjects with Child-Pugh scores of 8 and 9 (see section "Pharmacokinetics"). In these patients an assessment of renal function should be considered (see section "Administration details"). There is no experience of using the medicinal product in subjects with Child-Pugh scores above 9. The medicinal product Ozalex® is contraindicated in patients with active liver disease (see section "Contraindications").
Race
Patients of the Mongoloid race demonstrated an increased systemic exposure of the medicinal product (see sections "Pharmacokinetics", "Contraindications" and "Administration details"). The recommended starting dose for patients of the Mongoloid race is 5 mg; a dose of 40 mg is contraindicated in such patients.
Genetic polymorphism
Certain types of genetic polymorphism can lead to increased rosuvastatin exposure (see section "Pharmacokinetics"). For patients who are known to have such specific types of polymorphisms, a lower daily dose of the medicinal product Ozalex® is recommended.
Patients with pre-disposing factors to myopathy
The recommended starting dose in patients with predisposing factors to myopathy is 5* mg (see section "Administration details").

* Since the tablet is not divided, if the dosage is less than 10 mg, rosuvastatin preparations with the possibility of such dosage should be used.

The 40 mg dose is contraindicated in some of these patients (see section “Contraindications).
Concomitant administration
Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased upon concomitant administration of the medicinal product Ozalex® with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. cyclosporine and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir and/or tipranavir; see sections “Administration details” and “Interaction with other medical products and other forms of interaction”). Whenever possible, alternative medicinal products should be considered, and, if necessary, therapy with the medicinal product Ozalex® temporarily discontinued. If concomitant use of these medicinal products with the medicinal product Ozalex® is unavoidable, the benefit and risk of concomitant use should be carefully weighed and appropriate dose adjustment of the medicinal product Ozalex® should be made (see section "Interaction with other medical products and other forms of interaction").

Children.
The use of the medicinal product in children should only be carried out by specialists.
Children and adolescents 6 to 17 years of age (Tanner Stage < II-V)
Heterozygous familial hypercholesterolemia
In children and adolescents with heterozygous familial hypercholesterolemia the usual starting dose is 5* mg daily.
* Since the tablet is not divided, if the dosage is less than 10 mg, rosuvastatin preparations with the possibility of such dosage should be used.

- In children 6 to 9 years of age with heterozygous familial hypercholesterolemia, the usual dose is 5 mg to 10 mg orally once daily. Safety and efficacy of the medicinal product used at doses greater than 10 mg have not been studied in this population.
- In children 10 to 17 years of age with heterozygous familial hypercholesterolemia, the usual dose is 5 mg to 20 mg orally once daily. Safety and efficacy of the medicinal product used at doses greater than 20 mg have not been studied in this population.

Titration should be conducted according to the individual response and tolerability of the medicinal product in the child, as recommended by the pediatric treatment recommendations (see section “Administration details”). Prior to initiation of rosuvastatin treatment, children and adolescents should be placed on a standard cholesterol-lowering diet which should be continued during rosuvastatin treatment.
Homozygous familial hypercholesterolemia
In children 6 to 17 years of age with homozygous familial hypercholesterolemia, the recommended maximum dose is 20 mg once daily.
A starting dose of 5 mg to 10 mg once daily depending on age, bodyweight and prior statin use is recommended. Titration to the maximum dose of 20 mg once daily should be conducted according to the individual response and tolerability of the child, as recommended by the pediatric treatment recommendations (see section “Administration details”). Prior to initiation of rosuvastatin treatment, children and adolescents should be placed on a standard cholesterol-lowering diet which should be continued during treatment.
There is limited experience with doses over 20 mg in the treatment of this population.
40 mg tablets should not be used in children.
Children under 6 years of age
The safety and efficacy of the medicinal product in children under 6 years of age have not been studied. Therefore, the medicinal product Ozalex® is not recommended for use in children under 6 years of age.

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 should be instituted as required. Liver function and CK levels should be monitored. Hemodialysis is unlikely to be of benefit.

Adverse reactions.
The frequency category is defined as follows: very common (≥ 1/10); common (≥ 1/100 – < 1/10); uncommon (≥ 1/1000 – < 1/100); rare (≥ 1/10000 – < 1/1000); very rare: (< 1/10000); frequency unknown (cannot be estimated from the available data).
Blood and lymphatic system disorders: rare – thrombocytopenia.
Immune system disorders: rare – hypersensitivity reactions including angioedema.
Endocrine disorders: common – diabetes mellitus*.
Psychiatric disorders: frequency unknown – depression.
Nervous system disorders: common – headache, dizziness; very rare – polyneuropathy, memory loss; frequency unknown – peripheral neuropathy, sleep disturbances (including insomnia and nightmares), myasthenia gravis.
Eye disorders.
Frequency unknown: ocular myasthenia.
Respiratory, thoracic and mediastinal disorders: frequency unknown – cough, shortness of breath.
Gastro-intestinal disorders: common – constipation, nausea, abdominal pain; rare – pancreatitis; frequency unknown – diarrhea.
Hepatobiliary disorders: rare – increased hepatic transaminases; very rare – jaundice, hepatitis.
Skin and subcutaneous tissue disorders: uncommon – pruritus, rash, urticaria; frequency unknown – Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS).
Musculo-skeletal and connective tissue disorders: common – myalgia; rare – myopathy (including myositis), rhabdomyolysis, lupus-like syndrome, muscle rupture; very rare – arthralgia; frequency unknown – tendon disorders, sometimes complicated by rupture, immune-mediated necrotising myopathy.
Renal and urinary disorders: very rare – hematuria.
Reproductive system and breast disorders: very rare – gynecomastia.
General disorders and administration site conditions: common – asthenia; frequency unknown – edema.
*The frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/l, BMI > 30 kg/m^2, elevated triglycerides, history of hypertension).

As with other HMG-CoA inhibitors, the incidence of adverse reactions tends to depend on the dose.
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 times during the use of the medicinal product at doses of 10 mg and 20 mg, and in approximately 3 % of patients at 40 mg doses. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreased or disappeared 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.
Hematuria has been observed in patients treated with rosuvastatin and clinical trial data show that its occurrence is low.
Skeletal muscle effects
Effects on skeletal muscle such as myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with or 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 higher than ULN), treatment should be discontinued (see section “Administration details”).
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, isolated cases of interstitial lung disease, especially with long-term therapy (see section "Administration details").
The frequency of reports of rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose of the medicinal product.
Children
Creatine kinase elevations >10 times higher than 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 (see section "Administration details"), however, the safety profile of rosuvastatin in children and adolescents was similar to that of adults.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua/.

Shelf-life.
2 years.

Storage conditions.
Store at a temperature not more than 25 °C.
Keep out of reach of children.

Package.
Tablets of 10 mg: 14 tablets are in a blister. 2 or 6 blisters are in carton package.
Tablets of 20 mg and 40 mg: 14 tablets are in a blister. 2 blisters are in carton package.

Conditions of supply.
By prescription.

Manufacturer.
LLC "KUSUM PHARM".

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.

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