Lipirose® OBP

Rosuvastatin

FORMS AND PRESENTATION

Lipirose® OBP 10: Film coated tablets: Box of 30.

Lipirose® OBP 20: Film coated tablets: Box of 30.

COMPOSITION:

Lipirose® OBP 10: Each film coated tablet contains Rosuvastatin Calcium equivalent to Rosuvastatin 10 mg.

Excipients: microcrystalline cellulose, lactose, calcium carbonate, povidone, polysorbate, croscarmellose sodium, magnesium stearate, hydroxy propyl methyl cellulose, polyethylene glycol, talc, titanium dioxide.

Lipirose® OBP 20: Each film coated tablet contains Rosuvastatin Calcium equivalent to Rosuvastatin 20 mg.

Excipients: microcrystalline cellulose, lactose, calcium carbonate, povidone, polysorbate, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, sodium bicarbonate, methacrylic acid and ethyl acrylate copolymer, talc, titanium dioxide, red iron oxide, yellow iron oxide.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Lipid modifying agents.

ATC code: C10AA07.

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.

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I. Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

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.
- Age and sex: there was no clinically relevant 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.
- 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 hemodialysis 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.

Pediatric population: the pharmacokinetic parameters in pediatric patients with heterozygous familial hypercholesterolemia aged 10 to 17 years have not been fully characterised. A small pharmacokinetic study with Rosuvastatin in 18 pediatric patients demonstrated that exposure in pediatric patients appears comparable to exposure in adult patients. In addition, the results indicate that a large deviation from dose proportionality is not expected.

INDICATIONS

- Treatment of hypercholesterolemia:

Adults, adolescents and children aged 10 years or older with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Homozygous familial hypercholesterolemia 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.

CONTRAINDICATIONS

Rosuvastatin is contraindicated:

- in patients with hypersensitivity to Rosuvastatin or to any of the excipients.
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN).
- in patients with severe renal impairment (creatinine clearance <30 ml/min).
- in patients with myopathy.
- in patients receiving concomitant Ciclosporin.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

PRECAUTIONS

- Skeletal muscle effects: effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin-treated patients with all doses. Very rare cases of rhabdomyolysis have been reported with the use of Ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use.

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.

- Liver effects: as with other HMG-CoA reductase inhibitors, Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. In patients with secondary hypercholesterolemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin.
- Protease inhibitors: the concomitant use with protease inhibitors is not recommended.
- 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. 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: in patients with fasting glucose 5.6 to 6.9 mmol/L, treatment with Rosuvastatin has been associated with an increased risk of diabetes mellitus.
- Pediatric population: the evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in pediatric patients 10 to 17 years of age taking Rosuvastatin is limited to a one-year period. After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. The clinical trial experience in children and adolescent patients is limited and the long-term effects of Rosuvastatin (>1 year) on puberty are unknown.

PREGNANCY AND LACTATION

Rosuvastatin is contraindicated in pregnancy and lactation.

Women of child bearing potential should use appropriate contraceptive measures.

Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

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

DRUG INTERACTIONS

- Ciclosporin: during concomitant treatment with Rosuvastatin and Ciclosporin, Rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Concomitant administration did not affect plasma concentrations of Ciclosporin.
- Vitamin K antagonists: as with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of Rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g. Warfarin or another Coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of Rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.
- Ezetimibe: concomitant use of Rosuvastatin and Ezetimibe resulted in no change to AUC or C_{max} for either drug. However, a pharmacodynamic interaction, in terms of adverse effects, between Rosuvastatin and Ezetimibe cannot be ruled out.
- Gemfibrozil and other lipid-lowering products: concomitant use of Rosuvastatin and Gemfibrozil resulted in a 2-fold increase in Rosuvastatin C_{max} and AUC. Based on data from specific interaction studies, no pharmacokinetic relevant interaction with Fenofibrate is expected, however a or equal to pharmacodynamic interaction may occur. Gemfibrozil, Fenofibrate, other fibrates and lipid

lowering doses (> or equal to 1g/day) of Niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. These patients should also start with the 5 mg dose.

- Protease inhibitors: although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase Rosuvastatin exposure. In a pharmacokinetic study, co-administration of 20 mg Rosuvastatin and a combination product of two protease inhibitors (400 mg Lopinavir / 100 mg Ritonavir) in healthy volunteers was associated with an approximately two-fold and five-fold increase in Rosuvastatin steady-state $AUC_{(0-24)}$ and C_{max} respectively. Therefore, concomitant use of Rosuvastatin in HIV patients receiving protease inhibitors is not recommended.

- Antacid: the simultaneous dosing of Rosuvastatin 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 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 (0-t) and a 30% decrease in C_{max} of Rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

- Oral contraceptive / hormone replacement therapy (HRT): concomitant use of Rosuvastatin and an oral contraceptive resulted in an increase in Ethinyl Estradiol and Norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant Rosuvastatin and HRT and 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: based on data from specific interaction studies no clinically relevant interaction with Digoxin is expected.

- 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. 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). Concomitant administration of Itraconazole (an inhibitor of CYP3A4) and Rosuvastatin resulted in a 28% increase in AUC of Rosuvastatin. This small increase is not considered clinically significant. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected.

ADVERSE EFFECTS

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

The frequencies of adverse events are ranked according to the following: common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Immune system disorders: rare: hypersensitivity reactions including angioedema.

Endocrine disorders: common: diabetes mellitus.

Nervous system disorders: common: headache, dizziness.

Gastrointestinal disorders: common: constipation, nausea, abdominal pain; rare: pancreatitis.

Skin and subcutaneous tissue disorders: uncommon: pruritus, rash and urticaria.

Musculoskeletal, connective tissue and bone disorders: common: myalgia; rare: myopathy (including myositis) and rhabdomyolysis.

General disorders: common: asthenia.

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

Renal effects: proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg. 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. Hematuria has been observed in patients treated with Rosuvastatin and clinical trial data show that the occurrence is low.

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

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.

Post marketing experience: in addition to the above, the following adverse events have been reported during post marketing experience for Rosuvastatin:

Nervous system disorders: very rare: polyneuropathy, memory loss.

Respiratory, thoracic and mediastinal disorders: not known: cough, dyspnoea.

Gastrointestinal disorders: not known: diarrhea.

Hepatobiliary disorders: very rare: jaundice, hepatitis; rare: increased transaminases.

Skin and subcutaneous tissue disorders: not known: Stevens-Johnson syndrome.

Musculoskeletal disorders: very rare: arthralgia.

Renal disorders: very rare: hematuria.

General disorders and administration site conditions: not known: edema.

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

DOSAGE AND ADMINISTRATION

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dose should be individualized according to the goal of therapy and patient response, using current consensus guidelines. Lipirose® OBP may be given at any time of day, with or without food.

- Treatment of hypercholesterolemia:

The recommended start dose is 5 mg 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. A dose adjustment to the next dose level can be made after 4 weeks, if necessary.

- Prevention of cardiovascular events:

In the cardiovascular events risk reduction study, the dose used was 20 mg daily.

- Pediatric population:

Pediatric use should only be carried out by specialists.

Children and adolescents 10 to 17 years of age (boys Tanner Stage II and above, and girls who are at least 1 year post-menarche): in children and adolescents with heterozygous familial hypercholesterolemia the usual start dose is 5 mg daily. The usual dose range is 5-20 mg orally once daily. Titration should be conducted according to the individual response and tolerability in pediatric patients, as recommended by the pediatric treatment recommendations. Children and adolescents should be placed on standard cholesterol-lowering diet before Lipirose® OBP treatment initiation; this diet should be continued during Lipirose® treatment. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

Children younger than 10 years: experience in children younger than 10 years is limited to a small number of children (aged between 8 and 10 years) with homozygous familial hypercholesterolemia. Therefore, Lipirose® OBP is not recommended for use in children younger than 10 years.

- Use in the elderly:

A start dose of 5 mg is recommended in patients >70 years. 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 of <60 ml/min). The use of Lipirose® OBP in patients with severe renal impairment is contraindicated for all doses.

- Dosage in patients with hepatic impairment:

There was no increase in systemic exposure to Lipirose® OBP 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. In these patients an assessment of renal function should be considered. There is no experience in subjects with Child-Pugh scores above 9. Lipirose® OBP is contraindicated in patients with active liver disease.

- Dosage in patients with pre-disposing factors to myopathy:

The recommended start dose is 5 mg in patients with predisposing factors to myopathy.

OVERDOSAGE

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

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: May 2018.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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