

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rosetemib S.K. 5 mg/10 mg

Rosetemib S.K. 10 mg/10 mg

Rosetemib S.K. 20 mg/10 mg

Rosetemib S.K. 40 mg/10 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rosetemib S.K 5 mg/10 mg: Each film-coated tablet contains 5 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg ezetimibe.

Rosetemib S.K 10 mg/10 mg: Each film-coated tablet contains 10 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg ezetimibe.

Rosetemib S.K 20 mg/10 mg: Each film-coated tablet contains 20 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg ezetimibe.

Rosetemib S.K 40 mg/10 mg: Each film-coated tablet contains 40 mg of rosuvastatin (as rosuvastatin calcium) and 10 mg ezetimibe.

Excipients with known effect:

Each Rosetemib S.K 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg film-coated tablets contain 200.5 mg of lactose monohydrate and 1.669 mg of sodium.

Rosetemib S.K 40 mg/10 mg: Each film-coated tablet contains 205.5 mg of lactose (as lactose monohydrate) and 1.669 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Rosetemib S.K 5 mg/10 mg film-coated tablets

Light yellow, round, biconvex film-coated tablets with "EL 5" embossed on one side.

Rosetemib S.K 10 mg/10 mg film-coated tablets

Beige, round, biconvex film coated tablets with "EL 4" embossed on one side.

Rosetemib S.K 20 mg/10 mg film-coated tablets

Yellow, round, biconvex film coated tablets with "EL 3" embossed on one side.

Rosetemib S.K 40 mg/10 mg film-coated tablets

White, round, biconvex film coated tablets with "EL 2" embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia/Homozygous Familial Hypercholesterolaemia (HoFH)

ROSETEMIB S.K is indicated for substitution therapy in adult patients who are adequately

controlled with rosuvastatin and ezetimibe given concurrently at the same dose level as in the fixed combination, but as separate products, as adjunct to diet for treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or homozygous familial hypercholesterolaemia.

4.2 Posology and method of administration

Posology

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Rosetemib S.K.

Rosetemib S.K is not suitable for initial therapy.

When Rosetemib S.K is indicated for patients not controlled by statin alone, the dose of Rosetemib S.K should be individualized according to the target lipid levels and the patient's response.

When Rosetemib S.K is indicated for patients who are adequately controlled with rosuvastatin and ezetimibe given concurrently at the same dose level as in the fixed combination, but as separate product, treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Patient should use the strength corresponding to their previous treatment.

The recommended dose is one Rosetemib S.K tablet daily.

Co-administration with bile acid sequestrants

Dosing of Rosetemib S.K should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant (see section 4.5).

Paediatric population

The safety and efficacy of Rosetemib S.K in children below the age of 18 years have not yet been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly

A start dose of 5 mg rosuvastatin is recommended in patients >70 years (see section 4.4). The combination is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment (Child Pugh score 5 to 6). Treatment with Rosetemib S.K is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction (see sections 4.4 and 5.2). Rosetemib S.K is contraindicated in patients with active liver disease (see section 4.3).

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment.

The recommended start dose is rosuvastatin 5 mg in patients with moderate renal impairment (creatinine clearance <60 ml/min).

The 40 mg/10 mg dose is contraindicated in patients with moderate renal impairment. The use of Rosetemib S.K in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Race

Increased systemic exposure of rosuvastatin has been seen in Asian subjects (see sections 4.4 and 5.2). The recommended start dose is rosuvastatin 5 mg for patients of Asian ancestry. The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used

to start the treatment or to modify the dose. Rosetemib S.K_40 mg/10 mg film-coated tablets are contraindicated in these patients (see sections 4.3 and 5.2).

Genetic polymorphisms

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

Dosage in patients with pre-disposing factors to myopathy

The recommended start dose is rosuvastatin 5 mg in patients with pre-disposing factors to myopathy (see section 4.4). The fixed dose combination is not suitable for initial therapy. Monocomponent preparations should be used to start the treatment or to modify the dose. Rosetemib S.K_40 mg/10 mg film-coated tablets are contraindicated in some of these patients (see section 4.3).

Concomitant therapy

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when Rosetemib S.K_is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g. ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir; see sections 4.4 and 4.5).

Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing Rosetemib S.K_therapy. In situations where co-administration of these medicinal products with Rosetemib S.K_is unavoidable, the benefit and the risk of concurrent treatment and rosuvastatin dosing adjustments should be carefully considered (see section 4.5).

Method of administration

Route of administration is oral. Rosetemib S.K_can be administered at any time of the day, with or without food. The tablet should be swallowed whole with a drink of water.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Pregnancy, breast-feeding and in women of childbearing potential not using appropriate contraceptive measures (see section 4.6).
- Active liver disease or unexplained persistent elevations in serum transaminases and any serum transaminase elevation exceeding 3x the upper limit of normal (ULN) (see section 4.4).
- In patients with severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).
- In patients with myopathy (see section 4.4).
- In patients receiving concomitant ciclosporin (see section 4.5).

The 40 mg / 10 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- Moderate renal impairment (creatinine clearance <60 ml/min).
- Hypothyroidism.
- Personal or family history of hereditary muscular disorders.
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate.
- Alcohol abuse.
- Situations where an increase in plasma levels of rosuvastatin may occur.
- Asian patients.
- Concomitant use of fibrates.

(see sections 4.4, 4.5 and 5.2)

4.4 Special warnings and precautions for use

Skeletal muscle effects

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in particular with doses >20 mg. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis.

If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level, Rosetemb S.K. and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with Rosetemb S.K. should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Rosetemb S.K. should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Creatine kinase measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before treatment

Caution should be exercised in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment,
- hypothyroidism,
- personal or family history of hereditary muscular disorders,
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate,
- alcohol abuse,
- age >70 years,
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2),
- concomitant use of fibrates.

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (>5xULN) treatment should not be started.

Whilst on treatment

Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are \leq 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring of the patient. Routine monitoring of CK levels in asymptomatic patients is not warranted.

There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of

patients dosed with rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, cyclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics.

Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose of rosuvastatin is contraindicated with concomitant use of a fibrate (see sections 4.5 and 4.8).

Rosetemib S.K. should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Liver effects

In controlled co-administration trials in patients receiving ezetimibe with statin, consecutive transaminase elevations ($\geq 3 \times$ the upper limit of normal [ULN]) have been observed.

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with rosuvastatin.

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, Rosetemib S.K. is not recommended (see section 5.2).

Liver disease and alcohol

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.

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 4.8). The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI > 30 kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

In the JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/l.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Severe cutaneous adverse reactions

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

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

Protease inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of Rosetemib S.K_ in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of rosuvastatin is adjusted (see sections 4.2 and 4.5).

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established (see above and sections 4.3 and 4.5).

If cholelithiasis is suspected in a patient receiving Rosetemib S.K_ and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

Anticoagulants

If Rosetemib S.K_ is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Fusidic acid

Rosetemib S.K_ must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient 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 Rosetemib S.K_ and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Race

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

Paediatric population

Rosetemib S.K_ is not recommended for use in children and adolescents of less than 18 years of age, due to insufficient data on safety and efficacy.

Rosetemib S.K_ contains lactose and sodium

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations:

Ciclosporin: Concomitant administration of Rosetemib S.K_ with ciclosporin is contraindicated because of the rosuvastatin (see section 4.3). During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). Concomitant administration did not affect plasma concentrations of ciclosporin.

In a study of eight post-renal transplant patients with creatinine clearance of >50 ml/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3 to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted.

Not-recommended combinations:

Fibrates and other lipid-lowering products: In patients receiving fenofibrate and ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8). If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8). Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively).

Co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile, but not in all species (see section 5.3). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see section 4.4).

Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses ($>$ or equal to 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. The 40 mg/10 mg dose is contraindicated with concomitant use of a fibrate (see sections 4.3 and 4.4).

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see Table 1). In a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and C_{max} respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4 and 4.5 Table 1).

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 4.2, 4.4 and 4.5 Table 1).

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

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

Other interactions:

Cytochrome P450 enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

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.

Colestyramine: Concomitant colestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to colestyramine may be lessened by this interaction (see section 4.2).

Anticoagulants, Vitamin K antagonists: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased

International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If Rosetemib S.K_{is} is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

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.

Clopidogrel: Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold (C_{max}) after administration of 300 mg clopidogrel dose, and by 1.4-fold (AUC) without effect on C_{max} after repeated administration of 75 mg clopidogrel dose.

Ticagrelor: Ticagrelor might affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. Although the exact mechanism is not known, in some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis.

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 women 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. In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Other medicinal products: Based on data from specific interaction studies with rosuvastatin no clinically relevant interaction with digoxin is expected. In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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

Interactions requiring rosuvastatin dose adjustments (see also Table 1): When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses should be adjusted. The maximum daily dose should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of rosuvastatin with combination ritonavir/atazanavir (3.1-fold increase).

Table 1 Effect of co-administered medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Regorafenib 160 mg, OD, 14 days	5 mg single dose	3.8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Grazoprevir 200 mg/ elbasvir 50 mg OD, 11 days	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/ pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Clopidogrel 300 mg loading dose, followed by 75 mg OD, 7 days	40 mg, OD	2-fold ↑, 1.4-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as “↑”, no change as “↔”, decrease as “↓”.
**Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio
OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

4.6 Fertility, pregnancy and lactation

Rosetemib S.K is contraindicated during pregnancy and breast-feeding (see section 4.3). Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy

No clinical data are available on the use of ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofetal development, birth or postnatal development (see section 5.3).

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 Rosetemib S.K, treatment should be discontinued immediately.

Breast-feeding

Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans (see section 4.3).

Fertility

No clinical trial data are available on the effects of ezetimibe or rosuvastatin on human fertility. Ezetimibe had no effects on the fertility of male or female rats, rosuvastatin at higher doses showed testicular toxicity in monkeys and dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

4.8 Undesirable effects

Summary of safety profile

Adverse drug reactions previously reported with one of the individual components (ezetimibe or rosuvastatin) may be potential undesirable effects with Rosetemib S.K.

In clinical studies of up to 112 weeks duration, ezetimibe 10 mg daily was administered alone in 2,396 patients, with a statin in 11,308 patients or with fenofibrate in 185 patients.

Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between ezetimibe and placebo.

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.

Tabulated list of adverse reactions

The frequencies of adverse reactions are ranked according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

<u>MedDRA system organ class</u>	<u>Frequency</u>	<u>Undesirable effect</u>
Blood and lymphatic system disorders	rare	thrombocytopenia ²
	not known	thrombocytopenia ⁵
Immune system disorders	rare	hypersensitivity reactions including angioedema ²
	not known	hypersensitivity (including rash, urticaria, anaphylaxis and angioedema) ⁵
Endocrine disorders	common	diabetes mellitus ^{1, 2}
Metabolism and nutrition disorders	uncommon	decreased appetite ³
Psychiatric disorders	not known	depression ^{2, 5}
Nervous system disorders	common	headache ^{2, 4} , dizziness ²
	uncommon	paraesthesia ⁴
	very rare	polyneuropathy ² , memory loss ²
	not known	peripheral neuropathy ² , sleep disturbances (including insomnia and nightmares) ² , dizziness ⁵ ; paraesthesia ⁵ , myasthenia gravis ²
Eye disorders	not known	ocular myasthenia ²
Vascular disorders	uncommon	hot flush ³ , hypertension ³
Respiratory, thoracic and mediastinal disorders	uncommon	cough ³
	not known	cough ² , dyspnoea ^{2,5}
Gastrointestinal disorders	common	constipation ² , nausea ² , abdominal pain ^{2,3} , diarrhoea ³ , flatulence ³
	uncommon	dyspepsia ³ ; gastroesophageal reflux disease ³ ; nausea ³ , dry mouth ⁴ ; gastritis ⁴
	rare	pancreatitis ²
	not known	diarrhoea ² , pancreatitis ⁵ ; constipation ⁵
Hepatobiliary disorders	rare	increased hepatic transaminases ²
	very rare	jaundice ² , hepatitis ²
	not known	hepatitis ⁵ , cholelithiasis ⁵ , cholecystitis ⁵
	uncommon	pruritus ^{2, 4} , rash ^{2, 4} , urticaria ^{2,4}

Skin and subcutaneous tissue disorders	not known	Stevens Johnson syndrome ² , erythema multiforme ⁵ , drug reaction with eosinophilia and systemic symptoms (DRESS) ²
Musculoskeletal and connective tissue disorders	common	myalgia ^{2, 4}
	uncommon	arthralgia ³ ; muscle spasms ³ ; neck pain ³ , back pain ⁴ ; muscular weakness ⁴ ; pain in extremity ⁴
	rare	myopathy (including myositis) ² , rhabdomyolysis ² , lupus-like syndrome, muscle rupture
	very rare	arthralgia ²
	not known	immune-mediated necrotising myopathy ² , tendon disorders, sometimes complicated by rupture ² , myalgia ⁵ ; myopathy/rhabdomyolysis ⁵ (see section 4.4)
Renal and urinary disorders	very rare	haematuria ²
Reproductive system and breast disorders	very rare	gynaecomastia ²
Investigations	common	ALT and/or AST increased ⁴
	uncommon	ALT and/or AST increased ³ ; blood CPK increased ³ ; gamma-glutamyl transferase increased ³ ; liver function test abnormal ³
General disorders and administration site conditions	common	asthenia ² , fatigue ³
	uncommon	chest pain ³ , pain ³ , asthenia ⁴ ; oedema peripheral ⁴
	not known	oedema ² , asthenia ⁵

¹ Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/l, BMI > 30 kg/m², raised triglycerides, history of hypertension) – for rosuvastatin.

² Adverse reaction profile for rosuvastatin based on data from clinical studies and/ or extensive post-marketing experience.

³ Ezetimibe in monotherapy. Adverse reactions were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159).

⁴ Ezetimibe co administered with a statin. Adverse reactions were observed in patients with ezetimibe co-administered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361).

⁵ Additional adverse reactions of ezetimibe, reported in post-marketing experience (with or without statin).

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

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

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

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported 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 (>5xULN), treatment should be discontinued (see section 4.4).

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

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

The following adverse events have been reported with some statins:

- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

Laboratory values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between ezetimibe (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section 4.4).

In clinical trials, CPK >10 X ULN was reported for 4 of 1,674 (0.2%) patients administered ezetimibe alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered ezetimibe and a statin vs 4 of 929 (0.4%) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone) (see section 4.4).

Paediatric population

The safety and efficacy of Rosetemb S.K. in children below the age of 18 years have not yet been established (see section 5.1).

Rosuvastatin: 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.

Ezetimibe: In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n = 138), elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥ 10 X ULN). No cases of myopathy were reported.

In a separate study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of ALT and/or AST (≥ 3 X ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10 X ULN). No cases of myopathy were reported. These trials were not suited for comparison of rare adverse drug reactions.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

4.9 Overdose

In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. In animals, no toxicity was observed after single oral doses of 5,000 mg/kg of ezetimibe in rats and mice and 3,000 mg/kg in dogs.

A few cases of overdosage with ezetimibe have been reported: most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Rosuvastatin

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 in combination with other lipid modifying agents, rosuvastatin and ezetimibe

ATC code: C10BA06

Mechanism of action:

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. Rosetemib S.K_ contains rosuvastatin and ezetimibe, two lipid-lowering compounds with complementary mechanisms of action. Rosetemib S.K_ reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol synthesis and absorption.

Ezetimibe

Mechanism of action

Ezetimibe inhibits the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active, and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g. statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

Pharmacodynamic effects

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [¹⁴C]-cholesterol with no

effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

Clinical efficacy and safety

In controlled clinical studies, ezetimibe, either as monotherapy or co-administered with a statin significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

Primary hypercholesterolaemia

In a double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82%), significantly more patients randomised to ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72% and 19%, respectively. The corresponding LDL-C reductions were significantly different (25% and 4% for ezetimibe versus placebo, respectively). In addition, ezetimibe, added to on-going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10% or 0% from baseline, respectively.

In two, double-blind, randomised placebo-controlled, 12-week studies in 1,719 patients with primary hypercholesterolaemia, ezetimibe 10 mg significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. In addition, ezetimibe had no effect on the plasma concentrations of fat-soluble vitamins A, D, and E, no effect on prothrombin time, and, like other lipid-lowering agents, did not impair adrenocortical steroid hormone production.

Rosuvastatin

Mechanism of action

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

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

Pharmacodynamic effects

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 (see Table 2). Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Table 2: Dose response in patients with primary hypercholesterolaemia (type IIa and IIb) (adjusted mean percent change from baseline)

Dose	N	LDL-C	Total-C	HDL-C	TG	nonHDL-C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

A therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy and safety

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

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

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

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

Rosuvastatin/ezetimibe combination

Clinical efficacy and safety

Combination rosuvastatin with ezetimibe 10 mg enabled greater decreases in LDL cholesterol and allowed more patients to achieve LDL cholesterol goals. This has been demonstrated in a clinical study with 469 patients, who were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks.

The combination of rosuvastatin/ezetimibe reduced LDL cholesterol significantly more than rosuvastatin (3.4 mmol/l vs. 2.8 mmol/l). Other components of the lipid/lipoprotein profile were also significantly ($p < 0.001$) improved with rosuvastatin/ezetimibe. Both treatments generally were well tolerated.

Another 6-week, randomized, double-blind, parallel-group, clinical trial evaluated the safety and efficacy of ezetimibe (10 mg) added to stable rosuvastatin therapy versus up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg.

The study population included 440 subjects at moderately high/high risk of coronary heart disease with low-density lipoprotein (LDL) cholesterol levels higher than the National Cholesterol Education Program Adult Treatment Panel III recommendations (<100 mg/dl for moderately high/high-risk subjects without atherosclerotic vascular disease or <70 mg/dl for high-risk subjects with atherosclerotic vascular disease). Pooled data demonstrated that ezetimibe added to

stable rosuvastatin 5 mg or 10 mg reduced LDL cholesterol by 21%. In contrast, doubling rosuvastatin to 10 mg or 20 mg reduced LDL cholesterol by 5.7%. Individually, ezetimibe plus rosuvastatin 5 mg reduced LDL cholesterol more than did rosuvastatin 10 mg, and ezetimibe plus rosuvastatin 10 mg reduced LDL cholesterol more than did rosuvastatin 20 mg. Compared to rosuvastatin up-titration, ezetimibe add-on achieved significantly greater attainment of LDL cholesterol levels of <70 or <100 mg/dl, and <70 mg/dl in all subjects; produced significantly greater reductions in total cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B; and resulted in similar effects on other lipid parameters. In conclusion, compared to up-titration doubling of the rosuvastatin dose, ezetimibe 10 mg added to stable rosuvastatin 5 mg or 10 mg produced greater improvements in many lipid parameters. A multi-center, randomized, double blind, double-dummy, parallel arms, active-controlled study (LPS15021) was conducted in 452 patients with primary hypercholesterolaemia and at high risk (HR) or very high risk (VHR) for cardiovascular disease (CVD) and who are not adequately controlled with a 10 mg or 20 mg stable daily dose of rosuvastatin or equipotent statin, without any other lipid-modifying therapy (LMT).

During the 6-week double-blind treatment phase:

- 208 patients with HR were randomized to receive rosuvastatin 10 mg plus ezetimibe 10 mg as fixed dose combination (FDC) (R10/E10, n=104) or rosuvastatin 20 mg (R20, n=104).
- 244 patients with VHR were randomized to receive rosuvastatin 20 mg plus ezetimibe 10 mg as FDC (R20/E10, n=82) or rosuvastatin 40 mg plus ezetimibe 10 mg as FDC (R40/E10, n=79) or rosuvastatin 40 mg (R40, n=83).

The primary endpoint was the percent change in calculated LDL-C, from baseline to Week 6 in the modified intent-to-treat (mITT) population.

In the VHR stratum, the LS (least squares) mean change in LDL-C from baseline to Week 6 was -34.28% for the R40/E10 group, -26.90% for the R20/E10 group and -14.62% for the R40 group. Superiority of FDC (R40/E10 or R20/E10) over R40 was demonstrated with LS mean differences of -19.66% ($p < 0.001$) and -12.28% ($p = 0.015$), respectively.

In the HR stratum, greater reduction in LDL-C from baseline to Week 6 was also observed for the FDC: LS mean changes of -27.02% for the R10/E10 group and -21.82% for the R20 group. A clinically relevant decrease in LDL-C for R10/E10 arm was observed, even though statistical superiority of R10/E10 versus R20 could not be demonstrated (LS mean difference of -5.20%; $p = 0.306$).

After exclusion of data from one outlier participant in the R10/E10 arm, the difference in LDL-C percent change between treatment arms was statistically significant in the HR stratum (LS mean difference: R10/E10 versus R20: -8.84%; $p = 0.026$).

Overall safety findings observed in patients treated with all three strengths of Rosetemib S.K_ were in line with known safety profile of rosuvastatin and ezetimibe.

5.2 Pharmacokinetic properties

There is no substantial pharmacokinetic interaction between the two components of this fixed-dose preparation.

Mean AUC and C_{\max} values for total rosuvastatin and ezetimibe were not different between the monotherapy and coadministration groups of rosuvastatin 10 mg and ezetimibe 10 mg.

Absorption

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically-active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{\max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10-mg tablets. Ezetimibe can be administered with or without food.

Rosuvastatin

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

Distribution

Ezetimibe

Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

Rosuvastatin

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

Ezetimibe

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Rosuvastatin

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.

Elimination

Ezetimibe

Following oral administration of ^{14}C -ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and

11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Rosuvastatin

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

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

Special populations:

Hepatic impairment

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic impairment, ezetimibe is not recommended in these patients (see section 4.4).

Rosuvastatin

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.

Renal impairment

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl \leq 30 ml/min/1.73m²), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Rosuvastatin

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Age and gender

Ezetimibe

Plasma concentrations for total ezetimibe are about 2 - fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Rosuvastatin

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults.

Paediatric population

Ezetimibe

The pharmacokinetics of ezetimibe are similar between children ≥ 6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

Rosuvastatin

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

Race

Rosuvastatin

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

Genetic polymorphisms

Rosuvastatin

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

5.3 Preclinical safety data

In co-administration studies with statins and ezetimibe, the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than

observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2,000 times the AUC level for the active metabolites).

The co-administration of statins and ezetimibe was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed.

In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential.

Ezetimibe

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥ 0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1,000 mg/kg/day.

Rosuvastatin

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

Lactose monohydrate
Cellulose, Microcrystalline 102
Croscarmellose Sodium
Hypromellose 2910
Povidone K-29/32
Sodium Laurilsulfate
Magnesium stearate
Silica, Colloidal Anhydrous

Tablet Coating

Rosetemib S.K. 5 mg/10 mg - Opadry Yellow 02F220026 consisting of:

HPMC 2910/Hypromellose (E464)
Titanium dioxide (E171, CI 77891)
Macrogol/PEG (E1521 MW 4000)

Iron oxide yellow (E172, VI 77492)
Talc (E553b)
Iron oxide red (E172, CI 77492)
Purified water

Rosetemib S.K 10 mg/10 mg - Opadry Beige 02F270003 consisting of:

HPMC 2910/Hypromellose (E464)
Iron oxide yellow (E172, VI 77492)
Titanium dioxide (E171, CI 77891)
Iron oxide yellow (E172, VI 77492)
Macrogol/PEG (E1521 MW 4000)
Talc (E553b)
Purified water

Rosetemib S.K 20 mg/10 mg - VIVACOAT PC-2P-308 consisting of:

HPMC 2910/Hypromellose (E464)
Titanium dioxide (E171, CI 77891)
Talc (E553b)
Polyethylen glycol (PEG) (E1521, MW 4000)
Iron oxide yellow (E172, VI 77492)
Purified water

Rosetemib S.K 40 mg/10 mg - Opadry White OY-L-28900 consisting of:

Lactose monohydrate
HPMC 2910/Hypromellose (E464)
Titanium dioxide (E171, CI 77891)
Macrogol/PEG (E1521 MW 4000)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light and moisture.
It is recommended to store at room temperature

6.5 Nature and contents of container

OPA/Al/PVC//Al blisters packed into carton boxes.

Pack sizes of 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
K.S. KIM INTERNATIONAL (SK- PHARMA) LTD., ISRAEL
94 YIGAL ALON STR., TEL-AVIV-YAFO, 6789139

8 Manufactured by:
ELPEN Pharmaceutical Co., Inc.
Marathonos Ave. 95, Pikermi, Attiki, 19009, Greece

9 MARKETING AUTHORISATION NUMBER(S)

Rosetemib S.K. 5 mg/10 mg- 175-16-36802
Rosetemib S.K. 10 mg/10 mg- 175-17-36803
Rosetemib S.K. 20 mg/10 mg- 175-18-36804
Rosetemib S.K. 40 mg/10 mg- 175-19-36805

10 DATE OF REVISION OF THE TEXT

The leaflet was approved in February 2024 according to MOH guidelines

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