Approved Professional Information for Medicines for Human Use:

SUVEMIB

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SUVEMIB 5/10 mg FILM-COATED TABLETS

SUVEMIB 10/10 mg FILM-COATED TABLETS

SUVEMIB 20/10 mg FILM-COATED TABLETS

SUVEMIB 40/10 mg FILM-COATED TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SUVEMIB 5/10 mg film-coated tablets

Each film-coated tablet contains rosuvastatin calcium equivalent to 5 mg rosuvastatin and 10 mg ezetimibe.

SUVEMIB 10/10 mg film-coated tablets

Each film-coated tablet contains rosuvastatin calcium equivalent to 10 mg rosuvastatin and 10 mg ezetimibe.

SUVEMIB 20/10 mg film-coated tablets

Each film-coated tablet contains rosuvastatin calcium equivalent to 20 mg rosuvastatin and 10 mg ezetimibe.

SUVEMIB 40/10 mg film-coated tablets

Each film-coated tablet contains rosuvastatin calcium equivalent to

40 mg rosuvastatin and 10 mg ezetimibe.

Contains sugar (lactose monohydrate)

Each SUVEMIB 5/10 mg film-coated tablet contains 200,5 mg lactose monohydrate.

Each SUVEMIB 10/10 mg film-coated tablet contains 200,5 mg lactose monohydrate.

Each SUVEMIB 20/10 mg film-coated tablet contains 200,5 mg lactose monohydrate.

Each SUVEMIB 40/10 mg film-coated tablet contains 205,54 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

SUVEMIB 5/10 mg film-coated tablets

Light yellow, round (Ø10 mm), biconvex film coated tablets with “EL5” embossed on one side.

SUVEMIB 10/10 mg film-coated tablets

Beige, round (Ø10 mm), biconvex film coated tablets with “EL4” embossed on one side.

SUVEMIB 20/10 mg film-coated tablets

Yellow, round (Ø10 mm), biconvex film coated tablets with “EL3” embossed on one side.

SUVEMIB 40/10 mg film-coated tablets

White, round (Ø10 mm), biconvex film coated tablets with “EL2” embossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SUVEMIB can be taken as substitution therapy in adult patients adequately controlled with the individual medicines given concurrently at the same dose level as in the fixed dose combination, but as separate medicines.

SUVEMIB is indicated in adults for:

Primary hypercholesterolaemia

SUVEMIB is indicated as adjunctive therapy to diet, when response to diet and exercise is inadequate, for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous familial hypercholesterolaemia (HoFH)

SUVEMIB is indicated as adjunctive therapy to diet for the reduction of elevated total-C and LDL-C levels in patients with HoFH.

Prevention of cardiovascular events

SUVEMIB is indicated to reduce the increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease markers such as an elevated high sensitivity C- reactive protein level, age, hypertension, low HDL-C, smoking or family history of premature coronary heart disease.

SUVEMIB is indicated to reduce the risk of non-fatal stroke, non-fatal myocardial infarction and the need for arterial revascularisation in patients who are adequately controlled with the individual medicines given concurrently at the same dose level as in the fixed dose combination, but as separate products.

4.2 Posology and method of administration

Posology

Adults

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should be continued during treatment.

The recommended dose of SUVEMIB is one tablet per day.
The fixed dose combination is not suitable for initial therapy.

Treatment initiation or dose adjustment, if necessary, should only be done with the mono-components. After setting the appropriate doses, the switch to the fixed dose combination of the appropriate strength is possible.

SUVEMIB 5/10 mg, 10/10 mg and 20/10 mg film-coated tablets are not

suitable for the treatment of patients requiring 40 mg dose of rosuvastatin.

The dosage of rosuvastatin should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the start dose. However, if necessary, dose adjustment can be made after 4 weeks.

Primary hypercholesterolaemia

SUVEMIB can be taken as substitution therapy in adult patients adequately controlled with the individual medicines given concurrently at the same dose level as in the fixed dose combination, but as separate medicines.

The usual starting dose is 10 mg of rosuvastatin and 10 mg of ezetimibe once a day. For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg of rosuvastatin may be considered.

Homozygous familial hypercholesterolaemia

SUVEMIB can be taken as substitution therapy in adult patients adequately controlled with the individual medicines given concurrently at the same dose level as in the fixed dose combination, but as separate medicines.

Patients should be established on a dose of 20 mg of rosuvastatin and 10 mg of ezetimibe once a day.

Prevention of Cardiovascular Events

SUVEMIB can be taken as substitution therapy in adult patients adequately controlled with the individual medicines given concurrently at the same dose level as in the fixed dose combination, but as separate medicines.

The usual dose is 20 mg of rosuvastatin and 10 mg of ezetimibe once a day.

Concomitant therapy

Co-administration with bile acid sequestrants

SUVEMIB should be taken either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant (see section 4.5).

Co-administration with gemfibrozil

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant rosuvastatin and gemfibrozil.

If SUVEMIB is taken in combination with gemfibrozil, the dose of SUVEMIB should be limited to 10 mg + 10 mg once daily (see section 4.5).

Co-administration with atazanir and ritonavir, lopinavir and ritonavir or simeprevir

Initiate SUVEMIB therapy with 10 mg + 5 mg once daily. The dose of SUVEMIB should not exceed 10 mg + 10 mg once daily (see sections 4.4 and 4.5).

Co-administration with elbasvir or grazoprevir

The dose of SUVEMIB should not exceed 10 mg + 10 mg once daily (see sections 4.4 and 4.5).

Special populations

Elderly population

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 mono-components and after setting the appropriate doses, the switch to the fixed dose combination of the appropriate strength is possible.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. The use of SUVEMIB in patients with severe renal impairment is contraindicated for all doses.

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Hepatic impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with SUVEMIB 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). SUVEMIB is contraindicated in patients with active liver disease (see section 4.3).

Dosage in Asian patients

Initiation of therapy with SUVEMIB 5/10 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 5 mg + 10 mg, 10 mg + 10 mg or 20 mg + 10 mg once daily (see section 4.4 and 4.5).

SUVEMIB 40/10 mg film-coated tablets are contraindicated in these patients (see sections 4.3 and 5.2).

Paediatric population

The safety and efficacy of SUVEMIB in children below the age of 18 years have not yet been established. Therefore, treatment with SUVEMIB is contraindicated in children (see section 4.3, 4.4 and 5.2).

Method of administration

SUVEMIB is for oral administration.

SUVEMIB should be taken at any time of the day, with or without food.

The tablets should be swallowed whole with water.

4.3 Contraindications

SUVEMIB is contraindicated in:

- Patients with hypersensitivity to rosuvastatin and ezetimibe or to any of the excipients listed in section 6.1

- Moderate to severe hepatic impairment (Child Pugh score 7 or more) (see sections 4.2, 4.4 and 5.2)
- Patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN)
- Concomitant use with ciclosporin (see section 4.5)
- Patients with myopathy secondary to other lipid lowering medicines
- Pregnancy, lactation and in women of childbearing potential, unless they are taking adequate contraceptive precautions (see section 4.6).
- Children as safety and efficacy have not been demonstrated (see section 4.2 and 4.4)
- In patients with severe renal impairment (creatinine clearance < 30 mL/min)
- In patients receiving concomitant combination of sofosbuvir/velpatasvir/voxilaprevir (see section 4.5)
- Patients taking fusidic acid (see sections 4.4 and 4.5)
- Combination with fenofibrate in patients with gall bladder disease (see section 4.4).

SUVEMIB 40/10 mg tablets are contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis.

4.4 Special warnings and precautions for use

Skeletal Muscle Effects

Cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin, as in

SUVEMIB, and with other medicines in this class.

Uncomplicated myalgia has been reported in rosuvastatin treated patients (see sections 4.3 and 4.8).

In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 mg to 40 mg). In post-marketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin, as in SUVEMIB.
As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are higher at the highest marketed dose (40 mg).

The risk of myopathy during treatment with SUVEMIB may be increased in circumstances that increase rosuvastatin medicine levels.

In post-marketing experience with ezetimibe, as in SUVEMIB, cases of myopathy and rhabdomyolysis have been reported. All patients starting therapy with SUVEMIB should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).
SUVEMIB should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level greater than 10 times the ULN indicates myopathy.

Liver effects

In patients receiving ezetimibe with a statin, as in SUVEMIB, consecutive transaminase elevations (≥ 3 x the upper limit of normal [ULN]) have been observed.

It is recommended that liver functions tests be carried out 3 months following the initiation of rosuvastatin 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 hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with SUVEMIB.

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

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 (at least every 3 months) during routine follow-up of patients treated with a dose of 40 mg.

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 results.
If CK levels are significantly elevated at baseline (> 5 x ULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK > 5 x ULN, treatment should not be started.

Before Treatment

SUVEMIB, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age > 70 years
- situations where an increase in plasma levels may occur (see sections 4.5 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 (> 5 x ULN) 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 (> 5 x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5 x ULN). Routine monitoring of CK levels in asymptomatic patients is not warranted.

There have been 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, as in SUVEMIB, and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals,

protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of SUVEMIB and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of SUVEMIB with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

SUVEMIB 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).

Fusidic Acid

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

Race

Rosuvastatin pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see sections 4.2 and 5.2).

Protease inhibitors

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

Interstitial lung disease

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

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established.

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

Anticoagulants

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

Liver disease and alcohol

SUVEMIB should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

Severe Cutaneous Adverse Reactions

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

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

Parasomnias

Statins, as in SUVEMIB, may cause various parasomnias.

Parasomnia is an umbrella term for complex movements or behaviours during sleep, including abnormal dreaming, nightmares (paroniria) and sleepwalking (somnambulism). The Centre for Adverse Reactions Monitoring (CARM) received over 70 reports of various parasomnias over a period of five years. The most frequently reported terms are abnormal dreams, paroniria and sleep disorder. Commonly reported medicine includes statins (see section 4.8)

Endocrine effects

Increases in HbA1c and fasting serum glucose levels have been reported with rosuvastatin, as in SUVEMIB. Although clinical studies

have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if SUVEMIB is administered concomitantly with medicines that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Paediatric population

The safety and efficacy of SUVEMIB in children below the age of 18 years have not yet been established. Therefore, treatment with SUVEMIB is contraindicated in children (see section 4.2, 4.3 and 5.2).

Excipient: lactose monohydrate

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

4.5 Interaction with other medicines and other forms of interaction

Consult the prescribing information of all concomitantly used medicines to obtain further information about their potential interactions with SUVEMIB and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Ciclosporin

During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were reportedly on average 7 times higher than those observed in healthy volunteers (see section 4.3).

Concomitant administration did not affect plasma concentrations of ciclosporin.

Co-administration of SUVEMIB with ciclosporin is contraindicated (see section 4.3).

In a study of 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. In a different study, a renal transplant patient with severe renal insufficiency who was receiving ciclosporin and multiple other medications, reportedly demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in healthy participants, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on Day 7 resulted in a 15 % increase in ciclosporin AUC compared to a single 100 mg dose of ciclosporin alone.

Gemfibrozil and other lipid-lowering medicines

The 40 mg rosuvastatin dose is contraindicated with concomitant use of a fibrate (see sections 4.3 and 4.4).

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax and AUC (see section 4.4). Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur.

Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone.

In patients receiving fenofibrate and ezetimibe, health care providers should be aware of the possible risk of cholelithiasis and gallbladder disease (see section 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-fold 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.

Not-recommended combinations

Protease inhibitors

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see section 4.5 Table). For instance, in a reportedly 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 Cmax 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). 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.

Transporter protein inhibitors

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of SUVEMIB with medicines 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, as in SUVEMIB, treatment should be discontinued throughout the duration of the fusidic acid treatment. See section 4.4.

Other interactions

Antacid

The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

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.

Erythromycin

Concomitant use of rosuvastatin, as in SUVEMIB, and erythromycin resulted in a decrease in AUC and a decrease in Cmax of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes

Results from reported *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, medicine 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).

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.

Concomitant administration of ezetimibe (10 mg once daily) had no effect on bioavailability of warfarin and prothrombin time in a reportedly study of 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 SUVEMIB are added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Oral contraceptive/hormone replacement therapy (HRT)

Concomitant use of rosuvastatin and oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC. These increased plasma levels should be considered when selecting oral contraceptive doses.

Ezetimibe had no effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Colestyramine

Concomitant colestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide). 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).

Statins

No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.

Other medicines

Based on data from reported specific interaction studies, no clinically relevant interaction between rosuvastatin and digoxin is expected.
In reported 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.

Interactions requiring rosuvastatin dose adjustments (see also Table below)

When it is necessary to co-administer rosuvastatin with other medicines known to increase exposure to rosuvastatin, doses should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the expected

increase in exposure (AUC) is approximately 2-fold or higher. 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 medicines, for example a 20 mg dose of rosuvastatin with gemfibrozil (1,9-fold increase), and a 10 mg dose of rosuvastatin with combination atazanavir/ritonavir (3,1-fold increase).

Effect of co-administered medicines on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials		
Interacting medicine 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 ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3,1-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2,1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑

Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1,9-fold ↑
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 ↑
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	28 % ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47 % ↓
Regorafenib 160 mg, OD, 14 days	5 mg single dose	3,8-fold ↑
Simeprevir 150 mg, OD, 7 days	10 mg single dose	2,8-fold ↑
*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		

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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

SUVEMIB is contraindicated in pregnancy and breastfeeding.

Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures. SUVEMIB should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential risk. If the patient becomes pregnant while taking SUVEMIB, therapy should be discontinued, and the patient apprised of the potential hazard to the foetus (see section 4.3).

Pregnancy

No studies on the effect on embryo-foetal development have been conducted with ezetimibe and rosuvastatin in combination, as in SUVEMIB.

Atherosclerosis is a chronic process and discontinuation of lipid-lowering medicines during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolaemia. Cholesterol and other products of cholesterol biosynthesis are essential components for

foetal development (including synthesis of steroids and cell membranes).

Breastfeeding

No studies in lactating animals have been conducted with the combination of ezetimibe and rosuvastatin, as in SUVEMIB.

Studies in rats have shown that ezetimibe and rosuvastatin are excreted in milk. It is not known whether ezetimibe or rosuvastatin is excreted into human breast milk.
Therefore, SUVEMIB is contraindicated in breastfeeding women (see section 4.3).

Ezetimibe had no effects on pup development in rats treated with up to 1 000 mg/kg/day of ezetimibe during late pregnancy and lactation. Medicine exposures (based on AUC) in pups were approximately 1,5 % and 50 % of maternal exposures for ezetimibe and total ezetimibe respectively. A study in rats treated with rosuvastatin showed that unchanged medicine and metabolites are excreted in milk at concentrations up to 3 times greater than those in maternal plasma.

Fertility

No studies on the effect on fertility have been conducted with ezetimibe and rosuvastatin in combination.

4.7 Effects on ability to drive and use machines

SUVEMIB has no or negligible influence on the ability to drive and use machines. Studies to determine the effect of rosuvastatin and/or ezetimibe on the ability to drive and use machines have not been conducted. However, when driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent common adverse events related to rosuvastatin-ezetimibe combination treatment in hypercholesterolemic patients are increased hepatic transaminases, gastrointestinal problems and muscle pain.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during reported clinical trials and postmarket spontaneous reports with rosuvastatin and ezetimibe.

Table 1: Adverse reactions based on data from clinical studies and post-marketing experience

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders		Thrombocytopenia[2]	Thrombocytopenia[5]

Immune system disorders		Hypersensitivity reactions including angioedema[2]	Hypersensitivity (including rash, urticaria, anaphylaxis and angioedema)[5]
Endocrine disorders	Diabetes mellitus[1,2]		
Metabolism and nutrition disorders		Decreased appetite[3]	
Psychiatric disorders			Depression[2,5]
Nervous system disorders	Headache[2,4], dizziness[2],	Paraesthesia[4], polyneuropathy[2], memory loss	Peripheral neuropathy[2], Sleep disturbances (including insomnia and nightmares)[2], dizziness[5], paraesthesia[5]
Vascular disorders		Hot flush[3], Hypertension[3]	

Respiratory, thoracic and mediastinal disorders		Cough[3]	Cough[2], Dyspnoea[2,5]
Gastrointestinal disorders	Constipation[2], nausea[2], abdominal pain[2,3] diarrhoea[3], flatulence[3]	Dyspepsia[3], gastrooesophageal reflux disease[3], nausea[3], dry mouth[4], gastritis[4], pancreatitis[2]	Diarrhoea[2], pancreatitis[5], constipation[5]
Hepatobiliary disorders		Increased hepatic transaminases[2], jaundice[2], hepatitis[2]	Hepatitis[5], cholelithiasis[5], cholecystitis[5]
Skin and subcutaneous tissue disorders		Pruritus[2,4], rash[2,4], urticaria[2,4]	Stevens-Johnson syndrome[2], erythema multiforme[5]

Musculoskeletal and connective tissue disorders	Myalgia[2,4]	arthralgia[3], muscle spasms[3], neck pain[3], back pain[4], muscular weakness[4], pain in extremity[4], myopathy (including myositis)[2], rhabdomyolysis[2], lupus-like syndrome, muscle rupture, arthralgia[2]	arthralgia[5], 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		Haematuria[2]	

Reproductive system and breast disorders		Gynaecomastia[2]	
General disorders and administration site conditions	Asthenia[2], fatigue[3]	Chest pain[3], pain[3], asthenia[4], peripheral oedema[4]	Oedema[2], asthenia[5]
Investigations	ALT and/or AST increased[4]	ALT and/or AST increased[3]; Blood CPK increased[3], gamma-glutamyltransferase increased[3], liver function test abnormal[3]	

[1]Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5,6 mmol/L, BMI > 30 kg/m^2, raised triglycerides, history of hypertension) – for rosuvastatin.

[2] Adverse reaction profile for rosuvastatin based on data from reported clinical studies and extensive post-marketing experience.

[3] Ezetimibe in monotherapy. Adverse reactions were observed in patients treated with ezetimibe.

[4] Ezetimibe co-administered with a statin. Adverse reactions were observed in patients with ezetimibe co-administered with a statin.

[5] Additional adverse reactions of ezetimibe, reported in post-marketing experience. Because these adverse experiences have been identified from spontaneous reports, their true frequencies are not known and cannot be estimated.

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

Paediatric population

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

Rosuvastatin

Creatine kinase elevations > 10 x 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. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

Ezetimibe

In a 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. This trial was not suited for comparison of rare adverse drug reactions.

Paediatric (6 to 17 years of age) patients

In a reported 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.

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

Rhabdomyolysis, which were occasionally associated with impairment of renal function, have been reported with rosuvastatin. Rhabdomyolysis may be fatal. Examples of signs and symptoms of rhabdomyolysis are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac dysrhythmia (see sections 4.3, 4.4 and 4.5).

Liver effects

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

The following adverse events have been reported with some statins:

Sexual dysfunction.

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

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

The following adverse events have been reported with some statins

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Symptoms

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Treatment

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. Haemodialysis is unlikely to be of benefit. In symptomatic patients, monitor serum creatinine, BUN, creatinine phosphokinase and urine myoglobin for indications of renal impairment secondary to rhabdomyolysis. Liver function tests should be performed in symptomatic patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: Lipid modifying agents; HMG CoA reductase inhibitors in combination with other lipid modifying agents.

ATC Code: C10BA06

Mechanism of action

Rosuvastatin

Rosuvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol.

Rosuvastatin produces its lipid-modifying effects in 2 ways; it 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.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

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, nonHDL-C/HDL-C and ApoB/ApoA-I ratio's.

A therapeutic response is evident within 1 week of commencing therapy and 90 % of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol and related plant sterols.

In human studies, ezetimibe inhibited the intestinal absorption of cholesterol and related plant sterols.

Ezetimibe in experimental animals inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids progesterone, ethinyl estradiol, or the fat soluble vitamins A and D.

5.2 Pharmacokinetic properties

Absorption

Rosuvastatin

After oral administration peak plasma levels occur 5 hours after dosing. Absorption increases linearly over the dose range. The half-life is 19 hours and does not increase with increasing dose. Absolute bioavailability is 20 %. There is minimal accumulation on repeated once daily dosing.

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) 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 10 mg tablets. Ezetimibe can be administered with or without food.

Distribution

Rosuvastatin

Rosuvastatin undergoes first pass extraction in the liver.

Rosuvastatin is approximately 90 % bound to plasma proteins, mostly albumin. The parent compound, accounts for greater than 90 % of the circulating active HMG-CoA reductase inhibitor activity.
Volume of distribution of rosuvastatin at steady state is approximately 134 litres.

Ezetimibe
Ezetimibe and ezetimibe-glucuronide are bound 99,7 % and 88 to 92 % to human plasma proteins, respectively.

Biotransformation

Rosuvastatin
Rosuvastatin undergoes limited metabolism in humans (approximately 10 %), mainly to the N-desmethyl form, which is formed principally by cytochrome P450 2C9, and in vitro studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin.

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 compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine 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.

Elimination

Rosuvastatin

Rosuvastatin undergoes limited metabolism (approximately 10 %), mainly to the N-desmethyl form, and 90 % is eliminated as unchanged medicine in the faeces with the remainder being excreted in the urine.

Ezetimibe

Following oral administration of ^{14}C-ezetimibe (20 mg) to human patients, 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.

Linearity

Systemic exposure of rosuvastatin increases linearly over the dose range. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations

Rosuvastatin

Age and gender

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 hypercholesterolaemia was similar to that of adult volunteers (see “Paediatric population” below).

Race

Pharmacokinetic studies show a 1,26-2,31 fold elevation in geometric mean AUC (0-t) in Asian subjects compared with Caucasians.
A total of 62 (19 %) Caucasian, 61 (19 %) Chinese, 61 (19 %) Asian-Indian, 35 (11 %) Malay, 27 (8 %) Japanese, 27 (8 %) Philipino, 26 (8 %) Korean and 25 (8 %) Vietnamese subjects were evaluated for pharmacokinetic analyses in these studies.
A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Renal insufficiency

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment (CrCl < 30 mL/min) had a 3-fold increase in plasma concentration compared to healthy volunteers. Haemodialysis is unlikely to be of benefit for rosuvastatin removal.

Hepatic insufficiency

In a study with subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9

showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores.

There is no experience in subjects with Child-Pugh scores above 9.

Genetic polymorphisms

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

Paediatric population

The pharmacokinetic parameters of rosuvastatin in paediatric patients with heterozygous familial hypercholesterolaemia aged 10 to 17 years have not been fully characterised. A small pharmacokinetic study with rosuvastatin (given as tablets) in 18 paediatric patients demonstrated that exposure in paediatric patients appears comparable to exposure in adult patients. In addition, the results indicate that a large deviation from dose proportionality is not expected.

Ezetimibe

Age and gender

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (65 years or older) than in the young (18 to 45 years).

Plasma concentrations for total ezetimibe are slightly higher (less than 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.

Race

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

Renal insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (creatinine clearance (CrCl ≤ 30 mL/min/1,73 m^2), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy subjects.

An additional patient in this study (post-renal transplant and receiving multiple medications, including cyclosporine) had a 12-fold greater exposure to total ezetimibe (see section 4.5).

Hepatic insufficiency

After a single 10 mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1,7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency.

In a 14 day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (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. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic insufficiency, SUVEMIB are not recommended in these patients (see section 4.4).

Paediatric population

The absorption and metabolism of ezetimibe are similar between children 10 years of age or older and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population less than 10 years of age are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Cellulose, Microcrystalline (PH 102)

Croscarmellose Sodium

Hypromellose 2910 (E5 LV)

Lactose Monohydrate

Magnesium Stearate

Povidone K30

Silica, Colloidal Anhydrous

Sodium Laurilsulfate

Tablet coat

SUVEMIB 5/10 mg tablets

HPMC 2910/Hypromellose (E464)

Iron Oxide Red (E172)

Iron Oxide Yellow (E172)

Macrogol/PEG (E1521)

Talc (E553b)

Titanium Dioxide (E171)

SUVEMIB 10/10 mg and 20/10 mg tablets

Hypromellose (HPMC) (E464)

Iron Oxide Yellow (E172)

Macrogol/ Polyethylene glycol (PEG) (E1521)

Talc (E553b)

Titanium Dioxide (E171)

SUVEMIB 40/10 mg tablets

HPMC 2910/Hypromellose (E464)

Lactose Monohydrate

Macrogol/ Polyethylene glycol (PEG) (E1521)

Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister packs in the outer carton until required for use to protect from light and moisture.

6.5 Nature and contents of container

OPA/ Aluminium/PVC/Aluminium blisters.

Pack size of 30 or 100 film-coated tablets in a carboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBERS

SUVEMIB 5/10 mg film-coated tablets: 57/7.5/0561

SUVEMIB 10/10 mg film-coated tablets: 57/7.5/0562

SUVEMIB 20/10 mg film-coated tablets: 57/7.5/0563

SUVEMIB 40/10 mg film-coated tablets: 57/7.5/0564

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 September 2025

10. DATE OF REVISION OF THE TEXT