## 1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

**SCHEDULING STATUS**

**S4**

### 1. NAME OF THE MEDICINE

**REGUCHOLE 10/5 mg tablets**

**REGUCHOLE 10/10 mg tablets**

**REGUCHOLE 10/20 mg tablets**

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REGUCHOLE 10/5 mg:

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

Contains sugar: Lactose monohydrate 228,29 mg

REGUCHOLE 10/10 mg:

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

Contains sugar: Lactose monohydrate 238,69 mg

REGUCHOLE 10/20 mg:

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

Contains sugar: Lactose monohydrate 243,89 mg

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets.

REGUCHOLE 10/5: White to off-white, round, flat, uncoated tablet, engraved E2 on one side and 2 on the other side. The diameter of the tablet is 10 mm.

REGUCHOLE 10/10 mg: White to off-white, oval, biconvex, uncoated tablet, engraved E1 on one side and 1 on the other side. The dimensions of the tablet are 15 mm x 7 mm.

REGUCHOLE 10/20 mg: White to off-white, round, biconvex, uncoated tablet. The diameter of the tablet is 11 mm.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

REGUCHOLE 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.

REGUCHOLE is indicated in adults for:

- **Primary hypercholesterolaemia**

  REGUCHOLE 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)**

  REGUCHOLE 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**

  REGUCHOLE 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.

REGUCHOLE 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 REGUCHOLE 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.

REGUCHOLE 10/5 mg, REGUCHOLE 10/10 mg and REGUCHOLE 10/20 mg are not suitable for the treatment of patients requiring a 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:**

REGUCHOLE 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:**

REGUCHOLE 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**

REGUCHOLE 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.

**Dosage in patients taking other medicines**

*Co-administration with bile acid sequestrants*

REGUCHOLE 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 REGUCHOLE is taken in combination with gemfibrozil, the dose of REGUCHOLE 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 REGUCHOLE therapy with 10 mg + 5 mg once daily. The dose of REGUCHOLE 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 REGUCHOLE 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.

No dosage adjustment is required for elderly patients (see section 4.4).

*Renal impairment*

No dosage adjustment is required for patients with mild to moderate renal impairment.

The use of REGUCHOLE in patients with severe renal impairment is contraindicated for all doses.

*Hepatic impairment*

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6).

Treatment with REGUCHOLE is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction.

REGUCHOLE is contraindicated in patients with active liver disease (see sections 4.3, 4.4 and 5.2).

*Dosage in Asian patients*

Initiation of therapy with REGUCHOLE 10/5 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 10 mg+5 mg, 10 mg+10 mg or 10mg+20 mg once daily (see sections 4.4 and 5.2).

**Paediatric population**

No clinical data on safety and efficacy are available, therefore treatment with REGUCHOLE is contraindicated in children (see section 4.3, 4.4 and 5.2).

**Method of administration**

For oral administration.

REGUCHOLE may be given at any time of the day, with or without food.

## 4.3. Contraindications

REGUCHOLE is contraindicated in:

- Patients with hypersensitivity to rosuvastatin, ezetimibe or to any excipients in REGUCHOLE (see section 6.1).
- 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).
- 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 in serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN) (see section 4.4).
- Patients with severe renal impairment (CrCl < 30 mL/min).
- Patients receiving concomitant ciclosporin (see sections 4.4 and 4.5).
- Patients with myopathy secondary to other lipid lowering medicines.
- Combination with fenofibrate in patients with gall bladder disease (see section 4.4).
- Patients taking fusidic acid (see sections 4.4 and 4.5).

## 4.4. Special warnings and precautions for use

*Liver enzymes*

Liver function tests should be performed before initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of > 3 times ULN persist, reduction of dose or withdrawal of REGUCHOLE is recommended.

In controlled co-administration trials in patients receiving ezetimibe with a statin, as contained in REGUCHOLE, consecutive transaminase elevations (greater than or equal to 3 times upper limit of normal (ULN)) have been observed.

REGUCHOLE should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease (see section 4.3).

*Skeletal muscle*

***Rosuvastatin***

**Cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin, as in REGUCHOLE, 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 REGUCHOLE.
As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are higher at the highest marketed dose (40 mg).

Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥ 65 years), hypothyroidism, and renal insufficiency. The incidence of myopathy increased at doses of rosuvastatin above the recommended dosage range.

REGUCHOLE should be prescribed with caution in patients with predisposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism.

Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. REGUCHOLE therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with REGUCHOLE may be increased with concurrent administration of other lipid-lowering therapies, ciclosporin, or HIV/HCV antiviral medicines, such as atazanavir/ritonavir, lopinavir/ritonavir, simeprevir, or medicines containing elbasvir/grazoprevir (see sections 4.2 and 4.5).
Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, such as REGUCHOLE, co-administered with colchicine, and caution should be exercised when prescribing REGUCHOLE with colchicine (see section 4.5).

Combination therapy with REGUCHOLE and gemfibrozil should generally be avoided (see section 4.2 and 4.5). The combination of REGUCHOLE and other fibrates (except fenofibrate) is not recommended (see sections 4.3 and 4.5).

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

REGUCHOLE therapy should also be temporarily withheld or discontinued 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).

There have been reports of an immune-mediated necrotising myopathy clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin, as in REGUCHOLE (see section 4.8). Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive medicines may be required.

In rosuvastatin trials there was no evidence of increased skeletal muscle effects when rosuvastatin, as in REGUCHOLE, was dosed with any 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 ciclosporin, nicotinic acid, azole antifungals, macrolide antibiotics and fibric acid derivatives including gemfibrozil (see section 4.5 and 4.8).

Fusidic acid must not be co-administered with statins, as contained in REGUCHOLE. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

In patients where the use of systemic fusidic acid is considered essential, REGUCHOLE treatment should be discontinued throughout the duration of fusidic acid treatment.

The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. REGUCHOLE therapy may be reintroduced seven days after the last dose of fusidic acid (see sections 4.3, 4.5 and 4.8).

Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors, such as REGUCHOLE, coadministered with daptomycin. Caution should be used when prescribing HMGCoA reductase inhibitors with daptomycin, as either medicine can cause myopathy and/or rhabdomyolysis when given alone.
Consideration should be given to suspending REGUCHOLE temporarily in patients taking daptomycin (see section 4.5).

***Ezetimibe***

In clinical trials, the incidence of CPK greater than 10 times ULN was 0,2 % for ezetimibe vs. 0,1 % for placebo, and 0,1 % for ezetimibe co-administered with a statin vs. 0,4 % for statins alone.

In post-marketing experience with ezetimibe, as in REGUCHOLE, cases of myopathy and rhabdomyolysis have been reported. All patients starting therapy with REGUCHOLE should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.
REGUCHOLE 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.

*Endocrine effects*

Increases in HbA1c and fasting serum glucose levels have been reported with rosuvastatin, as in REGUCHOLE. Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if REGUCHOLE is administered concomitantly with medicines that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

*Caution in prevention of cardiovascular events*

The long-term safety and efficacy of rosuvastatin treatment, as in REGUCHOLE, in patients commencing treatment with LDL-C < 3,4 mmol/L who have been assessed to be at risk of cardiovascular events have not been established. There is also uncertainty associated with the safety of long-term intensive reduction of LDL-C to very low levels.
The risk benefit balance for longer term use of rosuvastatin in this population has therefore not been established.

Clinically significant benefit in using rosuvastatin, as in REGUCHOLE, in patients without clinically evident cardiovascular disease and who are assessed as having a low risk of cardiovascular events (men > 50 and women > 60 years of age with hsCRP>2 mg/L, but no other cardiovascular disease risk factor), has not been established.

*Diabetes mellitus*

Increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin. An increased frequency of diabetes mellitus has been reported with rosuvastatin, as in REGUCHOLE, in patients with risk factors for diabetes mellitus (see section 4.8).

*Interstitial lung disease*

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

*Parasomnias*

Statins, as in REGUCHOLE, 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 medicines include statins, varenicline and montelukast (see section 4.8).

*Race*

***Rosuvastatin***

The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian patients (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making REGUCHOLE dosing decisions for Asian patients (see sections 4.2 and 5.2).

*Age and gender*

There was no clinically relevant effect of age or gender on the pharmacokinetics of rosuvastatin, as in REGUCHOLE.

*Fibrates - other than fenofibrate*

The safety and efficacy of ezetimibe, as in REGUCHOLE, administered with fibrates, have not been established (see section 4.5).

*Fenofibrate*

If cholelithiasis is suspected in a patient receiving REGUCHOLE and fenofibrate, gallbladder studies are indicated, and alternative lipid-lowering therapy should be considered (see sections 4.5 and 4.8).

Co-administration of REGUCHOLE and fenofibrate is not recommended in patients with pre-existing gallbladder disease (see section 4.3).

*Ciclosporin*

Caution should be exercised when initiating ezetimibe, as in REGUCHOLE, in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ezetimibe, as in REGUCHOLE, and ciclosporin (see sections 4.3 and 4.5).

*Anticoagulants*

There have been post-marketing reports of increased International Normalized Ratio (INR) in patients who had ezetimibe, as in REGUCHOLE, added to warfarin. Most of these patients were also on other medicines. If REGUCHOLE is added to warfarin or another coumarin anticoagulant, the INR should be appropriately monitored (see section 4.5).

*Statins*

No clinically significant pharmacokinetic interactions were seen when ezetimibe, as in REGUCHOLE, was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin (see section 4.5).

*Use in hepatic impairment*

Due to unknown effects of the increased exposure of ezetimibe, as in REGUCHOLE, in patients with moderate to severe hepatic insufficiency, REGUCHOLE is not recommended in these patients (see section 4.2, 4.3 and 5.2).

In a study in patients with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin, as in REGUCHOLE, other than in the 2 patients with the most severe liver disease (Child-Pugh scores of 8 and 9). In these patients, systemic exposure was increased by at least 2-fold compared with patients with lower Child-Pugh scores.

*Use in renal impairment*

Pharmacokinetic evaluation in patients with varying degrees of renal impairment, determined that mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin, as in REGUCHOLE. However, patients with severe impairment (CrCl < 30 mL/min) had a 3-fold increase in plasma concentration compared to healthy volunteers.

*Use in the elderly*

No dosage adjustment is required for elderly patients. Because there is no specific data in the elderly with this combination and advanced age (≥ 65 years) is a predisposing factor for myopathy, REGUCHOLE should be prescribed with caution in the elderly (see section 4.2).

*Effects on laboratory tests*

See section 4.8.

**Paediatric population**

No clinical data on safety and efficacy are available in children, therefore treatment with REGUCHOLE is contraindicated (see sections 4.2, 4.3 and 5.2).

*Excipients*

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

Co-administration of ezetimibe with rosuvastatin resulted in a 19 % increase in the AUC of rosuvastatin. This small increase is not considered clinically significant (see section 4.4).

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

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors, such as REGUCHOLE. Medicines or herbal medicines that inhibit certain enzymes and/or transporter (e.g. OATP1B) pathways may increase rosuvastatin plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis (see section 4.4).

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

*Antacids*

***Ezetimibe***

Concomitant antacid administration decreased the rate of absorption of ezetimibe, as in REGUCHOLE, but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

***Rosuvastatin***

The simultaneous dosing of rosuvastatin, as in REGUCHOLE, 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, as in REGUCHOLE. The clinical relevance of this interaction has not been studied.

*Colestyramine*

Concomitant colestyramine administration decreased the mean AUC of total ezetimibe, as in REGUCHOLE, by approximately 55 %. The incremental LDL-C reduction due to

adding REGUCHOLE to colestyramine may be lessened by this interaction.
Therefore, dosing of REGUCHOLE and a bile acid binding sequestrant should take place several hours apart. However, efficacy and safety of such combination have not been studied (see section 4.2).

*Ciclosporin*

***Ezetimibe***

In a study of post renal transplant patients with creatinine clearance of greater than 50 mL/min on a stable dose of ciclosporin, a single 10 mg dose of ezetimibe, as in REGUCHOLE, resulted

in a 3,4 fold (range 2,3 to 7,9 fold) increase in the mean AUC for total ezetimibe compared to a historical healthy control population.

In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13,2 mL/min/1,73m$^2$) who was receiving multiple medicines, including ciclosporin, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls.

In a two-period crossover study in healthy patients, daily administration of 20 mg ezetimibe, as in REGUCHOLE, 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 (see section 4.4).

***Rosuvastatin***

Co-administration of rosuvastatin, as in REGUCHOLE, with ciclosporin resulted in no significant changes in ciclosporin plasma concentration. However, rosuvastatin steady state AUC(0-t) increased up to 7-fold over that seen in healthy volunteers administered the same dose. These increases are considered to be clinically significant (see sections 4.3 and 4.4).

*Fibrates including fenofibrates*

***Ezetimibe***

Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe, as in REGUCHOLE, concentrations by approximately 1,5 and 1,7 fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of REGUCHOLE administered with fibrates have not been established (see section 4.4).

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe, as in REGUCHOLE, increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of

REGUCHOLE with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

***Rosuvastatin***

Co-administration of fenofibrate with rosuvastatin, as in REGUCHOLE, resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate (see section 4.3).

*Gemfibrozil*

***Ezetimibe***

In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1,7 fold. This increase is not considered clinically significant. No clinical data are available.

***Rosuvastatin***

Concomitant use of rosuvastatin, as in REGUCHOLE, and gemfibrozil resulted in a 2-fold increase in rosuvastatin $C_{max}$ and AUC(0-t) (see section 4.2). This increase is considered to be clinically significant.

*Anticoagulants*

***Ezetimibe***

Ezetimibe, as in REGUCHOLE, had no significant effect on the pharmacokinetics of warfarin during co-administration.

There have been post marketing reports of increased INR in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medicines (see section 4.4).

***Rosuvastatin***

The pharmacokinetics of warfarin are not significantly affected following co-administration with rosuvastatin, as in REGUCHOLE.

Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (> 4, baseline 2 to 3). In patients taking vitamin K antagonists and rosuvastatin concomitantly, INR should be determined before starting REGUCHOLE and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on vitamin K antagonists. If the dose of REGUCHOLE is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.

*Cytochrome P450 enzymes*

***Ezetimibe***

In preclinical studies, it has been shown that ezetimibe, as in REGUCHOLE, does not induce cytochrome P450 medicine metabolizing enzymes.

No clinically significant pharmacokinetic interactions have been observed between ezetimibe, as in REGUCHOLE, and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

***Rosuvastatin***

*In vitro* and *in vivo* data indicate that rosuvastatin, as in REGUCHOLE, has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer), and rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant

extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketoconazole, erythromycin, itraconazole).

*Ketoconazole*

Co-administration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin, as in REGUCHOLE.

*Erythromycin*

Co-administration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and $C_{max}$ of rosuvastatin by 20 % and 31 %, respectively. These reductions are not considered clinically significant.

*Itraconazole*

Itraconazole (200 mg twice daily for 5 days) resulted in a 39 % and 28 % increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.

*Fluconazole*

Co-administration of fluconazole (200 mg twice daily for 11 days) with rosuvastatin (80 mg) resulted in a 14 % increase in AUC of rosuvastatin. This increase is not considered clinically significant.

*Transporter interactions*

Rosuvastatin, as in REGUCHOLE, is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP).

Concomitant administration of REGUCHOLE with medicines that are inhibitors of these transporter proteins (e.g. ciclosporin, certain HIV protease/HCV antiviral medicines) may result

in increased rosuvastatin plasma concentrations and an increased risk of myopathy; therefore, a dose adjustment of rosuvastatin may be necessary (see section 4.4).

*Oral contraceptives*

Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin, as in REGUCHOLE, resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26 % and 34 %, respectively. This increase is not considered clinically significant.

*Other medicines*

***Ezetimibe***

Ezetimibe, as in REGUCHOLE, had no significant effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide or midazolam during co-administration.

Cimetidine, co-administered with ezetimibe, as in REGUCHOLE had no effect on the bioavailability of ezetimibe.

***Rosuvastatin***

There were no clinically significant interactions with an oral contraceptive, digoxin or fenofibrate.

In clinical studies rosuvastatin, as in REGUCHOLE, was co- administered with antihypertensive medicines, antidiabetic medicines and hormone replacement therapy. These studies did not produce any evidence of clinically significant adverse interactions.

*Digoxin*

Co-administration of digoxin with rosuvastatin resulted in no change to digoxin plasma concentrations.

*Protease inhibitors*

Co-administration of rosuvastatin, as in REGUCHOLE, with certain protease inhibitors has differing effects on rosuvastatin exposure. Simeprevir, which is a hepatitis C virus (HCV) protease inhibitor, or combinations of atazanavir/ritonavir or lopinavir/ritonavir, which are HIV-1 protease inhibitors, increase rosuvastatin exposure (AUC) up to threefold. For these combinations the dose of REGUCHOLE should not exceed 10 mg ezetimibe + 10 mg rosuvastatin once daily.

The combinations of fosamprenavir/tironavir or tipranavir/ritonavir, which are HIV-1 protease inhibitors, produce little or no change in rosuvastatin exposure.

Caution should be exercised when REGUCHOLE is co-administered with protease inhibitors. Consideration should be given both to the benefit of lipid lowering by the use of REGUCHOLE in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating REGUCHOLE doses in patients treated with protease inhibitors (see sections 4.2 and 4.4).

*Inhibitors of Breast Cancer Resistance Protein (BCRP)*

Concomitant administration of medicines that are inhibitors of BCRP (e.g. elbasvir and grazoprevir) may lead to increased plasma concentrations of rosuvastatin, as in REGUCHOLE, and an increased risk of myopathy. In a pharmacokinetic study, concomitant administration of elbasvir (50 mg) and grazoprevir (200 mg) caused a 2,3-fold and 5,5-fold increase in rosuvastatin exposure ($AUC_{0-\infty}$ and $C_{max}$, respectively). Therefore, the dose of REGUCHOLE should not exceed 10 mg ezetimibe + 10 mg rosuvastatin once daily in patients receiving concomitant medicines containing elbasvir or grazoprevir (see sections 4.2 and 4.4).

*Fusidic acid*

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins, as in REGUCHOLE. Co-administration of this combination may cause increased plasma concentrations of both medicines. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. REGUCHOLE treatment should be discontinued throughout the duration of the fusidic acid treatment (see sections 4.3, 4.4 and 4.8).

*Colchicine*

Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, co-administered with colchicine, and caution should be exercised when prescribing REGUCHOLE with colchicine (see section 4.4).

*Daptomycin*

The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin (see section 4.4).

*Ticagrelor*

Cases of rhabdomyolysis have been reported in patients taking rosuvastatin, as in REGUCHOLE, with ticagrelor. The patients who developed rhabdomyolysis were high-risk patients, namely elderly with initially an excessive dose of rosuvastatin, and some patients taking ezetimibe as concomitant therapy.

One form of interaction is a worsening of the renal function caused by ticagrelor, resulting in the rise of plasma concentration of rosuvastatin, which then causes rhabdomyolysis.

The other possibility, or additional type, can be the pharmacogenomics polymorphism and interaction on the level of the transporters, which can raise the rosuvastatin level. Patients who

have developed elevated creatine kinase levels without clinical symptoms and patients with myositis who were also given rosuvastatin, as in REGUCHOLE, should be further assessed.

## 4.6. Fertility, pregnancy and lactation

The use of REGUCHOLE is contraindicated in pregnancy and lactation (see section 4.3).

**Women of childbearing potential**

Women of child-bearing potential should use appropriate contraceptive measures. REGUCHOLE should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential. If the patient becomes pregnant while taking REGUCHOLE, 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 REGUCHOLE.

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 REGUCHOLE.

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, REGUCHOLE 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

Pharmacology testing revealed no evidence of a sedative effect of rosuvastatin, as in REGUCHOLE. From the safety profile, rosuvastatin, as in REGUCHOLE, is not expected to adversely affect the ability to drive or use machines.

Certain side effects that have been reported, such as dizziness, may affect some patients' ability to drive or operate machinery. Individual responses may vary.

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that REGUCHOLE do not adversely affect their ability to do so safely (see section 4.8).

## 4.8. Undesirable effects

*a) Summary of the safety profile*

The incidence of adverse reactions tends to increase with increasing dose.

*b) Tabulated list of adverse reactions*

| System organ class | Frequent | Less frequent |
|---|---|---|
| **Infections and infestations** | Viral infection[1], pharyngitis[1], sinusitis[1] | |
| **Immune system disorders** | | Hypersensitivity reactions including angio-oedema[3] |
| **Metabolism and nutrition disorders** | Diabetes mellitus[2] | Decreased appetite[1] |
| **Nervous system disorders** | Headache[3], dizziness[3] | |
| **Psychiatric disorders** | | Parasomnias, including abnormal dreaming, nightmares, sleepwalking |
| **Vascular disorders** | | Hot flush[1], hypertension[1] |
| **Respiratory, thoracic and mediastinal disorders** | | Cough[1] |
| **Gastrointestinal disorders** | Abdominal pain[3], diarrhoea[1], constipation[3], flatulence[1], nausea[3] | Dyspepsia[1]; gastroesophageal reflux disease[1], pancreatitis[3] |
| **Hepato-biliary disorders** | Increased alanine transaminase (ALT) [1], increased aspartate transaminase (AST)[1] | |
| **Skin and subcutaneous tissue disorders** | | Pruritis[3], rash[3], urticaria[3] |
| **Musculoskeletal and connective tissue disorders** | Myalgia[3], arthralgia[3] | Myopathy[3], rhabdomyolysis[3], back pain[1], pain in extremity[1], muscle spasms[1], neck pain[1] |
| **Renal and urinary disorders** | | Proteinuria, which decreases or disappears spontaneously on reduction of dose[2] |
| **General disorders and administrative site conditions** | Fatigue[1] | Asthenia[3], oedema peripheral[3], chest pain[1], pain[1] |
| **Investigations** | | Gamma-glutamyltransferase increased[1], liver function test abnormal[3] |

1: effect reported for ezetimibe, as in REGUCHOLE, administered alone.

2: effect reported for rosuvastatin, as in REGUCHOLE, administered alone.

3: effect reported for both ezetimibe, administered alone and rosuvastatin, administered alone.

*c) Tabulated list of adverse reactions: Post-marketing*

| System organ class | Less frequent | **Frequency unknown** (cannot be estimated from the available data) |
|---|---|---|
| **Blood and the lymphatic system disorders** | Thrombocytopenia[3] | |
| **Immune system disorders** | Hypersensitivity reactions, including anaphylaxis, rash, urticaria, and (very rare) angio-oedema[3] | |
| **Psychiatric disorders** | Depression[3] | Sleep disorders[2], insomnia[2], nightmares[2] |
| **Nervous system disorders** | Dizziness[3], paraesthesia[1], memory loss[2] | |
| **Gastrointestinal disorders** | Nausea[3], pancreatitis[3], constipation[3] | |
| **Hepato-biliary disorders** | Hepatitis[3], cholelithiasis[1], cholecystitis[1], increased hepatic transaminases[3], jaundice[2] | Hepatic failure[2] |
| **Skin and subcutaneous tissue disorders** | Erythema multiforme[1] | |
| **Musculoskeletal and connective tissue disorders** | Myalgia[3], arthralgia[3], myopathy[3]/rhabdomyolysis[3] | Immune- mediated necrotising myopathy[2] |
| **Reproductive system and breast disorders** | | Gynaecomastia[2] |
| **General disorders and administrative site conditions** | Asthenia[3] | |
| **Investigations** | Increased transaminases[3]; increased CPK[3] | |

1: effect reported for ezetimibe, as in REGUCHOLE, administered alone.

2: effect reported for rosuvastatin, as in REGUCHOLE, administered alone.

3: effect reported for both ezetimibe, administered alone and rosuvastatin, administered alone.

*d) Description of selected adverse reactions*

***Laboratory values***

***Ezetimibe***

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST greater than or equal to 3 times the upper limit of normal

(ULN), consecutive) was not statistically different between ezetimibe (0,5 %) and placebo (0,3 %).

In coadministration 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).

Clinically important elevations of creatinine phosphokinase (CPK; greater than or equal to 10 times ULN) in patients treated with ezetimibe administered alone or co- administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

***Rosuvastatin***

As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases, CK, glucose, glutamyl transpeptidase, alkaline phosphatase and bilirubin and thyroid function abnormalities have been observed in a small number of patients taking rosuvastatin. Increases in HbA1c have also been observed in patients treated with rosuvastatin. Proteinuria and microscopic haematuria have been detected by dipstick testing in the clinical trial program in a small number of patients taking rosuvastatin and other HMG-CoA reductase inhibitors at their recommended doses.

*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).

*Other effects*

In a long-term controlled clinical trial rosuvastatin was shown to have no harmful effects on the ocular lens. In rosuvastatin-treated patients, there was no impairment of adrenocortical function.

*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 providers are asked to report any suspected adverse reactions to:

**SAHPRA:** https://www.sahpra.org.za/health-products-vigilance/

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088

### 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: HMG CoA reductase inhibitors in combination with other lipid modifying agents

ATC code: C10BA06

*Mechanism of action*

***Ezetimibe:***

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

Ezetimibe 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 sterols).

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 therefore inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

Statins reduce cholesterol synthesis in the liver. Together these distinct mechanisms provide complementary cholesterol reduction. Ezetimibe, administered with a statin, reduces total-C, LDL-C, Apo B, and TG and increases HDL-C in patients with hypercholesterolaemia, beyond either treatment alone.

Clinical studies demonstrate that elevated levels of total C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. 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. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

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

***Rosuvastatin:***

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

Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low-density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.

Rosuvastatin produces its lipid-modifying effects in two 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 functions, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C and TG, and low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to the lowering of non-HDLC (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

## 5.2. Pharmacokinetic properties

**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 10 mg tablets. Ezetimibe can be administered with or without food.

***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.

**Distribution**

***Ezetimibe:***

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

***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.

**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 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.

***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.

**Elimination**

***Ezetimibe:***

Following oral administration of 14C-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.

***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.

**Special populations**

*Paediatric patients*

The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population < 10 years of age are not available. Clinical experience in paediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH or sitosterolaemia (see sections 4.2, 4.3, and 4.4).

*Elderly patients*

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 is comparable

between elderly and young patients treated with ezetimibe.

Therefore, no dosage adjustment is necessary in the elderly (see section 4.2).

*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 patients. 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 patients. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic insufficiency, ezetimibe is not recommended in these patients (see sections 4.2, 4.3 and 4.4).

*Renal insufficiency*

***Ezetimibe:***

After a single 10 mg dose of ezetimibe in patients with severe renal disease (mean creatinine clearance (CrCl) less than or equal to 30 mL/min/1,73m$^2$), the mean AUC for total ezetimibe was increased approximately 1,5-fold, compared to healthy patients. An additional patient in this study (post-renal transplant and receiving multiple medicines, including ciclosporin) had a 12-fold greater exposure to total ezetimibe (see section 4.5).

***Rosuvastatin:***

In a study in patients with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, patients 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 medicine removal.

*Age and gender*

***Ezetimibe:***

Plasma concentrations for total ezetimibe are slightly higher (< 20 %) in women than in men. LDL-C reduction and safety profile is comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender (see section 4.2).

***Rosuvastatin:***

There was no clinically relevant effect of age or gender on the pharmacokinetics of rosuvastatin.

*Race*

***Ezetimibe:***

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

***Rosuvastatin:***

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. However, pharmacokinetic studies have demonstrated an approximate 2-fold elevation in median exposure (AUC and $C_{max}$) in Asian patients when compared with a Caucasian control group (see sections 4.2 and 4.4).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Croscarmellose sodium, crospovidone type A, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K-30 and sodium laurilsulfate.

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf life

36 months.

### 6.4. Special precautions for storage

Store at or below 30 °C.

Keep in original packaging until required for use.

### 6.5. Nature and contents of container

Tablets are packed in blisters consisting of Polyamide-Aluminium-Polyvinylchloride laminate and aluminium lidding foil with ten tablets per blister strip. The blisters are packed into carton boxes containing 30 tablets per pack.

### 6.6. Special precautions for disposal

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

## 8. REGISTRATION NUMBER

REGUCHOLE 10/5 mg: 54/7.5/0693

REGUCHOLE 10/10 mg: 54/7.5/0694

REGUCHOLE 10/20 mg: 54/7.5/0695

## 9. DATE OF FIRST AUTHORISATION

08 November 2022

## 10. DATE OF REVISION OF TEXT

08 November 2022

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