SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ezetimibe/Simvastatin 10mg/80mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg ezetimibe and 80mg of simvastatin.

Excipient with known effect
Each 10/80mg tablet contains 579mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Light pink to pink coloured with mosaic appearance, capsule shape biconvex uncoated tablet '338' on one side and plain on other side. The size of the tablet is approximately 17.25 x 8.30 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Cardiovascular Events
Ezetimibe/Simvastatin is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Hypercholesterolaemia
Ezetimibe/Simvastatin is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate:

- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)
Ezetimibe/Simvastatin is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).

4.2 Posology and method of administration

Posology

Hypercholesterolaemia
The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Ezetimibe/Simvastatin.

Route of administration is oral. The dosage range of Ezetimibe/Simvastatin is 10/10 mg/day through 10/80 mg/day in the evening. All dosages may not be available in all member states. The typical dose is 10/20 mg/day or 10/40 mg/day given as a single dose in the evening. The 10/80-mg dose is only recommended in patients with severe hypercholesterolaemia and at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see section 4.4 and 5.1). The patient's low-density lipoprotein cholesterol (LDL-C) level, coronary heart disease risk status, and response to current cholesterol- lowering therapy should be considered when starting therapy or adjusting the dose.

The dose of Ezetimibe/Simvastatin should be individualised based on the known efficacy of the various dose strengths of Ezetimibe/Simvastatin (see section 5.1, Table 2) and the response to the current cholesterol-lowering therapy. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks. Ezetimibe/Simvastatin can be administered with or without food. The tablet should not be split.

Patients with Coronary Heart Disease and ACS Event History
In the cardiovascular events risk reduction study (IMPROVE-IT), the starting dose was 10/40 mg once a day in the evening. The 10/80mg dose is only recommended when the benefits are expected to outweigh the potential risks.

Homozygous Familial Hypercholesterolaemia
The recommended starting dosage for patients with homozygous familial hypercholesterolaemia is Ezetimibe/Simvastatin 10/40 mg/day in the evening. The 10/80-mg dose is only recommended when the benefits are expected to outweigh the potential risks (see above; sections 4.3 and 4.4). Ezetimibe/Simvastatin may be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

In patients taking lomitapide concomitantly with Ezetimibe/Simvastatin, the dose of Ezetimibe/Simvastatin must not exceed 10/40 mg/day (see sections 4.3, 4.4 and 4.5).

Co-administration with other medicines
Dosing of Ezetimibe/Simvastatin should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

In patients taking amiodarone, amlodipine, verapamil, diltiazem, or products containing elbasvir or grazoprevir concomitantly with Ezetimibe/Simvastatin, the dose of Ezetimibe/Simvastatin should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

In patients taking lipid-lowering doses (≥ 1 g/day) of niacin concomitantly with Ezetimibe/Simvastatin, the dose of Ezetimibe/Simvastatin should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

Elderly

No dosage adjustment is required for elderly patients (see section 5.2).

Paediatric population
Initiation of treatment must be performed under review of a specialist.

Adolescents ≥ 10 years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche): The clinical experience in paediatric and adolescent patients (aged 10-17 years old) is limited. The recommended usual starting dose is 10/10 mg once a day in the evening. The recommended dosing range is 10/10 to a maximum of 10/40 mg/day (see sections 4.4 and 5.2).

Children < 10 years: Ezetimibe/Simvastatin is not recommended for use in children below age 10 due to insufficient data on safety and efficacy (see section 5.2). The experience in pre-pubertal children is limited.

Hepatic Impairment
No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Treatment with Ezetimibe/Simvastatin 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).

Renal Impairment
No modification of dosage should be necessary in patients with-mild renal impairment (estimated glomerular filtration rate ≥60 ml/min/1.73 m^2). In patients with chronic kidney disease and estimated glomerular filtration rate <60 ml/min/1.73 m^2, the recommended dose of Ezetimibe/Simvastatin is 10/20 mg once a day in the evening (see sections 4.4, 5.1, and 5.2). Higher doses should be implemented cautiously

Method of Administration

Ezetimibe/Simvastatin is for oral administration. Ezetimibe/Simvastatin can be administered as a single dose in the evening.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Pregnancy and lactation (see section 4.6).

Active liver disease or unexplained persistent elevations in serum transaminases.

Concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, and drugs containing cobicistat) (see sections 4.4 and 4.5).

Concomitant administration of gemfibrozil, ciclosporin, or danazol (see sections 4.4 and 4.5).

In patients with HoFH, concomitant administration of lomitapide with doses > 10/40 mg Ezetimibe/Simvastatin (see sections 4.2, 4.4 and 4.5).

4.4 Special warnings and precautions for use

Myopathy/Rhabdomyolysis

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis.

Ezetimibe/Simvastatin contains simvastatin. Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10 X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and very rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma (i.e. elevated simvastatin and simvastatin acid plasma levels), which may be due, in part, to interacting drugs that interfere with simvastatin metabolism and/or transporter pathways (see section 4.5).

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related for simvastatin. In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60 %) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03 %, 0.08 % and 0.61 % at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%. (See sections 4.8 and 5.1).

The risk of myopathy is greater in patients on Ezetimibe/Simvastatin 10/80 mg compared with other statin- based therapies with similar LDL-C-lowering efficacy. Therefore, the 10/80-mg dose of Ezetimibe/Simvastatin should only be used in patients with severe hypercholesterolemia and at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking Ezetimibe/Simvastatin 10/80 mg for whom an interacting agent is needed, a lower dose of Ezetimibe/Simvastatin or an alternative statin-based regimen with less potential for drug-drug interactions should be used (see below Measures to reduce the risk of myopathy caused by medicinal product interactions and sections 4.2, 4.3, and 4.5).

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with coronary heart disease and ACS event history were randomised to receive Ezetimibe/Simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.1 years, the incidence of myopathy was 0.2% for Ezetimibe/Simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for Ezetimibe/Simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 times ULN and <10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. (See section 4.8).

In a clinical trial in which over 9000 patients with chronic kidney disease were randomised to receive Ezetimibe/Simvastatin 10/20 mg daily (n=4650) or placebo (n=4620) (median follow-up 4.9 years), the incidence of myopathy was 0.2 % for Ezetimibe/Simvastatin and 0.1 % for placebo (see section 4.8).

In a clinical trial in which patients at high risk of cardiovascular disease were treated with simvastatin 40 mg/day (median follow-up 3.9 years), the incidence of myopathy was approximately 0.05 % for non-Chinese patients (n=7367) compared with 0.24 % for Chinese patients (n=5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing Ezetimibe/Simvastatin to Asian patients and the lowest dose necessary should be employed.

Reduced function of transport proteins
Reduced function of hepatic OATP transport proteins can increase the systemic exposure of simvastatin acid and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur as the result of inhibition by interacting medicines (eg ciclosporin) or in patients who are carriers of the SLCO1B1 c.521T>C genotype.

Patients carrying the SLCO1B1 gene allele (c.521T>C) coding for a less active OATP1B1 protein have an increased systemic exposure of simvastatin acid and increased risk of myopathy. The risk of high dose (80 mg) simvastatin related myopathy is about 1 % in general, without genetic testing. Based on the results of the SEARCH trial, homozygote C allele carriers (also called CC) treated with 80 mg have a 15% risk of myopathy within one year, while the risk in heterozygote C allele carriers (CT) is 1.5%. The corresponding risk is 0.3% in patients having the most common genotype (TT) (See section 5.2). Where available, genotyping for the presence of the C allele should be considered as part of the benefit-risk assessment prior to prescribing 80 mg simvastatin for individual patients and high doses avoided in those found to carry the CC genotype. However, absence of this gene upon genotyping does not exclude that myopathy can still occur.

Creatine Kinase measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (>5 X ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
All patients starting therapy with Ezetimibe/Simvastatin, or whose dose of Ezetimibe/Simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting treatment in the following situations:
- Elderly (age ≥65 years)
- Female gender
- Renal impairment
- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle

disorder on a fibrate or a statin, treatment with any statin-containing product (such as Ezetimibe/Simvastatin) should only be initiated with caution. If CK levels are significantly elevated at baseline (>5 X ULN), treatment should not be started.

Whilst on treatment
If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with Ezetimibe/Simvastatin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (>5 X ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are <5 X ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment (see section 4.8).

If symptoms resolve and CK levels return to normal, then re-introduction of Ezetimibe/Simvastatin or introduction of another statin-containing product may be considered at the lowest dose and with close monitoring.

A higher rate of myopathy has been observed in patients titrated to the 80 mg dose of simvastatin (see section 5.1). Periodic CK measurements are recommended as they may be useful to identify subclinical cases of myopathy. However, there is no assurance that such monitoring will prevent myopathy.

Therapy with Ezetimibe/Simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Measures to reduce the risk of myopathy caused by medicinal product interactions (see also section 4.5)

The risk of myopathy and rhabdomyolysis is significantly increased by concomitant use of Ezetimibe/Simvastatin with potent inhibitors of CYP3A4 (such as itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone medicinal products containing cobicistat), as well as ciclosporin, danazol, and gemfibrozil. Use of these medicinal products is contraindicated (see section 4.3).

Due to the simvastatin component of Ezetimibe/Simvastatin, the risk of myopathy and rhabdomyolysis is also increased by concomitant use of other fibrates, lipid-lowering doses (≥1 g/day) of niacin or by concomitant use of amiodarone, amlodipine, verapamil or diltiazem with certain doses of Ezetimibe/Simvastatin (see sections 4.2 and 4.5). The risk of myopathy including rhabdomyolysis may be increased by concomitant administration of fusidic acid with Ezetimibe/Simvastatin. For patients with HoFH, this risk may be increased by concomitant use of lomitapide with Ezetimibe/Simvastatin (see section 4.5).

Consequently, regarding CYP3A4 inhibitors, the use of Ezetimibe/Simvastatin concomitantly with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicinal products containing cobicistat is contraindicated (see sections 4.3 and 4.5). If treatment with potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) is unavoidable, therapy with Ezetimibe/Simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Moreover, caution should be exercised when combining Ezetimibe/Simvastatin with certain other less potent CYP3A4

inhibitors: fluconazole, verapamil, diltiazem (see sections 4.2 and 4.5). Concomitant intake of grapefruit juice and Ezetimibe/Simvastatin should be avoided.

Simvastatin 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 Ezetimibe/Simvastatin and fusidic acid should only be considered on a case-by-case basis under close medical supervision.

The combined use of Ezetimibe/Simvastatin at doses higher than 10/20 mg daily with lipid-lowering doses (≥ 1 g/day) of niacin should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

Rare cases of myopathy/rhabdomyolysis have been associated with concomitant administration of HMG-CoA reductase inhibitors and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid), either of which can cause myopathy when given alone.

In a clinical trial (median follow-up 3.9 years) involving patients at high risk of cardiovascular disease and with well-controlled LDL-C levels on simvastatin 40 mg/day with or without ezetimibe 10 mg, there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid). Therefore, physicians contemplating combined therapy with simvastatin and lipid-modifying doses (≥ 1 g/day) of niacin (nicotinic acid) or products containing niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and when the dose of either medicinal product is increased.

In addition, in this trial, the incidence of myopathy was approximately 0.24 % for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 1.24 % for Chinese patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with modified-release nicotinic acid/laropiprant 2000 mg/40 mg. While the only Asian population assessed in this clinical trial was Chinese, because the incidence of myopathy is higher in Chinese than in non-Chinese patients, co- administration of Ezetimibe/Simvastatin with lipid-modifying doses (≥1 g/day) of niacin (nicotinic acid) is not recommended in Asian patients.

Acipimox is structurally related to niacin. Although acipimox was not studied, the risk for muscle related toxic effects may be similar to niacin.

The combined use of Ezetimibe/Simvastatin at doses higher than 10/20 mg daily with amiodarone, amlodipine, verapamil, or diltiazem should be avoided. In patients with HoFH, the combined use of Ezetimibe/Simvastatin at doses higher than 10/40 mg daily with lomitapide must be avoided. (See sections 4.2, 4.3 and 4.5.)

Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 at therapeutic doses concomitantly with Ezetimibe/Simvastatin, particularly higher Ezetimibe/Simvastatin doses, may have an increased risk of myopathy. When co-

administering Ezetimibe/Simvastatin with a moderate inhibitor of CYP3A4 (agents that increase AUC approximately 2-5 fold), a dose adjustment may be necessary. For certain moderate CYP3A4 inhibitors e.g. diltiazem, a maximum dose of 10/20mg Ezetimibe/Simvastatin is recommended (see section 4.2).

Simvastatin is a substrate of the Breast Cancer Resistant Protein (BCRP) efflux transporter. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore a dose adjustment of simvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of Ezetimibe/Simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir** (see section 4.5).

The safety and efficacy of ezetimibe with simvastatin administered with fibrates have not been studied. There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates (especially gemfibrozil). Therefore, concomitant use of Ezetimibe/Simvastatin with gemfibrozil is contraindicated (see section 4.3) and concomitant use with other fibrates is not recommended (see section 4.5).

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend Ezetimibe/Simvastatin in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. Consult the prescribing information of Daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. simvastatin and ezetimibe/simvastatin) and for further guidance related to monitoring. (See section 4.5.).

Liver Enzymes

In controlled co-administration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥3 X ULN) have been observed (see section 4.8).

In IMPROVE-IT, 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe with simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe with simvastatin and 2.3% for simvastatin (see section 4.8).

In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomised to receive ezetimibe with simvastatin 10/20 mg daily (n=4650), or placebo (n=4620) (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (>3 X ULN) was 0.7 % for ezetimibe with simvastatin and 0.6 % for placebo (see section 4.8).

It is recommended that liver function tests be performed before treatment with Ezetimibe/Simvastatin begins and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 X ULN and are persistent, the drug should be discontinued. Note

that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see above *Myopathy/Rhabdomyolysis*).

There have been rare post-marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with Ezetimibe/Simvastatin promptly interrupt therapy. If an alternate etiology is not found, do not restart Ezetimibe/Simvastatin.

Ezetimibe/Simvastatin should be used with caution in patients who consume substantial quantities of alcohol.

Hepatic impairment
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, Ezetimibe/Simvastatin is not recommended (see section 5.2).

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.

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

Paediatric population
Efficacy and safety of ezetimibe co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys (Tanner stage II or above) and in girls who were at least one year post-menarche.

In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a treatment period > 33 weeks on growth and sexual maturation have not been studied (see sections 4.2 and 4.8).

The safety and efficacy of ezetimibe co-administered with doses simvastatin above 40mg daily have not been studied in paediatric patients 10 to 17 years of age.

Ezetimibe has not been studied in patients younger than 10 years of age or in pre-menarchal girls (see sections 4.2 and 4.8).

The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

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

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

Interstitial lung disease
Cases of interstitial lung disease have been reported with some statins, including simvastatin, 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, Ezetimibe/Simvastatin therapy should be discontinued.

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

4.5 Interaction with other medicinal products and other forms of interaction

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B) pathways may increase simvastatin and simvastatin acid plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

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

Pharmacodynamic interactions

Interactions with lipid-lowering medicinal products that can cause myopathy when given alone
The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration of simvastatin with fibrates. Additionally, there is a pharmacokinetic interaction of simvastatin with gemfibrozil resulting in increased simvastatin plasma levels (see below *Pharmacokinetic interactions* and sections 4.3 and 4.4). Rare cases of myopathy/rhabdomyolysis have been associated with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin (see section 4.4).

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see section 5.3). Although the relevance of this preclinical finding to humans is unknown, co-administration of Ezetimibe/Simvastatin with fibrates is not recommended (see section 4.4).

Pharmacokinetic interactions

Prescribing recommendations for interacting agents are summarized in the table below (further details are provided in the text; see also sections 4.2, 4.3, and 4.4).

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting agents	**Prescribing recommendations**

Potent CYP3A4 inhibitors, e.g. Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors (e.g. nelfinavir) Boceprevir Telaprevir Nefazodone Cobicistat Ciclosporin Danazol Gemfibrozil	**Contraindicated with Ezetimibe/Simvastatin**
Other Fibrates Fusidic acid	Not recommended with Ezetimibe/Simvastatin
Niacin (nicotinic acid) (≥ 1 g/day)	For Asian patients, not recommended with Ezetimibe/Simvastatin
Amiodarone Amlodipine Verapamil Diltiazem Niacin (≥1 g/day) Elbasvir Grazoprevir	Do not exceed 10/20 mg Ezetimibe/Simvastatin daily
Lomitapide	For patients with HoFH, do not exceed 10/40 mg Ezetimibe/Simvastatin daily
Daptomycin	It should be considered to temporarily suspend Ezetimibe/Simvastatin in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4)
Ticagrelor	Doses greater than 10/40 mg Ezetimibe/Simvastatin daily are not recommended
Grapefruit juice	Avoid grapefruit juice when taking Ezetimibe/Simvastatin

Effects of other medicinal products on Ezetimibe/Simvastatin

Ezetimibe with simvastatin

Niacin: In a study of 15 healthy adults, concomitant ezetimibe with simvastatin administration (10/20 mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22%) and nicotinuric acid (19%) administered as NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5 days following a low-fat breakfast). In the same study, concomitant NIASPAN slightly increased the mean AUCs of ezetimibe (9%), total ezetimibe (26%), simvastatin (20%) and simvastatin acid (35%) (see sections 4.2 and 4.4).

Drug interaction studies with higher doses of simvastatin have not been investigated.

Ezetimibe

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

Cholestyramine: Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding Ezetimibe/Simvastatin to cholestyramine may be lessened by this interaction (see section 4.2).

Ciclosporin: In a study of eight post-renal transplant patients with creatinine clearance of >50 ml/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medications demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15% increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Concomitant administration of Ezetimibe/Simvastatin with ciclosporin is contraindicated (see section 4.3).

Fibrates: Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5- and 1.7-fold, respectively. Although these increases are not considered clinically significant, co-administration of Ezetimibe/Simvastatin with gemfibrozil is contraindicated and with other fibrates is not recommended (see sections 4.3 and 4.4).

Simvastatin

Simvastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 increase the risk of myopathy and rhabdomyolysis by increasing the concentration of HMG-CoA reductase inhibitory activity in plasma during simvastatin therapy. Such inhibitors include itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, nefazodone, and medicinal products containing cobicistat. Concomitant administration of itraconazole resulted in a more than 10-fold increase in exposure to simvastatin acid (the active beta-hydroxyacid metabolite). Telithromycin caused an 11-fold increase in exposure to simvastatin acid.

Combination with itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (e.g. nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and medicinal products containing cobicistat is contraindicated, as well as gemfibrozil, ciclosporin, and danazol (see section 4.3). If treatment with potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) is unavoidable, therapy with Ezetimibe/Simvastatin must be suspended (and use of an alternative statin considered) during the course of treatment. Caution should be exercised when combining Ezetimibe/Simvastatin with certain other less potent CYP3A4 inhibitors: fluconazole, verapamil, or diltiazem (see sections 4.2 and 4.4).

Ticagrelor: Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC

by 52% with some individual increases equal to 2- to 3-fold. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. The concomitant use of ticagrelor with doses of simvastatin greater than 40 mg is not recommended.

Fluconazole: Rare cases of rhabdomyolysis associated with concomitant administration of simvastatin and fluconazole have been reported (see section 4.4).

Ciclosporin: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of ciclosporin with Ezetimibe/Simvastatin; therefore, use with ciclosporin is contraindicated (see sections 4.3 and 4.4). Although the mechanism is not fully understood, ciclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4 and/or OATP1B1.

Danazol: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol with Ezetimibe/Simvastatin; therefore, use with danazol is contraindicated (see sections 4.3 and 4.4).

Gemfibrozil: Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP1B1 (see sections 4.3 and 4.4). Concomitant administration with gemfibrozil is contraindicated.

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 pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. Co-administration of this combination may cause increased plasma concentrations of both agents.

If treatment with systemic fusidic acid is necessary, Ezetimibe/Simvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment (**also see section 4.4)**.

Amiodarone: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see section 4.4). In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. Therefore, the dose of Ezetimibe/Simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone.

Calcium Channel Blockers

- *Verapamil:* The risk of myopathy and rhabdomyolysis is increased by concomitant administration of verapamil with simvastatin 40 mg or 80 mg (see section 4.4). In a pharmacokinetic study, concomitant administration of simvastatin with verapamil resulted in 2.3-fold increase in exposure of simvastatin acid, presumably due, in part, to inhibition of CYP3A4. Therefore, the dose of Ezetimibe/Simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with verapamil.

- *Diltiazem:* The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with simvastatin 80 mg (see section 4.4). In a pharmacokinetic study, concomitant administration of diltiazem with simvastatin caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4. Therefore, the dose of Ezetimibe/Simvastatin should not exceed

10/20 mg daily in patients receiving concomitant medication with diltiazem.

- *Amlodipine:* Patients on amlodipine treated concomitantly with simvastatin have an increased risk of myopathy. In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid. Therefore, the dose of Ezetimibe/Simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with amlodipine.

Lomitapide: The risk of myopathy and rhabdomyolysis may be increased by concomitant administration of lomitapide with simvastatin (see sections 4.3 and 4.4). Therefore, in patients with HoFH, the dose of Ezetimibe/Simvastatin must not exceed 10/40 mg daily in patients receiving concomitant medication with lomitapide.

Moderate Inhibitors of CYP3A4: Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with Ezetimibe/Simvastatin, particularly higher Ezetimibe/Simvastatin doses, may have an increased risk of myopathy (see section 4.4).

Inhibitors of the Transport Protein OATP1B1: Simvastatin acid is a substrate of the transport protein OATP1B1. Concomitant administration of medicinal products that are inhibitors of the transport protein OATP1B1 may lead to increased plasma concentrations of simvastatin acid and an increased risk of myopathy (see sections 4.3 and 4.4).

Inhibitors of Breast Cancer Resistant Protein (BCRP): Concomitant administration of medicinal products that are inhibitors of BCRP, including products containing elbasvir or grazoprevir, may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy (see sections 4.2 and 4.4).

Grapefruit juice: Grapefruit juice inhibits cytochrome P450 3A4. Concomitant intake of large quantities (over 1 litre daily) of grapefruit juice and simvastatin resulted in a 7-fold increase in exposure to simvastatin acid. Intake of 240 ml of grapefruit juice in the morning and administration of simvastatin in the evening also resulted in a 1.9-fold increase. Intake of grapefruit juice during treatment with Ezetimibe/Simvastatin should therefore be avoided.

Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin, in patients with renal impairment. Close clinical monitoring of such patients taking this combination is advised.

Rifampicin: Because rifampicin is a potent CYP3A4 inducer, patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis) may experience loss of efficacy of simvastatin. In a pharmacokinetic study in normal volunteers, the area under the plasma concentration curve (AUC) for simvastatin acid was decreased by 93% with concomitant administration of rifampicin.

Niacin: Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day) of niacin (see section 4.4).

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

Effects of Ezetimibe/Simvastatin on the pharmacokinetics of other medicinal products

Ezetimibe

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

Anticoagulants: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If Ezetimibe/Simvastatin is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Simvastatin: Simvastatin does not have an inhibitory effect on cytochrome P450 3A4. Therefore, simvastatin is not expected to affect plasma concentrations of substances metabolised via cytochrome P450 3A4.

Oral anticoagulants: In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. Very rare cases of elevated INR have been reported. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting Ezetimibe/Simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of Ezetimibe/Simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

Ezetimibe with simvastatin

Ezetimibe/Simvastatin is contraindicated during pregnancy. No clinical data are available on the use of Ezetimibe/Simvastatin during pregnancy. Animal studies on combination therapy have demonstrated reproduction toxicity. (See section 5.3).

Simvastatin
The safety of simvastatin in pregnant women has not been established. No controlled clinical trials with simvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to simvastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the

general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking simvastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, Ezetimibe/Simvastatin must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Ezetimibe/Simvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3).

Ezetimibe
No clinical data are available on the use of ezetimibe during pregnancy.

Breast-feeding
Ezetimibe/Simvastatin is contraindicated during lactation. Studies on rats have shown that ezetimibe is excreted into breast milk. It is not known if the active components of Ezetimibe/Simvastatin are secreted into human breast milk. (See section 4.3).

Fertility

Ezetimibe
No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats (see section 5.3).

Simvastatin
No clinical trial data are available on the effects of simvastatin on human fertility. Simvastatin had no effect on the fertility of male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Ezetimibe / simvastatin (or co-administration of ezetimibe and simvastatin equivalent to ezetimibe / simvastatin) has been evaluated for safety in approximately 12,000 patients in clinical trials.

The following adverse reactions were observed in clinical studies of ezetimibe / simvastatin in patients treated with ezetimibe / simvastatin (n = 2,404) and at a greater incidence than placebo (n = 1,340), in patients treated with ezetimibe / simvastatin (n = 9,595) and at a greater incidence than statins administered alone (n = 8,883) in clinical studies of ezetimibe or simvastatin, and/or reported from post-marketing use with ezetimibe / simvastatin or

ezetimibe or simvastatin. These reactions are presented in Table 1 by system organ class and by frequency.

The frequencies of adverse events are ranked according to the following: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1000, < 1/100), Rare (≥ 1/10,000, < 1/1000), Very Rare (< 1/10,000) including isolated reports, and Not Known (cannot be estimated from the available data).

Table 1
Adverse Reactions

System organ class Frequency	**Adverse reaction**
Blood and lymphatic system disorders	
Not Known	thrombocytopaenia; anaemia
Immune system disorders	
Very Rare	anaphylaxis
Not Known	hypersensitivity
Metabolism and nutrition disorders	
Not Known	decreased appetite
Psychiatric disorders	
Uncommon	sleep disorder; insomnia
Not Known	depression
Nervous system disorders	
Uncommon	dizziness; headache; paraesthesia
Not Known	peripheral neuropathy; memory impairment; myasthenia gravis
Eye disorders	
Rare	vision blurred; visual impairment
Not Known	ocular myasthenia
Vascular disorders	
Not Known	hot flush; hypertension
Respiratory, thoracic and mediastinal disorders	
Not Known	cough; dyspnoea; interstitial lung disease (see section 4.4)
Gastrointestinal disorders	
Uncommon	abdominal pain; abdominal discomfort; abdominal pain upper; dyspepsia; flatulence; nausea; vomiting; abdominal distension; diarrhoea; dry mouth; gastroesophageal reflux disease
Not Known	constipation; pancreatitis; gastritis
Hepatobiliary disorders	
Not Known	hepatitis/jaundice; fatal and non-fatal hepatic failure; cholelithiasis; cholecystitis
Skin and subcutaneous tissue disorders	
Uncommon	pruritus; rash; urticaria
Very Rare	lichenoid drug eruptions
Not Known	alopecia; erythema multiforme; angioedema

Musculoskeletal and connective tissue disorders	
Common	myalgia
Uncommon	arthralgia; muscle spasms; muscular weakness; musculoskeletal discomfort; neck pain; pain in extremity; back pain; musculoskeletal pain
Very Rare	muscle rupture
Not Known	muscle cramps; myopathy* (including myositis); rhabdomyolysis with or without acute renal failure (see section 4.4); tendinopathy, sometimes complicated by rupture; immune-mediated necrotising myopathy (IMNM)**
Reproductive system and breast disorders	
Very Rare	gynaecomastia
Not Known	erectile dysfunction
General disorders and administration site conditions	
Uncommon	asthenia; chest pain; fatigue; malaise; oedema peripheral
Not Known	pain
Investigations	
Common	ALT and/or AST increased; blood CK increased
Uncommon	blood bilirubin increased; blood uric acid increased; gamma-glutamyltransferase increased; international normalised ratio increased; protein urine present; weight decreased
Not Known	elevated alkaline phosphatase; liver function test abnormal

* In a clinical trial, myopathy occurred commonly in patients treated with simvastatin 80 mg/day compared to patients treated with 20 mg/day (1.0% vs 0.02%, respectively) (see sections 4.4 and 4.5).

** There have been very rare reports of immune-mediated necrotising myopathy (IMNM), an autoimmune myopathy, during or after treatment with some statins. IMNM is clinically characterised by: persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotising myopathy without significant inflammation; improvement with immunosuppressive agents (see section 4.4).

Paediatric population

In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n=248), elevations of ALT and/or AST (≥3X 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 (≥ 10X ULN). No cases of myopathy were reported.

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

Patients with Coronary Heart Disease and ACS Event History

In the IMPROVE-IT study (see section 5.1), involving 18,144 patients treated with either ezetimibe / simvastatin 10/40 mg (n=9,067; of whom 6% were uptitrated to ezetimibe / simvastatin 10/80 mg) or simvastatin 40 mg (n=9,077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe / simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe / simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe / simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 times ULN and <10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe / simvastatin and 2.3% for simvastatin. (See section 4.4.) Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe / simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalisations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

Patients with Chronic Kidney Disease

In the Study of Heart and Renal Protection (SHARP) (see section 5.1), involving over 9,000 patients treated with ezetimibe / simvastatin 10/20 mg daily (n=4,650) or placebo (n=4,620), the safety profiles were comparable during a median follow-up period of 4.9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4 % in patients treated with ezetimibe / simvastatin, 9.8 % in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2 % in patients treated with ezetimibe / simvastatin and 0.1 % in patients treated with placebo. Consecutive elevations of transaminases (> 3X ULN) occurred in 0.7% of patients treated with ezetimibe / simvastatin compared with 0.6 % of patients treated with placebo (see section 4.4.). In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4 % for ezetimibe / simvastatin >, 9.5 % for placebo), hepatitis, cholycystectomy or complications of gallstones or pancreatitis.

Laboratory Values

In co-administration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 1.7% for patients treated with ezetimibe / simvastatin. 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 CK (≥10 X ULN) were seen in 0.2% of the patients treated with ezetimibe / simvastatin.

Post-marketing Experience

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features:

angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis,

thrombocytopaenia, eosinophilia, red blood cell sedimentation rate increased, arthritis and arthralgia, urticaria, photosensitivity reaction, pyrexia, flushing, dyspnoea and malaise.

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin.

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use, including simvastatin. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

The following additional adverse events have been reported with some statins:

- Sleep disturbances, including nightmares
- Sexual dysfunction
- Diabetes mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m2, raised triglycerides, history of hypertension).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Ezetimibe/Simvastatin
In the event of an overdose, symptomatic and supportive measures should be employed. Coadministration of ezetimibe (1000 mg/kg) and simvastatin (1000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD_{50} for both species was ezetimibe ≥1000 mg/kg/simvastatin ≥1000 mg/kg.

Ezetimibe
In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

Simvastatin
A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors in combination with other lipid modifying agents, ATC code: C10BA02

Ezetimibe/Simvastatin (ezetimibe/simvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

Mechanism of action

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

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

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

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [14C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

Simvastatin
After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed in the liver to the corresponding active β-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy - 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very-low-density protein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-cholesterol (VLDL-C) concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with simvastatin. In addition, simvastatin moderately increases HDL-C and reduces plasma TG. As a result of these changes, the ratios of total- to HDL-C and LDL- to HDL-C are reduced.

Clinical efficacy and safety
In controlled clinical studies, ezetimibe / simvastatin significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C in patients with hypercholesterolaemia.

Prevention of Cardiovascular Events
Ezetimibe / simvastatin has been shown to reduce major cardiovascular events in patients with coronary heart disease and ACS event history.

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicentre, randomised, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalisation for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤125 mg/dL (≤3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤100 mg/dL (≤2.6 mmol/L) if they had been receiving lipid-lowering therapy. All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n=9067) or simvastatin 40 mg (n=9077) and followed for a median of 6.0 years.

Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n=6390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid- lowering therapy (n=11594). Prior to the hospitalisation for the qualifying ACS event, 34% of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53.2 mg/dL (1.4 mmol/L) for the ezetimibe / simvastatin group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of cardiovascular death, major coronary events (MCE; defined as non-fatal myocardial infarction, documented unstable angina that required hospitalisation, or any coronary Revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. The study demonstrated that treatment with ezetimibe / simvastatin provided incremental benefit in reducing the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with simvastatin alone (relative risk reduction of 6.4%, p=0.016). The primary endpoint occurred in 2572 of 9067 patients (7-year Kaplan- Meier [KM] rate 32.72%) in the ezetimibe / simvastatin group and 2742 of 9077 patients (7-year KM rate 34.67%) in the simvastatin alone group. (See Figure 1 and Table 2.) Total mortality was unchanged in this high risk group (see Table 2).

There was an overall benefit for all strokes; however there was a small non-significant increase in haemorrhagic stroke in the ezetimibe-simvastatin group compared with simvastatin alone (see Table 2). The risk of haemorrhagic stroke for ezetimibe coadministered with higher potency statins in long- term outcome studies has not been evaluated.

The treatment effect of ezetimibe/simvastatin was generally consistent with the overall results across many subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, and hypertension.

Figure 1: Effect of ezetimibe / simvastatin on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

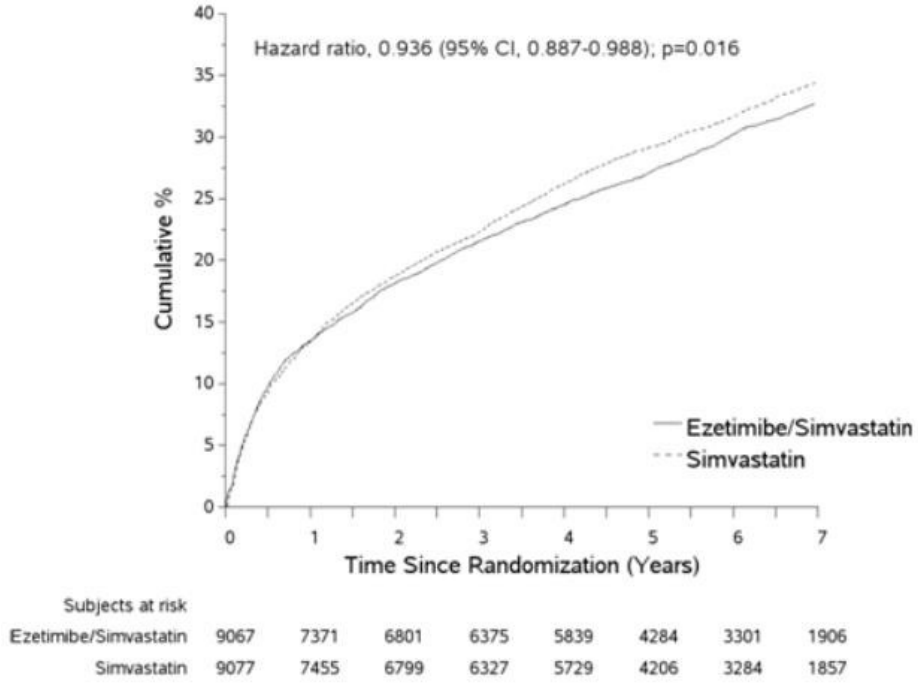

Table 2

Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE- IT

Outcome	**Ezetimibe-Simvastatin 10/40 mg[a] (N=9067)**		**Simvastatin 40 mg[b] (N=9077)**		**Hazard Ratio (95% CI)**	**p-value**
	n	K-M %[c]	n	K-M %[c]		
Primary Composite Efficacy Endpoint						
(CV death, Major Coronary Events and non-fatal stroke)	2572	32.72%	2742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, non-fatal MI, urgent coronary Revascularisation after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalisation, any Revascularisation, non-fatal stroke	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997

Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalisation	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary Revascularisation after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-haemorrhagic stroke[d]	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Haemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1215	15.36%	1231	15.28%	0.989 (0.914, 1.070)	0.782

[a] 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.
[b] 27% were uptitrated to simvastatin 80 mg.
[c] Kaplan-Meier estimate at 7 years.
[d] includes ischemic stroke or stroke of undetermined type.

Primary Hypercholesterolaemia
In a double-blind, placebo-controlled, 8-week study, 240 patients with hypercholesterolaemia already receiving simvastatin monotherapy and not at National Cholesterol Education Program (NCEP) LDL- C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going simvastatin therapy. Among simvastatin-treated patients not at LDL-C goal at baseline (~80%), significantly more patients randomised to ezetimibe co-administered with simvastatin achieved their LDL-C goal at study endpoint compared to patients randomised to placebo coadministered with simvastatin, 76% and 21.5%, respectively.

The corresponding LDL-C reductions for ezetimibe or placebo co-administered with simvastatin were also significantly different (27% or 3%, respectively). In addition, ezetimibe co-administered with simvastatin significantly decreased total-C, Apo B, and TG compared with placebo co-administered with simvastatin.

In a multicentre, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks with a mean LDL-C of 2.4 mmol/L (93 mg/dl), were randomised to receive either simvastatin 40 mg or the co-administered active ingredients equivalent to ezetimibe / simvastatin 10 mg/20 mg. ezetimibe / simvastatin 10

mg/20 mg was significantly more effective than doubling the dose of simvastatin to 40 mg in further reducing LDL-C (-21% and 0%, respectively), total-C (-14% and -1%, respectively), Apo B (-14% and -2%, respectively), and non-HDL-C (-20% and -2%, respectively) beyond the reductions observed with simvastatin 20 mg. Results for HDL-C and TG between the two treatment groups were not significantly different. Results were not affected by type of thiazolidinedione treatment.

The efficacy of the different dose-strengths of ezetimibe / simvastatin (10/10 to 10/80 mg/day) was demonstrated in a multicentre, double-blind, placebo-controlled 12-week trial that included all available doses of ezetimibe / simvastatin and all relevant doses of simvastatin. When patients receiving all doses of ezetimibe / simvastatin were compared to those receiving all doses of simvastatin, ezetimibe / simvastatin significantly lowered total-C, LDL-C, and TG (see Table 3) as well as Apo B (-42% and -29%, respectively), non-HDL-C (-49% and -34%, respectively) and C-reactive protein (-33% and -9%, respectively). The effects of ezetimibe / simvastatin on HDL-C were similar to the effects seen with simvastatin. Further analysis showed ezetimibe / simvastatin significantly increased HDL-C compared with placebo.

Table 3
Response to ezetimibe / simvastatin in Patients with Primary Hypercholesterolaemia
(Mean[a] % Change from Untreated Baseline[b])

Treatment					
(Daily Dose)	**N**	**Total-C**	**LDL-C**	**HDL-C**	**TG[a]**
Pooled data (all ezetimibe / simvastatin doses)[c]	353	-38	-53	+8	-28
Pooled data (all simvastain doses)[c]	349	-26	-38	+8	-15
Ezetimibe 10mg	92	-14	-20	+7	-13
Placebo	93	+2	+3	+2	-2
Ezetimibe / simvastatin by dose					
10/10	87	-32	-46	+9	-21
10/20	86	-37	-51	+8	-31
10/40	89	-39	-55	+9	-32
10/80	91	-43	-61	+6	-28
Simvastatin by dose					
10mg	81	-21	-31	+5	-4
20mg	90	-24	-35	+6	-14
40mg	91	-29	-42	+8	-19
80mg	87	-32	-46	+11	-25

[a] For triglycerides, median % change from baseline
[b] Baseline - on no lipid-lowering drug
[c] ezetimibe / simvastatin doses pooled (10/10-10/80) significantly reduced total-C, LDL-C, and TG, compared to simvastatin, and significantly increased HDL-C compared to placebo.

In a similarly designed study, results for all lipid parameters were generally consistent. In a pooled analysis of these two studies, the lipid response to ezetimibe / simvastatin was similar in patients with TG levels greater than or less than 200 mg/dl.

In a multicentre, double-blind, controlled clinical study (ENHANCE), 720 patients with heterozygous familial hypercholesterolemia were randomised to receive ezetimibe 10 mg in combination with simvastatin 80 mg (n=357) or simvastatin 80 mg (n=363) for 2 years. The primary objective of the study was to investigate the effect of the ezetimibe/simvastatin combination therapy on carotid artery intima-media thickness (IMT) compared to simvastatin monotherapy. The impact of this surrogate marker on cardiovascular morbidity and mortality is still not demonstrated.

The primary endpoint, the change in the mean IMT of all six carotid segments, did not differ significantly (p= 0.29) between the two treatment groups as measured by B-mode ultrasound. With ezetimibe 10 mg in combination with simvastatin 80 mg or simvastatin 80 mg alone, intima-medial thickening increased by 0.0111 mm and 0.0058 mm, respectively, over the study's 2 year duration (baseline mean carotid IMT 0.68 mm and 0.69 mm respectively).

Ezetimibe 10 mg in combination with simvastatin 80 mg lowered LDL-C, total-C, Apo B, and TG significantly more than simvastatin 80 mg. The percent increase in HDL-C was similar for the two treatment groups. The adverse reactions reported for ezetimibe 10 mg in combination with simvastatin 80 mg were consistent with its known safety profile.

Ezetimibe/Simvastatin contains simvastatin. In two large placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (20-40 mg; N=4,444 patients) and the Heart Protection Study (40 mg; N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularisation procedures.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) evaluated the effect of treatment with simvastatin 80 mg versus 20 mg (median follow-up 6.7 yrs) on major vascular events (MVEs; defined as fatal CHD, non-fatal MI, coronary revascularisation procedure, non-fatal or fatal stroke, or peripheral revascularisation procedure) in 12,064 patients with a history of myocardial infarction. There was no significant difference in the incidence of MVEs between the 2 groups; simvastatin 20 mg (n = 1553; 25.7 %) vs. simvastatin 80 mg (n = 1477; 24.5%); RR 0.94, 95 % CI: 0.88 to 1.01. The absolute difference in LDL-C between the two groups over the course of the study was 0.35 ± 0.01 mmol/L. The safety profiles were similar between the two treatment groups except that the incidence of myopathy was approximately 1.0 % for patients on simvastatin 80 mg compared with 0.02 % for patients on 20 mg. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1 %.

Paediatric population
In a multicentre, double-blind, controlled study, 142 boys (Tanner stage II and above) and 106 post- menarchal girls, 10 to 17 years of age (mean age 14.2 years) with heterozygous familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 4.1 and 10.4 mmol/l were randomised to either ezetimibe 10 mg co-administered with simvastatin (10, 20 or 40 mg) or simvastatin (10, 20 or 40 mg) alone for 6 weeks, co-administered ezetimibe and 40 mg simvastatin or 40 mg simvastatin alone for the next 27 weeks, and open-label co-administered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.

At Week 6, ezetimibe co-administered with simvastatin (all doses) significantly reduced total-C (38 % vs 26 %), LDL-C (49 % vs 34 %), Apo B (39 % vs 27 %), and non-HDL-C (47 % vs 33 %) compared to simvastatin (all doses) alone. Results for the two treatment groups were similar for TG and HDL-C (-17 % vs -12 % and +7 % vs +6 %, respectively). At Week 33, results were consistent with those at Week 6 and significantly more patients receiving ezetimibe and 40 mg simvastatin (62 %) attained the NCEP AAP ideal goal (< 2.8 mmol/L [110 mg/dL]) for LDL-C compared to those receiving 40 mg simvastatin (25 %). At Week 53, the end of the open label extension, the effects on lipid parameters were maintained.

The safety and efficacy of ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

The European Medicines Agency has waived the obligation to submit the results of studies with ezetimibe / simvastatin in all subsets of the paediatric population in Hypercholesterolaemia (see section 4.2 for information on paediatric use).

Homozygous Familial Hypercholesterolaemia (HoFH)
A double-blind, randomised, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analysed from a subgroup of patients (n=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Co-administered ezetimibe and simvastatin equivalent to ezetimibe / simvastatin (10 mg/40 mg and 10 mg/80 mg pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients co-administered ezetimibe and simvastatin equivalent to ezetimibe / simvastatin (10 mg/80 mg, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)
The Study of Heart and Renal Protection (SHARP) was a multi-national, randomised, placebo- controlled, double-blind study conducted in 9438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. A total of 4650 patients were allocated to ezetimibe / simvastatin 10/20 and 4620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 and 63 % were male, 72 % Caucasian, 23 % diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 ml/min/1.73 m2. There were no lipid entry criteria. Mean LDL-C at baseline was 108 mg/dL. After one year, including patients no longer taking study medication, LDL-C was reduced 26 % relative to placebo by simvastatin 20 mg alone and 38 % by ezetimibe / simvastatin 10/20 mg.

The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as non-fatal MI or cardiac death, stroke, or any revascularisation procedure) in only those patients initially randomised to the ezetimibe / simvastatin (n=4193) or placebo (n=4191) groups. Secondary analyses included the same composite analyzed for the full cohort randomised (at study baseline or at year 1) to ezetimibe / simvastatin (n=4650) or placebo (n=4620) as well as the components of this composite.

The primary endpoint analysis showed that ezetimibe / simvastatin significantly reduced the risk of major vascular events (749 patients with events in the placebo group vs. 639 in the ezetimibe / simvastatin group) with a relative risk reduction of 16 % (p=0.001).

Nevertheless, this study design did not allow for a separate contribution of the monocomponent ezetimibe to efficacy to significantly reduce the risk of major vascular

events in patients with CKD. The individual components of MVE in all randomised patients are presented in Table 4. Ezetimibe / simvastatin significantly reduced the risk of stroke and any revascularisation, with non-significant numerical differences favouring ezetimibe / simvastatin for non-fatal MI and cardiac death.

Table 4
Major Vascular Events by Treatment Group in all randomised patients in SHARP[a]

Outcome	**Ezetimibe / simvastatin 10/20 (N=4650)**	**Placebo (N=4620)**	**Risk Ratio (95% Cl)**	**P-value**
Major vascular events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Non-fatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-haemorrhagic stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.11
Haemorrhagic stroke	45 (1.0%)	37 (0.8%)	1.21 (078-1.86)	0.40
Any Revascularisation	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004
Major Atherosclerotic Events (MAE)[b]	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.002

[a]Intention-to-treat analysis on all SHARP patients randomised to ezetimibe / simvastatin or placebo either at baseline or year 1
[b] MAE; defined as the composite of non-fatal myocardial infarction, coronary death, non- haemorrhagic stroke, or any Revascularisation

The absolute reduction in LDL cholesterol achieved with ezetimibe / simvastatin was lower among patients with a lower baseline LDL-C (<2.5 mmol/l) and patients on dialysis at baseline than the other patients, and the corresponding risk reductions in these two groups were attenuated.

Aortic Stenosis
The Simvastatin and Ezetimibe for the Treatment of Aortic Stenosis (SEAS) study was a multi-centre, double-blind, placebo-controlled study with a median duration of 4.4 years conducted in 1873 patients with asymptomatic aortic stenosis (AS), documented by Doppler-measured aortic peak flow velocity within the range of 2.5 to 4.0 m/s. Only patients who were considered not to require statin treatment for purposes of reducing atherosclerotic cardiovascular disease risk were enrolled. Patients were randomised 1:1 to receive placebo or co-administered ezetimibe 10 mg and simvastatin 40 mg daily.

The primary endpoint was the composite of major cardiovascular events (MCE) consisting of cardiovascular death, aortic valve replacement (AVR) surgery, congestive heart failure (CHF) as a result of progression of AS, non-fatal myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), hospitalisation for unstable angina, and non-haemorrhagic stroke. The key secondary endpoints were composites of subsets of the primary

endpoint event categories.

Compared to placebo, ezetimibe/simvastatin 10/40 mg did not significantly reduce the risk of MCE.

The primary outcome occurred in 333 patients (35.3%) in the ezetimibe / simvastatin group and in 355 patients (38.2%) in the placebo group (hazard ratio in the ezetimibe / simvastatin group, 0.96; 95% confidence interval, 0.83 to 1.12; p = 0.59). Aortic valve replacement was performed in 267 patients (28.3%) in the ezetimibe / simvastatin group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; p = 0.97). Fewer patients had ischemic cardiovascular events in the ezetimibe / simvastatin group (n=148) than in the placebo group (n=187) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; p = 0.02), mainly because of the smaller number of patients who underwent coronary artery bypass grafting.

Cancer occurred more frequently in the ezetimibe / simvastatin group (105 versus 70, p = 0.01). The clinical relevance of this observation is uncertain as in the bigger SHARP trial the total number of patients with any incident cancer (438 in the ezetimibe/ simvastatin versus 439 placebo group) did not differ. In addition, in the IMPROVE-IT trial the total number of patients with any new malignancy (853 in the ezetimibe/simvastatin group versus 863 in the simvastatin group) did not differ significantly and therefore the finding of SEAS trial could not be confirmed by SHARP or IMPROVE-IT.

5.2 Pharmacokinetic properties

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.

Absorption

Ezetimibe/Simvastatin
Ezetimibe/Simvastatin is bioequivalent to co-administered ezetimibe and simvastatin.

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 10mg tablets.

Simvastatin
The availability of the active β-hydroxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose, consistent with extensive hepatic first-pass extraction. The major metabolites of simvastatin present in human plasma are the β-hydroxyacid and four additional active metabolites.

Relative to the fasting state, the plasma profiles of both active and total inhibitors were not affected when simvastatin was administered immediately before a test meal.

Distribution

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

Simvastatin
Both simvastatin and the β-hydroxyacid are bound to human plasma proteins (95%).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of drug occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post-dose.

Biotransformation

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

Simvastatin
Simvastatin is an inactive lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Hydrolysis takes place mainly in the liver; the rate of hydrolysis in human plasma is very slow.

In man simvastatin is well absorbed and undergoes extensive hepatic first-pass extraction. The extraction in the liver is dependent on the hepatic blood flow. The liver is its primary site of action, with subsequent excretion of drug equivalents in the bile. Consequently, availability of active drug to the systemic circulation is low.

Following an intravenous injection of the β-hydroxyacid metabolite, its half-life averaged 1.9 hours.

Elimination

Ezetimibe
Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Simvastatin
Simvastatin acid is taken up actively into the hepatocytes by the transporter OATP1B1. Simvastatin is a substrate of the efflux transporter BCRP.

Following an oral dose of radioactive simvastatin to man, 13% of the radioactivity was excreted in the urine and 60% in the faeces within 96 hours. The amount recovered in the faeces represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Following an intravenous injection of the β-hydroxyacid metabolite, an average of only 0.3% of the IV dose was excreted in urine as inhibitors.

Special Populations

Paediatric Population

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 includes patients with HoFH, HeFH, or sitosterolaemia (see section 4.2).

Elderly

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and younger subjects treated with ezetimibe (see section 4.2).

Hepatic impairment

After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, ezetimibe is not recommended in these patients (see sections 4.2 and 4.4).

Renal impairment

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 ml/min), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). (see section 4.2).

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

Simvastatin

In a study of patients with severe renal impairment (creatinine clearance < 30 ml/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

Gender

Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.

SLCO1B1 polymorphism

Carriers of the SLCO1B1 gene c.521T>C allele have lower OATP1B1 activity. The mean exposure (AUC) of the main active metabolite, simvastatin acid is 120% in heterozygote carriers (CT) of the C allele and 221% in homozygote (CC) carriers relative to that of patients who have the most common genotype (TT). The C allele has a frequency of 18% in the European population. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of simvastatin acid, which may lead to an increased risk of rhabdomyolysis (see section 4.4).

5.3 Preclinical safety data

Ezetimibe / Simvastatin

In co-administration studies with ezetimibe and simvastatin, the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and/or pharmacodynamic interactions following coadministration. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for simvastatin and 1800 times the AUC level for the active metabolite). There was no evidence that coadministration of ezetimibe affected the myotoxic potential of simvastatin.

In dogs co-administered ezetimibe and statins, some liver effects were observed at low exposures (≤1 times human AUC). Marked increases in liver enzymes (ALT, AST) in the absence of tissue necrosis were seen. Histopathologic liver findings (bile duct hyperplasia, pigment accumulation, mononuclear cell infiltration and small hepatocytes) were observed in dogs co-administered ezetimibe and simvastatin. These changes did not progress with longer duration of dosing up to 14 months. General recovery of the liver findings was observed upon discontinuation of dosing. These findings were consistent with those described with HMG-CoA inhibitors or attributed to the very low cholesterol levels achieved in the affected dogs.

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

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

Ezetimibe

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

Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day.

Simvastatin

Based on conventional animal studies regarding pharmacodynamics, repeated dose toxicity, genotoxicity and carcinogenicity, there are no other risks for the patient than may be expected on account of the pharmacological mechanism. At maximally tolerated doses in

both the rat and the rabbit, simvastatin produced no foetal malformations, and had no effects on fertility, reproductive function or neonatal development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Iron oxide red (E172)
Croscarmellose sodium
Microcrystalline cellulose
Citric acid monohydrate
Hypromellose 2910 3cps
Propyl gallate
Butylated hydroxy anisole
Ascorbic acid
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

No special storage conditions required.

6.5 Nature and contents of container

Aluminium/Aluminium blisters.
Pack sizes: 28, 30, and 100.
Not all pack sizes may be marketed..

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/1372

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/04/2025

10 DATE OF REVISION OF THE TEXT

09/04/2025