# NEW ZEALAND DATA SHEET

# ZIMYBE® 10/10; ZIMYBE® 10/20; ZIMYBE® 10/40 and ZIMYBE® 10/80

## 1. Product Name

Zimybe 10/10, Zimybe 10/20, Zimybe 10/40 or Zimybe 10/80, tablets

## 2. Qualitative and Quantitative Composition

Each tablet contains 10 mg ezetimibe and 10, 20, 40 or 80 mg of simvastatin.

Excipient(s) with known effect: lactose.

Allergen declaration: sugars as lactose.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

Zimybe 10/10: A white to off-white, oval, biconvex tablet debossed with M on one side of the tablet and ES1 on the other side, containing 10 mg ezetimibe and 10 mg simvastatin.

Zimybe 10/20: A white to off-white, oval, biconvex tablet debossed with M on one side of the tablet and ES2 on the other side, containing 10 mg ezetimibe and 20 mg simvastatin.

Zimybe 10/40: A white to off-white, oval, biconvex tablet debossed with M on one side of the tablet and ES3 on the other side, containing 10 mg ezetimibe and 40 mg simvastatin.

Zimybe 10/80: A white to off-white, oval, biconvex tablet debossed with M on one side of the tablet and ES4 on the other side, containing 10 mg ezetimibe and 80 mg simvastatin.

## 4. Clinical Particulars

### *4.1 Therapeutic indications*

**Primary hypercholesterolaemia**

Zimybe is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in adult and adolescent (10 to 17 years of age) patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia in patients not adequately treated on a statin alone.

**Homozygous familial hypercholesterolaemia (HoFH)**

Zimybe is indicated for the reduction of elevated total-C and LDL-C levels in adult and adolescent (10 to 17 years of age) patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

## *4.2 Dose and method of administration*

### Dose

The patient should be placed on a standard cholesterol-lowering diet before receiving Zimybe and should continue on this diet during treatment with Zimybe. The dosage should be individualised according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. Zimybe should be taken as a single daily dose in the evening, with or without food.

The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of Zimybe, lipid levels may be analysed after 2 or more weeks and dosage adjusted, if needed. The 10/80 mg dose of Zimybe is only recommended in patients 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).

#### *Dosage in patients with homozygous familial hypercholesterolaemia*

The recommended dosage for patients with homozygous familial hypercholesterolaemia is Zimybe 10/40 mg/day or 10/80 mg/day in the evening. The 10/80 mg dose is only recommended when the benefits are expected to outweigh the potential risks (see sections 4.3 and 4.4)

Zimybe should 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 Zimybe, the dose of Zimybe should not exceed 10/40 mg/day (see sections 4.4 and 4.5).

#### *Concomitant therapy*

Dosing of Zimybe should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

In patients taking amiodarone, verapamil, diltiazem, amlodipine or ≥ 1 g/day of niacin, or products containing elbasvir or grazoprevir concomitantly with Zimybe, the dose of Zimybe should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

The safety and effectiveness of ezetimibe/simvastatin administered with fibrates have not been studied. Therefore, the combination of Zimybe and fibrates should be avoided (see sections 4.4 and 4.5).

Because the incidence of myopathy when simvastatin is co-administered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products is higher in Chinese than in non-Chinese patients, co-administration of Zimybe with lipid-modifying doses of niacin-containing products is not recommended in Asian patients (see section 4.4).

#### *Special populations*

**Renal impairment/chronic kidney disease (CKD)**

In patients with mild renal insufficiency (estimated GFR ≥ 60 mL/min/1.73 $m^2$) no dosage adjustment is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$, the dose of Zimybe is 10/20 mg once a day in the evening. Efficacy and safety at higher doses have not been evaluated in this CKD population (see sections 5.1 and 5.2).

**Elderly**

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

**Paediatric (10 to 17 years of age) patients**

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

The use of Zimybe in children and adolescent patients (10 to 17 years) is recommended only for patients with Heterozygous Familial Hypercholesterolaemia (HeFH) or Homozygous Familia Hypercholesterolaemia (HoFH).

There are no clinical safety and efficacy data on the use of ezetimibe/simvastatin in children and adolescent patients (10 to 17 years) with non-familial hypercholesterolaemia or mixed hyperlipidaemia.

Adolescents 10 to 17 years old (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 to 17 years old) is limited and mostly includes children and adolescents (10 to 17 years old) with Heterozygous Familial Hypercholesterolaemia. There are also no long-term (> 1 year) safety data in this population.

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 section 5.2). Doses should be individualised according to the recommended goal of therapy.

Children < 10 years: Zimybe is not recommended for use in children below age 10 due to very limited data on safety and efficacy (see section 5.2 and section 4.4). Ezetimibe/simvastatin has not been studied in pre-menarchal girls or in pre-pubertal boys and is not recommended in children < 10 years.

**Hepatic impairment**

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with Zimybe is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) liver dysfunction (see section 4.4 and section 5.2).

## *4.3 Contraindications*

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see section 4.6).
- Myopathy secondary to other lipid lowering agents.
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicines containing cobicistat (see section 4.4 and section 4.5).
- Concomitant administration of gemfibrozil, ciclosporine or danazol (see section 4.4 and section 4.5).
- Concomitant use with fusidic acid (see section 4.4 and section 4.5).

## *4.4 Special warnings and precautions for use*

### Myopathy/rhabdomyolysis

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 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). Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

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. This includes rhabdomyolysis for which the incidence was 0.1 to 0.2%, all allocated to simvastatin 80 mg/day. There is no universally accepted definition of rhabdomyolysis. In this trial, rhabdomyolysis was defined as a subset of myopathy with CK > 40 X ULN plus evidence of end organ damage (e.g. elevated creatinine, dark urine). 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%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-base therapies with similar LDL-C lowering efficacy. Therefore the 10/80 mg dose of ezetimibe/simvastatin should only be used in patients 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-ezetimibe regimen with less potential for drug-drug interactions should be used (see section 4.2 and 4.3).

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. Ezetimibe/simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and a CK level > 10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from simvastatin treatment, muscle symptoms and CK increases resolved (see section 4.8). Periodic CK determinations may be considered in patients starting therapy with ezetimibe/simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 10/80 mg dose. There is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients taking ezetimibe/simvastatin merit closer monitoring. 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.

In a clinical trial, 18,144 patients with CHD were randomized to receive ezetimibe/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 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, pain or tenderness with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 X ULN and < 10 X 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/rhabdomyolysis was 0.2% for ezetimibe/simvastatin and 0.1% for placebo (see section 4.8).

An increased risk of myopathy in Chinese subjects has been identified. 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=4 of 7367) compared with 0.24% for Chinese patients (n= 13 of 5468). While the only Asian population assessed in this clinical trial was Chinese, caution should be used when prescribing ezetimibe/simvastatin to any Asian patients and the lowest dose necessary should be employed.

## Drug interactions

Prescribing recommendations for interacting agents are summarised in Table 1 below (see sections 4.2, 4.3 and 4.5).

Because Zimybe contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of ezetimibe/simvastatin with the following medicines:

***Contraindicated medicines***

**Potent inhibitors of CYP3A4:** Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone or medicines containing cobicistat) is contraindicated. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with ezetimibe/simvastatin should be suspended during the course of treatment (see section 4.3 and 4.5).

**Gemfibrozil, ciclosporine or danazol:** Concomitant use of these drugs with ezetimibe/simvastatin is contraindicated (see section 4.3 and 4.5).

**Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see section 4.5). Fusidic acid must not be co-administered with statins (see section 4.3). In patients where the use of systemic fusidic acid is considered essential, ezetimibe/simvastatin should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Ezetimibe/simvastatin therapy may be reintroduced seven days after the last dose of fusidic acid.

***Other medicines***

**Amiodarone:** In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. A significant interaction at lower simvastatin doses cannot be excluded. Therefore, the dose of ezetimibe/simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone (see section 4.2 and 4.5).

**Calcium channel blockers:**

- **Verapamil or diltiazem:** Co-administration of verapamil increased the incidence of myopathy to 0.7% (with simvastatin 40 mg) or 1% (with simvastatin 80 mg). Co-administration of diltiazem and simvastatin 80 mg led to a mean 70% increase in systemic exposure to simvastatin-derived HMG-CoA reductase inhibitory activity, with individual increases ranging up to 200%. In patients taking diltiazem with simvastatin 80 mg, the incidence of myopathy was about 1%. The dose of ezetimibe/simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with verapamil or diltiazem (see section 4.2 and section 4.5).
- **Amlodipine:** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of ezetimibe/simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with amlodipine (see section 4.2 and section 4.5).

**Lomitapide:** The dose of ezetimibe/simvastatin should not exceed 10/40 mg daily in patients with HoFH receiving concomitant medication with lomitapide (see section 4.5).

**Moderate inhibitors of CYP3A4:** Patients taking other medicines labelled as having a moderate inhibitor effect on CYP3A4 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, a dose adjustment of ezetimibe/simvastatin may be necessary.

**Inhibitors of breast cancer resistant protein (BCRP):** 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 ezetimibe/simvastatin may be necessary. 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).

**Other fibrates:** The safety and effectiveness of ezetimibe/simvastatin administered with fibrates have not been studied. Therefore, the concomitant use of ezetimibe/simvastatin and fibrates should be avoided. Concomitant use of gemfibrozil is contraindicated (see section 4.3 and 4.5).

**Niacin (≥ 1 g/day):** The dose of ezetimibe/simvastatin should not exceed 10/20 mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1 g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid modifying doses (≥ 1 g/day) of niacin. 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. Therefore, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. 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 extended release niacin/laropiprant 2 g/40 mg. In comparison, in European/Non-Chinese patients the incidence of myopathy was approximately 0.05% for patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg compared with 0.09% for patients on simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with extended-release niacin/laropiprant 2 g/ 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 simvastatin with lipid-modifying doses (≥ 1 g/day) of niacin is not recommended in Asian patients (see section 4.5).

**Daptomycin:** Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors 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 suspending ezetimibe/simvastatin temporarily in patients taking daptomycin (see section 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).

*Table 1: Drug interactions associated with increased risk of myopathy/rhabdomyolysis*

| Interacting agents | Prescribing recommendations |
|---|---|
| Potent CYP3A4 Inhibitors, e.g.<br>• Itraconazole<br>• Ketoconazole<br>• Posaconazole<br>• Voriconazole<br>• Erythromycin<br>• Clarithromycin<br>• Telithromycin<br>• HIV protease inhibitors<br>• Boceprevir<br>• Telaprevir<br>• Nefazodone<br>• Cobicistat<br>Ciclosporine<br>Danazol<br>Gemfibrozil<br>Fusidic acid | Contraindicated with ezetimibe/simvastatin |
| Other fibrates (except fenofibrate)<br>Grapefruit juice | Use with ezetimibe/simvastatin should be avoided |
| Niacin (≥ 1 g/day) | For Asian patients, not recommended with ezetimibe/simvastatin |
| Amiodarone<br>Verapamil<br>Diltiazem<br>Niacin (≥ 1 g/day)<br>Elbasvir<br>Grazoprevir<br>Amlodipine | Do not exceed ezetimibe/simvastatin 10/20 mg daily |
| Lomitapide | For patients with HoFH, do not exceed ezetimibe/simvastatin 10/40 mg daily |
| Daptomycin | Is not recommended with ezetimibe/simvastatin |

## Myasthenia gravis/ocular myasthenia

In a few cases, statins have been reported to induce new onset or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). Ezetimibe/simvastatin should be discontinued in case these conditions occur. There have been reports of recurrences of these conditions when the same or a different statin was (re-) administered.

## Liver enzymes

In three placebo-controlled, 12-week trials, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.7% overall for patients treated with ezetimibe/simvastatin and appeared to be dose-related with an incidence of 2.6% for patients treated with ezetimibe/simvastatin 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-

treated patients, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with ezetimibe/simvastatin 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

In another trial, 18,144 patients with CHD were randomized to receive ezetimibe/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/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/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/simvastatin and 0.6% for placebo (see section 4.8).

It is recommended that LFTs be performed before treatment with ezetimibe/simvastatin begins and periodically 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., semi-annually) 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 medicine should be discontinued. Note that ALT may emanate from muscle; therefore, ALT rising with CK may indicate myopathy (see section 4.4*).*

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 aetiology is not found do not restart ezetimibe/simvastatin.

Ezetimibe/simvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of ezetimibe/simvastatin.

### Immune mediated necrotizing myopathy

There have been rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatinine kinase, which persists despite discontinuation of statin treatment.

### New-onset type 2 diabetes mellitus

There is sufficient evidence to support an association between statin use and new-onset type 2 diabetes mellitus; however the risk appears to be mainly in patients already at increased risk of developing diabetes. Risk factors for the development of diabetes include raised fasting blood glucose, history of hypertension, raised triglycerides and raised body mass. Patients at risk should be monitored both clinically and biochemically according to national guidelines. There is insufficient evidence to confirm or exclude an increased risk for any individual statin or a dose-response relationship. The cardiovascular benefits of statin therapy continue to outweigh the risk of diabetes.

### 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, statin therapy should be discontinued.

### Thyroid function

### *Simvastatin*

The concentration of serum thyroxin has been measured at baseline and at the end of simvastatin treatment in 785 patients enrolled in multicentre studies. The results of this analysis indicate that simvastatin has little if any effect upon thyroxin activity. In one study involving 183 patients treated with simvastatin, four patients had TSH levels within the normal range before commencing simvastatin, but had an elevated TSH after two years of simvastatin therapy.

## Transient hypotension

### *Simvastatin*

Three cases of symptomatic hypotension in the first few days following the start of simvastatin therapy have been reported. Two of the patients were on antihypertensive medication. The hypotension resolved with continued therapy with simvastatin.

## Neurological effects

### *Simvastatin*

The neurological adverse effects reported to date include cases of peripheral neuropathy and paraesthesia possibly due to simvastatin.

## Effects on laboratory tests

See section 4.8.

## Special populations

### *Hepatic impairment*

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

### *Renal impairment*

see section 4.2.

### *Paediatric use*

The use of ezetimibe/simvastatin in children and adolescent patients (10 to 17 years old) is recommended only for patients with Heterozygous Familial Hypercholesterolaemia (HeFH) or Homozygous Familial Hypercholesterolaemia (HoFH).

However, clinical efficacy/safety study experience in paediatric and adolescent patients (aged 10 to 17 years) has been mostly limited to patients with Heterozygous Familial Hypercholesterolaemia (see section 5.1). There are also no long term (> 1 year) safety data in this population.

The clinical safety and efficacy of ezetimibe/simvastatin in children and adolescents (10 to 17 years old) with hypercholesterolaemia other than Heterozygous Familial Hypercholesterolaemia have not been studied.

Safety and effectiveness of ezetimibe/simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least one year post-menarche. **Doses greater than 10/40 mg/day have not been studied in this population and are not recommended.** In this limited controlled study, there was 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/simvastatin for a treatment period > 33 weeks on growth, sexual maturation, intellectual and psychosocial development have not been studied (see sections 4.2, 4.8 and 5.1). Adolescent females should be counselled on

appropriate contraceptive methods while on ezetimibe/simvastatin therapy (see sections 4.3 and 4.6).

The safety and efficacy of ezetimibe/simvastatin doses above 10/40 mg daily have not been studied in children and adolescents (10 to 17 years old) and are not recommended. The long-term efficacy of therapy with ezetimibe/simvastatin in children and adolescents (10 to 17 years old) to reduce morbidity and mortality in adulthood has not been studied.

Ezetimibe/simvastatin has not been studied in in pre-menarchal girls or in pre-pubertal boys and is not recommended in children < 10 years of age.

***Use in the elderly***

No dosage adjustment is required for elderly patients (see section 5.2). Because advanced age (≥ 65 years) is a predisposing factor for myopathy, ezetimibe/simvastatin should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients < 65 years of age.

## *4.5 Interaction with other medicines and other forms of interaction*

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin. Specific pharmacokinetic drug interaction studies with ezetimibe/simvastatin have not been performed.

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

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.

### Contraindicated medicines

Concomitant use of the following medicines is contraindicated:

***Potent inhibitors of CYP3A4***

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

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore, it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4.

Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of ezetimibe/simvastatin.

Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone or medicines containing cobicistat) is contraindicated (see sections 4.3 and 4.4).

***Gemfibrozil, ciclosporine or danazol***

See sections 4.3 and 4.4.

**Gemfibrozil:** In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold; this increase is not considered clinically significant. No clinical data are available.

**Ciclosporine:** In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporine, 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 from another study (n=17).

In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m2) who was receiving multiple medications, including ciclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. 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 ciclosporine on Day 7 resulted in a mean 15% increase in ciclosporine AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of ciclosporine alone (see sections 4.3 and 4.4). The pharmacokinetic interactions between ezetimibe at steady-state and ciclosporine also at steady-state have not been studied.

***Fusidic acid***

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of simvastatin with fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. 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 fusidic acid and statins. Where the use of fusidic acid is considered essential, ezetimibe/simvastatin should be discontinued throughout the duration of fusidic acid treatment (see section 4.3 and section 4.4).

## Other medicine interactions

***Amiodarone:*** The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with ezetimibe/simvastatin (see sections 4.2 and 4.4). During co-administration of amiodarone and simvastatin 80 mg in a clinical trial, the risk of myopathy was approximately 6% (see section 4.4).

***Colestyramine:*** Concomitant colestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding ezetimibe/simvastatin to colestyramine may be lessened by this interaction.

***Calcium channel blockers:*** The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine. The dose of ezetimibe/simvastatin should not exceed 10/20mg daily in patients receiving concomitant medication with verapamil, diltiazem or amlodipine (see sections 4.2 and 4.4).

***Lomitapide:*** The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide (see sections 4.2 and 4.4).

***Moderate inhibitors of CYP3A4:*** Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with simvastatin, particularly higher 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):*** Simvastatin is a substrate of the efflux transporter BCRP. 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. When co-administering simvastatin with an inhibitor of BCRP, a dose adjustment of ezetimibe/simvastatin may be necessary (see sections 4.2 and 4.4).

***Fibrates:*** Concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold; however, this increase is not considered clinically significant. The safety and effectiveness of ezetimibe/simvastatin administered with fibrates have not been established. 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 until use in patients is studied.

***Niacin:*** In a study of 15 healthy adults, concomitant ezetimibe/simvastatin (10/20 mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22%, 90% Confidence Interval (CI), -28 to 105) and nicotinuric acid (19%, 90% CI, -1 to 43) [n = 13] 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%, 90% CI, -2 to 22), total ezetimibe (26%, 90% CI, 10 to 44), simvastatin (20%, 90% CI, 3 to 40) and simvastatin acid (35%, 90% CI, -3 to 88) [n = 15].

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

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

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

***Grapefruit juice:*** Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of medicines metabolised by CYP3A4. The effect of typical consumption (one 250 mL glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, because larger quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided while taking ezetimibe/simvastatin therapy (see section 4.4).

***Anticoagulants (coumarin derivates):*** 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 Normalised 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. 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.

Concomitant administration of ezetimibe (10 mg once daily) for 11 days had no significant effect on bioavailability of a single dose 25 mg warfarin, administered on Day 7, and prothrombin time in a cross-over study of twelve healthy adult males. There have been post-marketing reports of increased International Normalised Ratio in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications (see section 4.4).

The effect of ezetimibe/simvastatin on the prothrombin time has not been studied.

***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.

***Digoxin:*** Concomitant administration of simvastatin and digoxin in normal volunteers resulted in a slight elevation (less than 0.3 nanogram/mL) in plasma drug concentrations (as measured by a digoxin radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

***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. There was no effect of simvastatin on ticagrelor plasma levels. There is the potential for an increase in simvastatin-related adverse reactions such as myopathy and rhabdomyolysis with co-administration; no cases of rhabdomyolysis were reported when ticagrelor was co-administered with simvastatin 40 mg daily or lower. Therefore, concomitant use of ticagrelor with doses of simvastatin greater than 40 mg daily is not recommended.

## *4.6 Fertility, pregnancy and lactation*

### Pregnancy

#### *Ezetimibe/simvastatin*

(Category D)

Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Ezetimibe/simvastatin is contraindicated during pregnancy (see sections 4.3 and 5.3). HMG-CoA reductase inhibitors, including simvastatin, a component of Zimybe, are contraindicated in pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor, or medicines containing an HMG-CoA reductase inhibitor, therapy during pregnancy.

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

The safety of ezetimibe/simvastatin combinations in pregnant women has not been established.

Cholesterol and other products of the cholesterol biosynthesis pathway are essential components for foetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthetic pathway, Zimybe, which contains simvastatin, is contraindicated during pregnancy. Zimybe should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, Zimybe should be discontinued and the patient informed of the potential hazard to the foetus (see section 4.3).

Ezetimibe in combination with statins in rats and rabbits resulted in higher exposures to ezetimibe and/or statins than either drug administered alone. Skeletal malformations (hemivertebrae in rats and shortened/filamentous tail associated with fused and reduced number of caudal vertebrae in rabbits) and other less severe foetal abnormalities were observed in rats and rabbits dosed with ezetimibe/statin combinations during organogenesis.

#### *Simvastatin*

In two series of 178 and 134 cases where pregnant women took an HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant woman is exposed to a HMG-CoA reductase

inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to a HMG-CoA reductase inhibitor is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Maternal treatment with simvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. For this reason, ezetimibe/simvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with ezetimibe/simvastatin should 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 on exposed pregnancies are available for ezetimibe.

Ezetimibe crossed the placenta in rats and rabbits. There was no evidence of foetal abnormalities in rats dosed with up to 1000 mg/kg/day ezetimibe by oral gavage during organogenesis, corresponding to exposures about 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively, based on AUC. There was an increase in the incidence of extra thoracic ribs in rabbits at doses of 250 to 1000 mg/kg/day, corresponding to exposures 0.5 to 1 times and 100 to 150 times the adult human exposure for ezetimibe and total ezetimibe, respectively. The relevance of this finding to humans is not known.

## Breast-feeding

***Ezetimibe/simvastatin***

There are no human or animal data addressing the use of ezetimibe/simvastatin combinations during lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions, women taking ezetimibe/simvastatin should not breastfeed their infants (see section 4.3).

***Ezetimibe***

Studies in rats showed that ezetimibe is excreted in milk. Ezetimibe had no effects on pup development in rats treated with up to 1000 mg/kg/day ezetimibe during late pregnancy and lactation. Drug exposures (based on AUC) in pups were approximately 1.5% (free ezetimibe) and 50% (total ezetimibe) of maternal exposures. It is not known whether ezetimibe is excreted into human breast milk; therefore, women who are breast feeding should not take ezetimibe/simvastatin.

***Simvastatin***

Animal studies have shown that weight gain during lactation is reduced in the offspring of rats dosed with simvastatin at dosages of 12.5 to 25 mg/kg/day. There is no information from animal studies on whether simvastatin or its metabolites are excreted in breast milk.

## Fertility

***Ezetimibe/simvastatin***

There are no human data addressing the effects of ezetimibe/simvastatin combinations on fertility. In animal reproductive/fertility studies, no effect on pregnancy rates was observed in rats treated orally with ezetimibe/simvastatin at up to 1000/12.5 mg/kg. These doses correspond to exposure levels (based on AUC) approximately 1x (free ezetimibe), 20x (total ezetimibe), 0.8x (simvastatin), and 72x (hydroxysimvastatin) that expected in humans over the ezetimibe/simvastatin combination dose range (10/10 mg to 10/80 mg).

***Simvastatin***

In several studies of over 800 men with hypercholesterolaemia treated with simvastatin 20 mg to 80 mg per day for 12 to 48 weeks, basal testosterone levels were mildly decreased during simvastatin therapy, but there were no consistent changes in LH and FSH. In 86 men treated with

simvastatin 20 mg to 80 mg per day, there was no impairment of hCG-stimulated testosterone secretion.

Testicular degeneration has been seen in two dog safety studies with simvastatin. Special studies designed to further define the nature of these changes have not met with success since the effects are poorly reproducible and unrelated to dose, serum cholesterol levels, or duration of treatment. Simvastatin has been administered for up to two years to dogs at a dose of 50 mg/kg/day without any testicular effects.

## *4.7 Effects on ability to drive and use machines*

No studies of the effects on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with ezetimibe/simvastatin may affect some patients' ability to drive or operate machinery. Individual responses to ezetimibe/simvastatin may vary (see section 4.8).

## *4.8 Undesirable effects*

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

The following common (≥ 1/100, < 1/10) or uncommon (≥ 1/1000, < 1/100) medicine-related adverse experiences were reported in patients taking ezetimibe/simvastatin (n=2404) and at a greater incidence than placebo (n=1340):

***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

***Nervous system disorders:***

*Uncommon:* dizziness; headache

***Gastrointestinal disorders:***

*Uncommon:* abdominal pain; abdominal discomfort; abdominal pain upper; dyspepsia; flatulence; nausea; vomiting

***Skin and subcutaneous tissue disorders:***

*Uncommon:* pruritus; rash

***Musculoskeletal and connective tissue disorders:***

*Uncommon:* arthralgia; muscle spasms; muscular weakness; musculoskeletal discomfort; neck pain; pain in extremity

***General disorders and administration site conditions:***

*Uncommon:* asthenia; fatigue; malaise; oedema peripheral

***Psychiatric disorders:***

*Uncommon:* sleep disorder

The following common (≥ 1/100, < 1/10) or uncommon (≥ 1/1000, < 1/100); medicine-related adverse experiences were reported in patients taking ezetimibe/simvastatin (n=9595) and at a greater incidence than statins administered alone (n=8883):

***Investigations:***

*Common:* ALT and/or AST increased
*Uncommon:* blood bilirubin increased; blood CK increased; gamma-glutamyltransferase increased

***Nervous system disorders:***

*Uncommon:* headache; paresthesia

***Gastrointestinal disorders:***

*Uncommon:* abdominal distension; diarrhoea; dry mouth; dyspepsia; flatulence; gastroesophageal reflux disease; vomiting

***Skin and subcutaneous tissue disorders:***

*Uncommon:* pruritus; rash; urticaria

***Musculoskeletal and connective tissue disorders:***

*Common:* myalgia
*Uncommon:* arthralgia; back pain; muscle spasms; muscular weakness; musculoskeletal pain; pain in extremity

***General disorders and administration site conditions:***

*Uncommon:* asthenia; chest pain; fatigue; oedema peripheral

***Psychiatric disorders:***

*Uncommon:* insomnia

## Paediatric (10 to 17 years of age) patients

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 (≥ 10 X ULN). No cases of myopathy were reported(see section 4.4).

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/simvastatin for a treatment period > 33 weeks on growth, sexual maturation, intellectual and psychosocial development have not been studied (see sections 4.2, 4.4 and 5.1).

## The study was not of sufficient duration to detect long term adverse events.

## Laboratory values

In controlled clinical 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.

## Patients with coronary heart disease

In the IMPROVE-IT study (see section 5.1), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n=9067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n=9077; 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, pain or tenderness with a serum CK ≥ 10 times ULN with evidence of renal injury, ≥ 5 X ULN and < 10 X 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 hospitalizations 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 9000 patients treated with ezetimibe/simvastatin 10/20 mg daily (n=4650) or placebo (n=4620), 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 (> 3xULN) 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, cholecystectomy or complications of gallstones or pancreatitis.

### Post-marketing experience

The adverse reactions reported for ezetimibe/simvastatin are consistent with those previously reported with ezetimibe and/or simvastatin.

Additional adverse events reported commonly with ezetimibe during clinical trials:

| | |
|---|---|
| Gastrointestinal disorders: | gastritis |
| Investigations: | liver function test abnormal |
| Respiratory, thoracic and mediastinal disorders: | cough |
| Metabolism and nutrition disorders: | decreased appetite |
| Vascular disorders: | hot flush; hypertension |
| General disorders and administration site conditions: | pain |

Additional adverse events reported rarely, regardless of causality assessment, with ezetimibe during post-marketing use:

| | |
|---|---|
| Blood and lymphatic system disorders: | thrombocytopaenia |
| Hepatobiliary disorders: | cholelithiasis; cholecystitis, |

| | |
|---|---|
| | hepatitis; drug-induced liver injury |
| Musculoskeletal and connective tissue disorders: | very rarely myopathy/rhabdomyolysis (see section 4.4) |
| Psychiatric disorders: | depression |
| Skin and subcutaneous tissue disorders: | hypersensitivity reactions, including rash and urticaria (rare [≥ 1/10,000, < 1/1000]) and anaphylaxis and angioedema (very rare [< 1/10,000]), severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilic and systemic symptoms (DRESS) and erythema multiforme |
| Gastrointestinal disorders: | pancreatitis (very rare) |
| Laboratory values: | increased CPK,<br>elevations of liver transaminases |

Additional adverse events reported rarely with simvastatin during clinical studies and/or post-marketing use:

| | |
|---|---|
| Blood and lymphatic system disorders: | Rare: anaemia |
| Gastrointestinal disorders: | Rare: constipation; pancreatitis |
| Hepatobiliary disorders: | Rare: hepatitis/jaundice and very rarely, fatal and non-fatal hepatic failure |
| Eye disorders: | Rare: vision blurred, visual impairment |
| Skin and subcutaneous tissue disorders: | Very rare: lichenoid drug eruptions |
| Musculoskeletal, connective tissue and bone disorders: | Rare: muscle cramps;<br>myopathy/ rhabdomyolysis (see section 4.4)<br>Very rare: muscle rupture |
| Reproductive system and breast disorders: | Rare: erectile dysfunction<br>Very rare: gynaecomastia |

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persists despite discontinuation of statin treatment: muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see section 4.4).

| | |
|---|---|
| Nervous system disorders: | peripheral neuropathy; myasthenia gravis (see section 4.4) |
| Eye disorders: | ocular myasthenia (see section 4.4) |
| Respiratory, thoracic and mediastinal disorders: | interstitial lung disease |
| Skin and subcutaneous tissue disorders: | alopecia |

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopaenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

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

| | |
|---|---|
| Laboratory test findings**:** | Elevated alkaline phosphatase and γ-glutamyl transpeptidase have been reported with simvastatin.Increases in HbA1c and fasting serum glucose levels have been reported with statins, including simvastatin. |

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

## *4.9 Overdose*

### Zimybe

No specific treatment of overdosage with Zimybe can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. Co-administration 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, 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, and 40 mg/day to 13 patients with homozygous sitosterolemia for 26 weeks, 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.

### Simvastatin

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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

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

ATC code: C10BA02

Zimybe (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 homeostasis depends on the balance between intestinal absorption and endogenous synthesis. Zimybe contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. Zimybe reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases 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 [$^{14}$C] cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat-soluble vitamins A and D.

### *Simvastatin*

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed in the liver to the corresponding active β-hydroxy-acid 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 catabolised 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 cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and nonhigh-density lipoprotein cholesterol (non-HDL-C), and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

### *Ezetimibe/simvastatin*

**Prevention of cardiovascular disease**

In brief, ezetimibe/simvastatin has been shown in the IMPROVE-IT trial to reduce the major cardiovascular events of non-fatal myocardial infarction and stroke in patients with coronary heart disease and a history of Acute Coronary Syndrome. Total mortality, cardiovascular mortality and rates of unstable angina requiring hospitalisation and all coronary revascularisations were unchanged. There was a small increase in the rate of haemorrhagic stroke that was not statistically significant.

The IMProved Reduction of Outcomes: IMPROVE-IT was a multicenter, randomized, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalization for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤ 3.2 mmol/L (≤ 125 mg/dL) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤ 2.6 mmol/L (≤ 100 mg/dL) if they had been receiving lipid-lowering therapy. All patients were randomized 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.

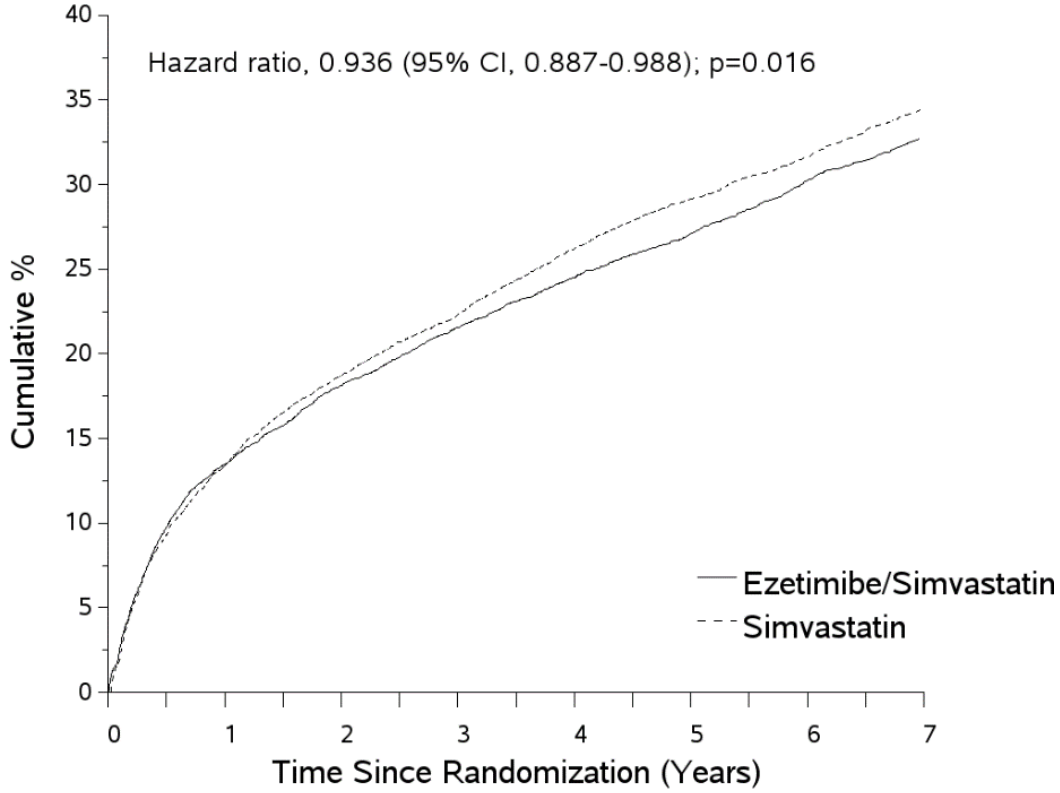
Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 2.1 mmol/L (80 mg/dL) for those on lipid-lowering therapy (n=6390) and 2.6 mmol/L (101 mg/dL) for those not on previous lipid-lowering therapy (n=11594). Prior to the hospitalization 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 1.4 mmol/L (53.2 mg/dL) for the ezetimibe/simvastatin group and 1.8 mmol/L (69.9 mg/dL) 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 hospitalization, or any coronary revascularization procedure occurring at least 30 days after randomized 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 co-administered 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*




| Subjects at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ezetimibe/Simvastatin | 9067 | 7371 | 6801 | 6375 | 5839 | 4284 | 3301 | 1906 |
| Simvastatin | 9077 | 7455 | 6799 | 6327 | 5729 | 4206 | 3284 | 1857 |

*Table 2: Major cardiovascular events by treatment group in all randomized patients in IMPROVE-IT*

| Outcome | Ezetimibe/simvastatin 10/40 mg[1] (N=9067) | | Simvastatin 40 mg[2] (N=9077) | | Ratio (95% CI) | p-value |
|---|---|---|---|---|---|---|
| | n | K – M %[3] | n | K – M %[3] | | |
| 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, nonfatal MI, urgent coronary revascularization 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 |

1 6% were uptitrated to ezetimibe/simvastatin 10/80 mg
2 27% were uptitrated to simvastatin 80 mg
3 Kaplan-Meier estimated at 7 years

| | | | | | | |
|---|---|---|---|---|---|---|
| CV death, non-fatal MI, unstable angina requiring hospitalization, any revascularization, 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 hospitalization | 156 | 2.06% | 148 | 1.92% | 1.059 (0.846, 1.326) | 0.618 |
| Coronary revascularization 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-hemorrhagic stroke[4] | 242 | 3.48% | 305 | 4.23% | 0.793 (0.670, 0.939) | 0.007 |
| Hemorrhagic 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 |

**Prevention of major vascular events in chronic kidney disease (CKD)**

The Study of Heart and Renal Protection (SHARP) was a multinational, randomised, placebo-controlled, double-blind study conducted in 9,438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. Patients with a definite history of myocardial infarction (MI) or coronary revascularisation procedure, existing or planned renal transplant, recent acute uraemic emergency, evidence of active inflammatory muscle disease or creatine kinase (CK) > 3xULN were excluded. For the first year, patients were randomised in a ratio of 4:4:1, respectively, to ezetimibe/simvastatin 10/20, placebo, or simvastatin 20 mg daily. The 1-year simvastatin arm was included to enable the comparison of ezetimibe/simvastatin to simvastatin alone with regard to safety and lipids. At 1 year the simvastatin-only arm was re-randomised 1:1 to ezetimibe/simvastatin 10/20 or placebo. A total of 4,650 patients were allocated to ezetimibe/simvastatin 10/20 and 4,620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 (ranging in age from 39 to 94.5 years old); 63% were male, 72% were Caucasian, and 23% were diabetic; and, for those not on dialysis, the median serum creatinine was 0.22 mmol/L and the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 $m^2$, with 94% of patients having an eGFR < 45 mL/min/1.73 $m^2$. There were no lipid entry criteria. Mean LDL-C at baseline was 2.8 mmol/L. As of the 1-year measurement, LDL-C was reduced 26% relative to placebo by simvastatin 20 mg alone and 38% for ezetimibe/simvastatin 10/20. At the midpoint of the study (2.5 years) mean LDL-C reduction for ezetimibe/simvastatin relative to placebo was 32%. All lipid measurements included patients no longer taking study medication.

[4] Includes ischemic stroke or stroke of undetermined type

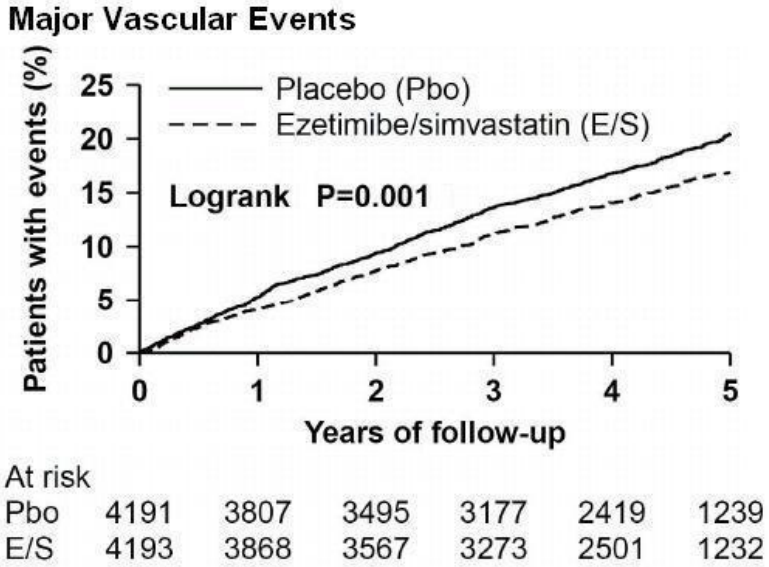
The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularisation procedure) in only those patients initially randomised to the ezetimibe/simvastatin (n=4,193) or placebo (n=4,191) groups. Secondary analyses included the same composite analysed for the full cohort randomised (at study baseline or at year 1) to ezetimibe/simvastatin (n=4,650) or placebo (n=4,620), as well as the components of this composite.

The primary endpoint analysis showed that ezetimibe/simvastatin significantly reduced the risk of MVE (749 patients with events in the placebo group vs. 639 in the ezetimibe/simvastatin group) with an absolute risk reduction of 2.3% (number needed to treat, 43) and a relative risk reduction of 16% (p=0.001) (see Figure 2). An analysis of major atherosclerotic events (MAE, a subset of the MVE composite that excluded non-coronary cardiac deaths and haemorrhagic stroke) showed that ezetimibe/simvastatin significantly reduced the risk of MAE (526 (11.3%) of 4650 patients ever allocated to ezetimibe/simvastatin and 619 (13.4%) of 4620 patients ever allocated to placebo), corresponding to an absolute risk reduction of 2.1% (number needed to treat, 48) and a relative risk reduction of 17% (p=0.002).

The risk reduction for the MVE composite was directionally consistent (i.e. ezetimibe/simvastatin numerically superior to placebo) with that of the entire cohort of patients for the following key baseline predefined subgroups: age, gender, dialysis vs. non-dialysis, eGFR, diabetes, pre-existing atherosclerotic disease, blood pressure, or tertiles of baseline LDL-C.

Compliance rates with placebo and study medication declined over the course of the study. For example, at 20-25 months of follow-up, 68% of patients allocated to ezetimibe/simvastatin and 67% of patients allocated to placebo were taking 80% or more of the study medication, while at 44-49 months, compliance had fallen to 60% and 56%, respectively.

*Figure 2: Effect of ezetimibe/simvastatin on the primary endpoint of risk of major vascular events*




The individual components of MVE in all randomised patients are presented in Table 3. Ezetimibe/simvastatin significantly reduced the risk of stroke and any revascularisation, with non-significant numerical differences favouring ezetimibe/simvastatin for nonfatal MI and cardiac death.

*Table 3: Major vascular events by treatment group in all randomised patients in SHARP[5]*

| Outcome | Ezetimibe/simvastatin 10/20 (N=4650) | Placebo (N=4620) | Risk Ratio (95% CI) | 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-hemorrhagic stroke | 131 (2.8%) | 174 (3.8%) | 0.75 (0.60-0.94) | 0.011 |
| Hemorrhagic stroke | 45 (1.0%) | 37 (0.8%) | 1.21 (0.78-1.86) | 0.40 |
| Any revascularisation | 284 (6.1%) | 352 (7.6%) | 0.79 (0.68-0.93) | 0.004 |
| Major atherosclerotic events (MAE)[6] | 526 (11.3%) | 619 (13.4%) | 0.83 (0.74-0.94) | 0.002 |

No significant treatment effect of ezetimibe/simvastatin on MVE was found in the subgroup of patients on dialysis at baseline compared with those not on dialysis at baseline. Among 3023 patients on dialysis at baseline, ezetimibe/simvastatin reduced the risk of MVE by 6% (RR 0.94: 95% CI 0.80-1.09) compared with 22% (RR 0.78: 95% CI 0.69-0.89) among 6247 patients not on dialysis at baseline (interaction P=0.08).

Among patients not on dialysis at baseline, ezetimibe/simvastatin did not reduce the risk of progressing to end-stage renal disease compared with placebo.

There were no significant differences between the ezetimibe/simvastatin and placebo groups on all cause mortality, or on any specific cause of death.

The study design precluded drawing conclusions regarding the independent contribution of either ezetimibe or simvastatin to the observed effect, and was not able to provide evidence of efficacy for the combination of ezetimibe/simvastatin 10/20 compared to either the lower dose combination (i.e. ezetimibe/simvastatin 10/10) or to treatment with statin alone (i.e. simvastatin 20 mg).

**Primary hypercholesterolaemia**

Five multicentre, double-blind studies conducted with ezetimibe/simvastatin in patients with primary hypercholesterolaemia are reported: two were comparisons with simvastatin and two were comparisons with atorvastatin and one was a comparison with rosuvastatin.

In a multicentre, double-blind, placebo-controlled, 12-week trial, 887 hypercholesterolaemic patients were randomised to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or co-administered ezetimibe and simvastatin (10/10, 10/20, 10/40, and 10/80). Ezetimibe/simvastatin significantly lowered total-C, LDL-C, Apo B, TG, non-HDL-C, and C-reactive protein compared to all doses of simvastatin. 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. (See Tables 4 [mean absolute change] and 5 [mean percent change]).

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5 Intention-to-treat analysis on all SHARP patients randomised to ezetimibe/simvastatin or placebo either at baseline or year 1

6 MAE; defined as the composite of nonfatal myocardial infarction, coronary death, non-haemorrhagic stroke, or any revascularisation

*Table 4: Response to ezetimibe/simvastatin in patients with primary hypercholesterolaemia (mean[7] absolute change from untreated baseline[8])*

| Treatment (Daily dose) | N | Total-C Abs[9] [Baseline] | LDL-C Abs[9] [Baseline] | Apo B Abs[9] [Baseline] | HDL-C Abs[9] [Baseline] | TG[7] Abs[9] [Baseline] | Non-HDL-C Abs[9] [Baseline] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ezetimibe/simvastatin doses) | 353 | -2.55 [6.73] | -2.42 [4.52] | -0.68 [1.60] | +0.10 [1.31] | -0.48 [1.90] | -2.65 [5.42] |
| Pooled data (All simvastatin doses) | 349 | -1.78 [6.70] | -1.75 [4.52] | -0.47 [1.59] | +0.09 [1.28] | -0.26 [1.89] | -1.87 [5.42] |
| Ezetimibe 10 mg | 92 | -0.94 [6.79] | -0.91 [4.55] | -0.23 [1.58] | +0.08 [1.32] | -0.21 [1.85] | -1.02 [5.46] |
| Placebo | 93 | +0.13 [6.66] | +0.11 [4.49] | +0.04 [1.59] | +0.02 [1.30] | -0.03 [1.83] | +0.11 [5.36] |
| Ezetimibe/simvastatin by dose: | | | | | | | |
| 10/10 | 87 | -2.13 [6.70] | -2.09 [4.49] | -0.59 [1.62] | +0.11 [1.31] | -0.39 [1.87] | -2.24 [5.39] |
| 10/20 | 86 | -2.52 [6.88] | -2.35 [4.63] | -0.69 [1.63] | +0.09 [1.33] | -0.53 [2.00] | -2.62 [5.55] |
| 10/40 | 89 | -2.69 [6.71] | -2.47 [4.45] | -0.72 [1.60] | +0.10 [1.31] | -0.56 [1.93] | -2.79 [5.40] |
| 10/80 | 91 | -2.88 [6.64] | -2.76 [4.50] | -0.74 [1.57] | +0.08 [1.29] | -0.46 [1.81] | -2.95 [5.35] |
| Simvastatin by dose: | | | | | | | |
| 10 mg | 81 | -1.41 [6.69] | -1.44 [4.53] | -0.38 [1.59] | +0.05 [1.30] | -0.8 [1.82] | -1.47 [5.39] |
| 20 mg | 90 | -1.61 [6.66] | -1.58 [4.49] | -0.41 [1.58] | +0.07 [1.29] | -0.25 [1.85] | -1.68 [5.38] |
| 40 mg | 91 | -1.95 [6.71] | -1.90 [4.55] | -0.55 [1.61] | +0.10 [1.25] | -0.33 [1.90] | -2.04 [5.47] |
| 80 mg | 87 | -2.16 [6.72] | -2.09 [4.52] | -0.57 [1.59] | +0.13 [1.28] | -0.43 [1.94] | -2.29 [5.44] |

*Table 5: Response to ezetimibe/simvastatin in patients with primary hypercholesterolaemia (mean[10] percent change from untreated baseline[11])*

| Treatment (Daily dose) | N | Total-C Pct[12] [Baseline[13]] | LDL-C Pct[12] [Baseline[13]] | Apo B Pct[12] [Baseline[13]] | HDL-C Pct[12] [Baseline[13]] | TG[10] Pct[12] [Baseline[13]] | Non-HDL-C Pct[12] [Baseline[13]] |
|---|---|---|---|---|---|---|---|

7 For triglycerides, median absolute change from baseline
8 Baseline – on no lipid-lowering drug
9 Mean absolute change from baseline
(units are mmol/L for all parameters except Apo B, which is in g/L)
10 For triglycerides, median % change from baseline
11 Baseline – on no lipid-lowering drug
12 Mean absolute change from baseline
13 Baseline units are mmol/L for all parameters except Apo B, which is in g/L

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pooled data (All ezetimibe/simvastatin doses)[14] | 353 | -38 [6.73] | -53 [4.52] | -42 [1.60] | +8 [1.31] | -28 [1.90] | -49 [5.42] |
| Pooled data (All simvastatin doses)[14] | 349 | -26 [6.70] | -38 [4.52] | -29 [1.59] | +8 [1.28] | -15 [1.89] | -34 [5.42] |
| Ezetimibe 10 mg | 92 | -14 [6.79] | -20 [4.55] | -15 [1.58] | +7 [1.32] | -13 [1.85] | -19 [5.46] |
| Placebo | 93 | +2 [6.66] | +3 [4.49] | +3 [1.59] | +2 [1.30] | -2 [1.83] | +2 [5.36] |
| Ezetimibe/simvastatin by dose: | | | | | | | |
| 10/10 | 87 | -32 [6.70] | -46 [4.49] | -36 [1.62] | +9 [1.31] | -21 [1.87] | -41 [5.39] |
| 10/20 | 86 | -37 [6.88] | -51 [4.63] | -41 [1.63] | +8 [1.33] | -31 [2.00] | -47 [5.55] |
| 10/40 | 89 | -39 [6.71] | -55 [4.45] | -44 [1.60] | +9 [1.31] | -32 [1.93] | -51 [5.40] |
| 10/80 | 91 | -43 [6.64] | -61 [4.50] | -47 [1.57] | +6 [1.29] | -28 [1.81] | -55 [5.35] |
| Simvastatin by dose: | | | | | | | |
| 10 mg | 81 | -21 [6.69] | -31 [4.53] | -23 [1.59] | +5 [1.30] | -4 [1.82] | -27 [5.39] |
| 20 mg | 90 | -24 [6.66] | -35 [4.49] | -25 [1.58] | +6 [1.29] | -14 [1.85] | -31 [5.38] |
| 40 mg | 91 | -29 [6.71] | -42 [4.55] | -33 [1.61] | +8 [1.25] | -19 [1.90] | -37 [5.47] |
| 80 mg | 87 | -32 [6.72] | -46 [4.52] | -35 [1.59] | +11 [1.28] | -26 [1.94] | -41 [5.44] |

In a similarly designed study, results for all lipid parameters were generally consistent. In a pooled analysis of these two studies, the incremental reduction of LDL-C concentration with the combination tablet was generally consistent across subgroups tested, including risk factor status, age, and baseline lipid profile. In addition, the lipid response to ezetimibe/simvastatin was similar in patients with TG levels greater than or less than 2.3 mmol/L (200 mg/dL).

In a multicentre, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C ≥ 3.4 mmol/L (130 mg/dL) were randomised to one of four treatment groups: co-administered ezetimibe and simvastatin (10/10, 10/20, and 10/40), or simvastatin 20 mg. Patients not reaching an LDL-C < 2.6 mmol/L (100 mg/dL) had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg. At Week 5, the LDL-C reductions with ezetimibe/simvastatin 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg. In addition, at Week 5, significantly more patients receiving ezetimibe/simvastatin 10/10, 10/20, or 10/40 attained LDL-C target compared to those receiving simvastatin 20 mg (see Tables 6 [mean absolute change] and 7 [mean percent change]). Week 5 results for LDL-C reduction and percentage attaining LDL-C target were consistent with the end of study results (Week 23).

[14] Ezetimibe/simvastatin doses pooled (10/10 – 10/80) significantly reduced total-C, LDL-C, Apo B, TG, and non-HDL-C compared to simvastatin, and significantly increased HDL-C compared to placebo

*Table 6: Response to ezetimibe/simvastatin after 5 weeks in patients with CHD or CHD risk equivalents and an LDL-C ≥ 3.4 mmol/L (130 mg/dL) (mean absolute change from baseline)*

| | Simvastatin 20 mg [Baseline] | Ezetimibe/simvastatin 10/10 [Baseline] | Ezetimibe/simvastatin 10/20 [Baseline] | Ezetimibe/simvastatin 10/40 [Baseline] |
|---|---|---|---|---|
| N | 253 | 251 | 109 | 97 |
| LDL-C Abs[15] | -1.6 [4.49] | -2.0 [4.26] | -2.3 [4.33] | -2.6 [4.41] |
| Percent attaining LDL-C goal | 46 | 75 | 83 | 88 |

*Table 7: Response to ezetimibe/simvastatin after 5 weeks in patients with CHD or CHD risk equivalents and an LDL- C ≥ 3.4 mmol/L (130 mg/dL) (mean percent change from untreated baseline)*

| | Simvastatin 20 mg [Baseline[16]] | Ezetimibe/simvastatin 10/10 [Baseline[16]] | Ezetimibe/simvastatin 10/20 [Baseline[16]] | Ezetimibe/simvastatin 10/40 [Baseline[16]] |
|---|---|---|---|---|
| N | 253 | 251 | 109 | 97 |
| LDL-C Pct[17] | -38 [4.49] | -47 [4.26] | -53 [4.33] | -59 [4.41] |
| Percent attaining LDL-C goal | 46 | 75 | 83 | 88 |

In a multicentre, double-blind, 6-week study, 1902 patients with primary hypercholesterolaemia, who had not met their NCEP ATP III target LDL-C goal, were randomised to one of eight treatment groups: ezetimibe/simvastatin (10/10, 10/20, 10/40 or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg or 80 mg). When patients receiving all doses of ezetimibe/simvastatin were compared to those receiving all doses of atorvastatin, ezetimibe/simvastatin lowered total-C, LDLC, Apo B and non-HDL-C, and increased HDL-C significantly more than atorvastatin. The effects of ezetimibe/simvastatin on TG were similar to the effects seen with atorvastatin (see Tables 8 [mean absolute change] and 9 [mean percent change]).

*Table 8: Response to ezetimibe/simvastatin and atorvastatin in patients with primary hypercholesterolaemia (mean[18] absolute change from untreated baseline[19])*

| Treatment (Daily dose) | N | Total-C Abs[20] [Baseline] | LDL-C Abs[20] [Baseline] | Apo B Abs[20] [Baseline] | HDL-C Abs[20] [Baseline] | TG[18] Abs[20] [Baseline] | Non-HDL-C Abs[20] [Baseline] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ezetimibe/simvastatin doses) | 951 | -2.64 [6.83] | -2.46 [4.60] | -0.71 [1.65] | +0.09 [1.27] | -0.51 [1.93] | -2.73 [5.56] |

15 Mean absolute change from untreated baseline, expressed as mmol/L
16 Baseline values expressed as mmol/L
17 Mean percent change from untreated baseline
18 For triglycerides, median absolute change from baseline
19 Baseline – on no lipid-lowering drug
20 Mean absolute change from baseline
(units are mmol/L for all parameters except Apo B, which is in g/L)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pooled data (All atorvastatin doses) | 951 | -2.32 [6.84] | -2.11 [4.63] | -0.63 [1.65] | +0.04 [1.26] | -0.45 [1.89] | -2.36 [5.58] |
| Ezetimibe/simvastatin by dose: | | | | | | | |
| 10/10 | 238 | -2.33 [6.83] | -2.17 [4.57] | -0.62 [1.65] | +0.09 [1.27] | -0.44 [1.96] | -2.41 [5.56] |
| 10/20 | 238 | -2.52 [6.84] | -2.36 [4.62] | -0.67 [1.64] | +0.08 [1.27] | -0.42 [1.89] | -2.60 [5.57] |
| 10/40 | 238 | -2.81 [6.85] | -2.64 [4.60] | -0.77 [1.66] | +0.10 [1.27] | -0.55 [1.94] | -2.91 [5.58] |
| 10/80 | 237 | -2.90 [6.81] | -2.68 [4.59] | -0.80 [1.65] | +0.08 [1.27] | -0.60 [1.92] | -2.98 [5.54] |
| Atorvastatin by dose: | | | | | | | |
| 10 mg | 238 | -1.82 [6.77] | -1.67 [4.53] | -0.51 [1.63] | +0.07 [1.25] | -0.41 [1.93] | -1.89 [5.52] |
| 20 mg | 237 | -2.23 [6.86] | -2.03 [4.61] | -0.61 [1.67] | +0.05 [1.26] | -0.46 [1.96] | -2.28 [5.60] |
| 40 mg | 237 | -2.46 [6.85] | -2.25 [4.65] | -0.67 [1.64] | +0.04 [1.30] | -0.41 [1.82] | -2.49 [5.55] |
| 80 mg | 239 | -2.78 [6.89] | -2.49 [4.72] | -0.74 [1.67] | +0.10 [1.24] | -0.59 [1.87] | -2.79 [5.65] |

*Table 9: Response to ezetimibe/simvastatin and atorvastatin in patients with primary hypercholesterolaemia (mean[21] percent change from untreated baseline[19])*

| Treatment (Daily dose) | N | Total-C Pct[22] [Baseline[23]] | LDL-C Pct[22] [Baseline[23]] | Apo B Pct[22] [Baseline[23]] | HDL-C Pct[22] [Baseline[23]] | TG[21] Pct[22] [Baseline[23]] | Non-HDL-C Pct[22] [Baseline[23]] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ezetimibe/simvastatin doses) | 951 | -38[24] [6.83] | -53[24] [4.60] | -43[24] [1.65] | +8[24] [1.27] | -27 [1.93] | -49[24] [5.56] |
| Pooled data (All atorvastatin doses) | 951 | -34 [6.84] | -45 [4.63] | -38 [1.65] | +4 [1.26] | -26 [1.89] | -42 [5.58] |
| Ezetimibe/simvastatin by dose: | | | | | | | |
| 10/10 | 238 | -34[25] [6.83] | -47[25] [4.57] | -37[25] [1.65] | +8 [1.27] | -26 [1.96] | -43[25] [5.56] |
| 10/20 | 238 | -37[25] [6.84] | -51[25] [4.62] | -40[25] [1.64] | +7 [1.27] | -25 [1.89] | -46[25] [5.57] |
| 10/40 | 238 | -41[25] [6.85] | -57[25] [4.60] | -46[25] [1.66] | +9[25] [1.27] | -27 [1.94] | -52[25] [5.58] |
| 10/80 | 237 | -43[25] [6.81] | -59[25] [4.59] | -48[25] [1.65] | +8[25] [1.27] | -31 [1.92] | -54[25] [5.54] |
| Atorvastatin by dose: | | | | | | | |
| 10 mg | 238 | -27 [6.77] | -36 [4.53] | -31 [1.63] | +7 [1.25] | -21 [1.93] | -34 [5.52] |

21 For triglycerides, median % change from baseline
22 Mean percent change from baseline
23 Baseline units are mmol/L for all parameters except Apo B, which is in g/L
24 $p < 0.05$ for difference with atorvastatin
25 $p < 0.05$ for difference with atorvastatin at equal mg doses of the simvastatin component

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 20 mg | 237 | -32 [6.86] | -44 [4.61] | -37 [1.67] | +5 [1.26] | -25 [1.96] | -41 [5.60] |
| 40 mg | 237 | -36 [6.85] | -48 [4.65] | -40 [1.64] | +4 [1.30] | -24 [1.82] | -45 [5.55] |
| 80 mg | 239 | -40 [6.89] | -53 [4.72] | -44 [1.67] | +1 [1.24] | -32 [1.87] | -50 [5.65] |

In a multicentre, double-blind, 24-week, forced titration study, 788 patients with primary hypercholesterolaemia, who had not met their NCEP ATP III target LDL-C goal, were randomised to receive co-administered ezetimibe and simvastatin (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison, ezetimibe/simvastatin lowered LDL-C to a greater degree than atorvastatin (see Tables 10 [mean absolute change] and 11 [mean percent change]).

*Table 10: Response to ezetimibe/simvastatin and atorvastatin in patients with primary hypercholesterolaemia (mean[26] absolute change from untreated baseline[27])*

| Treatment | N | Total-C Abs[28] [Baseline] | LDL-C Abs[28] [Baseline] | Apo B Abs[28] [Baseline] | HDL-C Abs[28] [Baseline] | TG[26] Abs[28] [Baseline] | Non-HDL-C Abs[28] [Baseline] |
|---|---|---|---|---|---|---|---|
| Week 6 | | | | | | | |
| Atorvastatin 10 mg[29] | 262 | -1.95 [6.90] | -1.75 [4.67] | -0.54 [1.70] | +0.05 [1.21] | -0.42 [1.94] | -2.00 [5.68] |
| Ezetimibe/ simvastatin 10/10[30] | 263 | -2.34 [6.87] | -2.15 [4.65] | -0.65 [1.72] | +0.08 [1.21] | -0.52 [1.97] | -2.42 [5.66] |
| Ezetimibe/ simvastatin 10/20[31] | 263 | -2.48 [6.83] | -2.33 [4.63] | -0.70 [1.69] | +0.11 [1.21] | -0.46 [1.99] | -2.59 [5.62] |
| Week 12 | | | | | | | |
| Atorvastatin 20 mg | 246 | -2.29 [6.89] | -2.06 [4.66] | -0.64 [1.69] | +0.07 [1.20] | -0.52 [1.95] | -2.36 [5.68] |
| Ezetimibe/ simvastatin 10/20 | 250 | -2.52 [6.86] | -2.35 [4.65] | -0.07 [1.71] | +0.10 [1.21] | -0.52 [1.95] | -2.62 [5.65] |
| Ezetimibe/ simvastatin 10/40 | 252 | -2.69 [6.83] | -2.52 [4.64] | -0.76 [1.69] | +0.14 [1.21] | -0.54 [1.98] | -2.83 [5.62] |
| Week 18 | | | | | | | |
| Atorvastatin 40 mg | 237 | -2.56 [6.88] | -2.28 [4.64] | -0.72 [1.69] | +0.08 [1.21] | -0.59 [1.95] | -2.64 [5.67] |
| Ezetimibe/ simvastatin 10/40[32] | 482 | -2.78 [6.84] | -2.58 [4.64] | -0.77 [1.70] | +0.12 [1.21] | -0.60 [1.97] | -2.90 [5.63] |
| Week 24 | | | | | | | |
| Atorvastatin 80 mg | 228 | -2.79 [6.88] | -2.45 [4.64] | -0.76 [1.69] | +0.07 [1.21] | -0.66 [1.95] | -2.85 [5.68] |

26 For triglycerides, median absolute change from baseline
27 Baseline – on no lipid-lowering drug
28 Mean absolute change from baseline
(units are mmol/L for all parameters except Apo B, which is in g/L)
29 Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through weeks 6, 12, 18 and 24
30 Ezetimibe/simvastatin 10/10 start dose titrated to 10/20, 10/40, and 10/80 through weeks 6, 12, 18 and 24
31 Ezetimibe/simvastatin 10/20 start dose titrated to 10/40, and 10/80 through weeks 6, 12, 18 and 24
32 Data pooled for common doses of ezetimibe/simvastatin weeks 18 and 24

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ezetimibe/ simvastatin 10/80[32] | 459 | -2.97 [6.84] | -2.75 [4.64] | -0.83 [1.70] | +0.14 [1.21] | -0.68 [1.97] | -3.11 [5.63] |

*Table 11: Response to ezetimibe/simvastatin and atorvastatin in patients with primary hypercholesterolaemia (mean[33] percent change from untreated baseline[34])*

| Treatment | N | Total-C Pct[35] [Baseline[36]] | LDL-C Pct[35] [Baseline[36]] | Apo B Pct[35] [Baseline[36]] | HDL-C Pct[35] [Baseline[36]] | TG[33] Pct[35] [Baseline[36]] | Non-HDL-C Pct[35] [Baseline[36]] |
|---|---|---|---|---|---|---|---|
| Week 6 | | | | | | | |
| Atorvastatin 10 mg[37] | 262 | -28 [6.90] | -37 [4.67] | -32 [1.70] | +5 [1.21] | -23 [1.94] | -35 [5.68] |
| Ezetimibe/ simvastatin 10/10[38] | 263 | -34[39] [6.87] | -46[39] [4.65] | -38[39] [1.72] | +8[39] [1.21] | -0.26 [1.97] | -43[39] [5.66] |
| Ezetimibe/ simvastatin 10/20[40] | 263 | -36[39] [6.83] | -50[39] [4.63] | -41[39] [1.69] | +10[39] [1.21] | -25 [1.99] | -46[39] [5.62] |
| Week 12 | | | | | | | |
| Atorvastatin 20 mg | 246 | -33 [6.89] | -44 [4.66] | -38 [1.69] | +7 [1.20] | -28 [1.95] | -42 [5.68] |
| Ezetimibe/ simvastatin 10/20 | 250 | -37[39] [6.86] | -50[39] [4.65] | -41[39] [1.71] | +9 [1.21] | -28 [1.95] | -46[39] [5.65] |
| Ezetimibe/ simvastatin 10/40 | 252 | -39[39] [6.83] | -54[39] [4.64] | -45[39] [1.69] | +12[39] [1.21] | -31 [1.98] | -50[39] [5.62] |
| Week 18 | | | | | | | |
| Atorvastatin 40 mg | 237 | -37 [6.88] | -49 [4.64] | -42 [1.69] | +8 [1.21] | -31 [1.95] | -47 [5.67] |
| Ezetimibe/ simvastatin 10/40[41] | 482 | -40[39] [6.84] | -56[39] [4.64] | -45[39] [1.70] | +11[39] [1.21] | -32 [1.97] | -52[39] [5.63] |
| Week 24 | | | | | | | |
| Atorvastatin 80 mg | 228 | -40 [6.88] | -53 [4.64] | -45 [1.69] | +6 [1.21] | -35 [1.95] | -50 [5.68] |
| Ezetimibe/ simvastatin 10/80[32] | 459 | -43[39] [6.84] | -59[39] [4.64] | -49[39] [1.70] | +12[39] [1.21] | -35 [1.97] | -55[39] [5.63] |

In a multicentre, double-blind, 6-week study, 2959 patients with hypercholesterolaemia, who had not met their NCEP ATP III target LDL-C goal, were randomised to one of six treatment groups: ezetimibe/simvastatin (10/20, 10/40 or 10/80) or rosuvastatin (10 mg, 20 mg or 40 mg). When patients receiving all doses of ezetimibe/simvastatin were compared to those receiving all doses of

33 For triglycerides, median % change from baseline
34 Baseline – on no lipid-lowering drug
35 Mean percent change from baseline
36 Baseline values expressed as mmol/L except Apo B, which is in g/L
37 Atorvastatin: 10 mg start dose titrated to 20 mg, 40 mg, and 80 mg through weeks 6, 12, 18 and 24
38 Ezetimibe/simvastatin 10/10 start dose titrated to 10/20, 10/40, and 10/80 through weeks 6, 12, 18 and 24
39 $p \leq 0.05$ for difference with atorvastatin in the specified week
40 Ezetimibe/simvastatin 10/20 start dose titrated to 10/40, and 10/80 through weeks 6, 12, 18 and 24
41 Data pooled for common doses of ezetimibe/simvastatin weeks 18 and 24

rosuvastatin, ezetimibe/simvastatin lowered total-C, LDL-C, Apo B and non-HDL-C significantly more than rosuvastatin. The effects of ezetimibe/simvastatin on HDL-C were similar to the effects seen with rosuvastatin (see Tables 12 [mean absolute change] and 13 [mean percent change]).

*Table 12: Response to ezetimibe/simvastatin and rosuvastatin in patients with hypercholesterolaemia - Modified-Intention-To-Treat Approach (mean[42] absolute change from untreated baseline[43])*

| Treatment (Daily dose) | N | Total-C Abs[44] [Baseline[45]] | LDL-C Abs[44] [Baseline[45]] | Apo B Abs[44] [Baseline[45]] | HDL-C Abs[44] [Baseline[45]] | TG[42] Abs[44] [Baseline[45]] | Non-HDL-C Abs[44] [Baseline[45]] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ezetimibe/simvastatin MSD doses) | 1427 | -2.71[46] [6.65] | -2.55[46] [4.47] | -0.73[46] [1.58] | +0.09 [1.30] | -0.42 [1.77] | -2.80[46] [5.35] |
| Pooled data (All rosuvastatin doses) | 1428 | -2.50 [6.66] | -2.37 [4.48] | -0.69 [1.59] | +0.09 [1.29] | -0.42 [1.80] | -2.59 [5.36] |
| Ezetimibe/simvastatin MSD by dose: | | | | | | | |
| 10/20 | 476 | -2.47[47] [6.62] | -2.35[47] [4.46] | -0.67[47] [1.58] | +0.08 [1.31] | -0.35 [1.70] | -2.55[47] [5.32] |
| 10/40 | 477 | -2.68[48] [6.69] | -2.52[48] [4.48] | -0.73[48] [1.59] | +0.10 [1.30] | -0.45 [1.85] | -2.78[48] [5.38] |
| 10/80 | 474 | -2.97[49] [6.63] | -2.78[49] [4.47] | -0.80[49] [1.58] | +0.09 [1.30] | -0.50[49] [1.76] | -3.06[49] [5.34] |
| Rosuvastatin by dose: | | | | | | | |
| 10 mg | 475 | -2.21 [6.65] | -2.11 [4.45] | -0.61 [1.58] | +0.08 [1.31] | -0.33 [1.83] | -2.29 [5.34] |
| 20 mg | 478 | -2.53 [6.66] | -2.39 [4.48] | -0.70 [1.59] | +0.10 [1.29] | -0.44 [1.80] | -2.63 [5.37] |
| 40 mg | 475 | -2.75 [6.66] | -2.61 [4.50] | -0.76 [1.59] | +0.10 [1.29] | -0.46 [1.75] | -2.85 [5.37] |

42 For triglycerides, median absolute change from baseline
43 Baseline – on no lipid-lowering drug
44 Mean absolute change from baseline
45 Baseline values expressed as mmol/L except Apo B, which is in g/L
46 $p < 0.05$ for difference with rosuvastatin
47 $p < 0.05$ vs. rosuvastatin 10 mg
48 $p < 0.05$ vs. rosuvastatin 20 mg
49 $p < 0.05$ vs. rosuvastatin 40 mg

*Table 13: Response to ezetimibe/simvastatin and rosuvastatin in patients with primary hypercholesterolaemia - Modified-Intention-To-Treat Approach (mean[50] % change from untreated baseline[51])*

| Treatment (Daily dose) | N | Total-C Pct[52] [Baseline[53]] | LDL-C Pct[52] [Baseline[23]] | Apo B Pct[52] [Baseline[23]] | HDL-C Pct[52] [Baseline[23]] | TG[50] Pct[52] [Baseline[23]] | Non-HDL-C Pct[52] [Baseline[23]] |
|---|---|---|---|---|---|---|---|
| Pooled data (All ezetimibe/simvastatin MSD doses) | 1427 | -40[54] [6.65] | -56[54] [4.47] | -45[54] [1.58] | +8 [1.30] | -26 [1.77] | -51[54] [5.35] |
| Pooled data (All rosuvastatin doses) | 1428 | -37 [6.66] | -52 [4.48] | -42 [1.59] | +8 [1.29] | -25 [1.80] | -47 [5.36] |
| Ezetimibe/simvastatin MSD by dose: | | | | | | | |
| 10/20 | 476 | -37[55] [6.62] | -52[55] [4.46] | -42[55] [1.58] | +7 [1.31] | -23[55] [1.70] | -47[55] [5.32] |
| 10/40 | 477 | -39[56] [6.69] | -55[56] [4.48] | -44[56] [1.59] | +8 [1.30] | -27 [1.85] | -50[56] [5.38] |
| 10/80 | 474 | -44[57] [6.63] | -61[57] [4.47] | -50[57] [1.58] | +8 [1.30] | -30[57] [1.76] | -56[57] [5.34] |
| Rosuvastatin by dose: | | | | | | | |
| 10 mg | 475 | -32 [6.65] | -46 [4.45] | -37 [1.58] | +7 [1.31] | -20 [1.83] | -42 [5.34] |
| 20 mg | 478 | -37 [6.66] | -52 [4.48] | -43 [1.59] | +8 [1.29] | -26 [1.80] | -48 [5.37] |
| 40 mg | 475 | -41 [6.66] | -57 [4.50] | -47 [1.59] | +8 [1.29] | -28 [1.75] | -52 [5.37] |

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 co-administered with simvastatin, 76% and 21.5%, respectively. The additional 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 co-administered ezetimibe/simvastatin 10/20.

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50 For triglycerides, median % change from baseline
51 Baseline – on no lipid-lowering drug
52 Mean percent change from baseline
53 Baseline values expressed as mmol/L except Apo B, which is in g/L
54 $p < 0.05$ for difference with rosuvastatin
55 $p < 0.05$ vs. rosuvastatin 10 mg
56 $p < 0.05$ vs. rosuvastatin 20 mg
57 $p < 0.05$ vs. rosuvastatin 40 mg

Ezetimibe/simvastatin 10/20 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.

**ENHANCE study**

This randomised, double-blind trial recruited 720 patients with heterozygous familial hypercholesterolaemia. The primary variable was the mean change in carotid intima media thickness (cIMT) from baseline to endpoint. Patients were treated with either simvastatin alone, 80 mg simvastatin daily or ezetimibe 10 mg in combination with simvastatin 80 mg once daily for up to two years. The mean cIMT increased by 0.0058 mm following simvastatin and 0.0111 mm following combined therapy with ezetimibe and simvastatin. The difference between treatments was not statistically significant (p-value 0.29 based on ANCOVA model). The reason for the lack of difference between treatment groups in the change in cIMT is unknown.

The combination had a significantly greater effect on lipid parameters compared with simvastatin alone. Mean LDL-cholesterol decreased by 56% following ezetimibe/simvastatin compared with 39% reduction following simvastatin alone (p <0.01, based on ANOVA model). There were statistically greater reductions in total-C, Apo B, TG, campesterol and sitosterol following ezetimibe/simvastatin. Clinical outcome was not an objective of the ENHANCE trial.

***Clinical studies in paediatric (10 to 17 years of age) patients***

In a multicentre, double-blind, controlled study, 142 boys and 106 post-menarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% Multiracial) with heterozygous familial hypercholesterolaemia (HeFH) were randomised to receive either co-administered ezetimibe and simvastatin or simvastatin alone. Inclusion in this study required

- a baseline LDL-C level between 4.1 and 10.4 mmol/L (160 and 400 mg/dL) and
- a medical history and clinical presentation consistent with HeFH.

The mean baseline LDL-C value was 5.8 mmol/L (range: 4.2-9.1 mmol/L) in the ezetimibe co-administered with simvastatin group compared to 5.7 mmol/L (range: 3.9-8.7 mmol/L) in the simvastatin monotherapy group. The patients received ezetimibe/simvastatin (10/10, 10/20 or 10/40) or simvastatin alone (10 mg, 20 mg or 40 mg) for 6 weeks, ezetimibe/simvastatin 10/40 or simvastatin 40 mg alone for the next 27 weeks, and open-label ezetimibe/simvastatin (10/10, 10/20 or 10/40) for 20 weeks thereafter.

The primary hypothesis was that the percent change in LDL-C from baseline to Week 6 in the pooled ezetimibe/simvastatin groups would be greater than in the pooled simvastatin monotherapy groups. At Week 6, ezetimibe/simvastatin (all doses) lowered LDL-C significantly more than simvastatin (all doses) alone (49% vs 34% respectively). The results of the study at Week 6 are summarised in Tables 14 and 15. Results at Week 33 were consistent with those at Week 6. At Week 53, the end of the open-label extension, the effects on lipid parameters were maintained.

*Table 14: Absolute[58] difference at Week 6 between pooled ezetimibe/simvastatin group and pooled simvastatin group in adolescent patients with heterozygous familial hypercholesterolaemia*

| | Total-C | LDL-C | Apo B | TG[59] | HDL-C | Non-HDL-C |
|---|---|---|---|---|---|---|
| Mean absolute difference between treatment groups | -0.96 | -0.93 | -0.23 | -0.04 | -0.01 | -0.95 |

58 Mean (or median) absolute change from baseline (units are mmol/L for all parameters except Apo B, which is in g/L)

59 For triglycerides, median absolute change from baseline

| | | | | | | |
|---|---|---|---|---|---|---|
| 95% confidence interval | -1.19, -0.73 | -1.15, -0.72 | -0.30, -0.17 | -12, +0.04 | -0.04, +0.03 | -1.18, -0.72 |

*Table 15: Mean percent difference at Week 6 between pooled ezetimibe/simvastatin group and pooled simvastatin group in adolescent patients with heterozygous familial hypercholesterolaemia*

| | Total-C | LDL-C | Apo B | TG[60] | HDL-C | Non-HDL-C |
|---|---|---|---|---|---|---|
| Mean percent difference between treatment groups | -12% | -15% | -12% | -2% | +0.1% | -14% |
| 95% confidence interval | -15%, -9% | -18%, -12% | -15%, -9% | -9, +4 | -3, +3 | -17%, -11% |

From the start of the trial to the end of Week 33, discontinuations due to an adverse reaction occurred in 7 (6%) patients in the ezetimibe co-administered with simvastatin group and in 2 (2%) patients in the simvastatin monotherapy group.

The clinical safety and efficacy of ezetimibe/simvastatin in children and adolescents (10-17 years old) with hypercholesterolaemia other than Heterozygous Familial Hypercholesterolaemia have not been studied.

The safety and efficacy of ezetimibe 10 mg co-administered with doses of simvastatin above 40 mg daily have not been studied in children and adolescents (10-17 years old) and are not recommended. The long-term efficacy of therapy with ezetimibe/simvastatin in children and adolescents (10-17 years old) to reduce morbidity and mortality in adulthood has not been studied.

***Homozygous Familial Hypercholesterolemia (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 (10/40 and 10/80 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 (10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

***Ezetimibe***

In two multicentre, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C (13%), LDL-C (19%), Apo B (14%), and TG (8%) and increased HDL-C (3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, race, and baseline LDL-C. In addition, ezetimibe had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, had no effect on prothrombin time, and did not impair adrenocortical steroid hormone production.

***Simvastatin***

In two large placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (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.

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60 For triglycerides, median % change from baseline

## 5.2 Pharmacokinetic properties

### Absorption

***Ezetimibe***

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

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as ezetimibe 10 mg tablets.

***Simvastatin***

The availability of the β-hydroxy-acid 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-hydroxy-acid 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-hydroxy-acid are bound to human plasma proteins (95%).

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicine 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 medicine-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total medicine in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

***Simvastatin***

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding β-hydroxy-acid, 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 medicine equivalents in the bile. Consequently, availability of active medicine to the systemic circulation is low.

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

In dose proportionality studies utilising doses of simvastatin of 5 mg, 10 mg, 20 mg, 60 mg, 90 mg and 120 mg there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose.

## 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*

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 medicine equivalents excreted in bile as well as unabsorbed medicine. Following an intravenous injection of the β-hydroxy-acid metabolite an average of only 0.3% of the IV (intravenous) dose was excreted in urine as inhibitors.

## Characteristics in special populations

### *Ezetimibe*

#### Paediatric patients

The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population < 10 years of age are not available.

#### 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 young subjects treated with ezetimibe (see section 4.4).

#### Gender

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

#### Race

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

#### Hepatic insufficiency

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

#### Renal insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 mL/min/1.73 $m^2$), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9).

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

***Simvastatin***

**Paediatric patients**

The pharmacokinetics of simvastatin has not been studied in the paediatric population.

**Renal insufficiency**

In a study of patients with severe renal insufficiency (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.

### Medicine interactions

**Diltiazem:** In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4.

**Amlodipine:** In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid.

## *5.3 Preclinical safety data*

### Acute toxicology

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.

The oral $LD_{50}$ of simvastatin in mice is approximately 3.8 g/kg and in rats is approximately 5 g/kg.

### Chronic toxicology

***Ezetimibe/simvastatin***

The safety of concomitant administration of ezetimibe and simvastatin was assessed in rats and dogs. When ezetimibe was co-administered with simvastatin for three months, toxicologic findings were consistent with those seen with statins administered alone.

***Ezetimibe***

Ezetimibe was well tolerated by mice, rats and dogs. No target organs of toxicity were identified in chronic studies at daily doses up to 1500 (males) and 500 mg/kg (females) in rats, up to 500 mg/kg in mice, or up to 300 mg/kg in dogs.

***Simvastatin***

Administration of high dosage levels of simvastatin and related analogs to a variety of animal species has revealed a spectrum of changes in several tissues. These changes were not unexpected in view of the large doses used, the potency of these medicines in inhibiting mevalonate synthesis, and the essential role of the target enzyme in maintenance of cellular homeostasis. Extensive data generated on several of these changes indicate that they represent an exaggeration of the biochemical effect of these medicines at the high end of the dose-response curve. Thus, morphologic changes in the livers of rats, squamous epithelial hyperplasia of the forestomach of rats and mice and hepatotoxicity in rabbits have all been shown to be directly related to inhibition of HMG-CoA reductase.

Cataracts have been detected at high dosage levels in dog studies with simvastatin, although at a very low incidence. While there is no clear correlation between the magnitude of serum lipid-lowering

and the development of cataracts, a consistent relationship has been observed between high serum levels of medicine and cataract development with simvastatin and related HMG-CoA reductase inhibitors.

Serum levels (expressed as total inhibitors) in dogs receiving the minimally cataractogenic dose of simvastatin of 50 mg/kg/day are 5 times higher than those in man receiving the maximally anticipated therapeutic dose of 1.6 mg/kg (based on 80 mg/day for a 50 kg man).

Elevated serum transaminases have been observed in dogs receiving simvastatin. These occur either as chronic low level elevations or as transient enzyme spikes in approximately 10-40% of the dogs receiving this medicine. None of the dogs experiencing these transaminase elevations demonstrated any symptoms of illness; and none of the transaminase elevations have progressed to levels associated with frank hepatic necrosis, despite continued medicine administration. No histopathological changes have been identified in the liver of any dogs receiving simvastatin.

Testicular degeneration has been seen in two dog safety studies with simvastatin. Special studies designed to further define the nature of these changes have not met with success since the effects are poorly reproducible and unrelated to dose, serum cholesterol levels, or duration of treatment. Simvastatin has been administered for up to 2 years to dogs at a dose of 50 mg/kg/day without any testicular effects.

Skeletal muscle necrosis was seen in one study in rats given 90 mg/kg twice daily, but this was a lethal dosage in rats.

## Carcinogenicity

### *Ezetimibe/simvastatin*

Carcinogenicity studies with ezetimibe/simvastatin combinations have not been performed.

### *Ezetimibe*

Two-year dietary studies with ezetimibe alone in mice and rats showed no evidence of carcinogenic potential. The highest ezetimibe dose (500 mg/kg/day) in mice corresponds to exposure levels approximately 4 and $\geq$ 150 times the adult human exposure for ezetimibe and total ezetimibe, respectively, based on AUC. Exposures in rats at the highest dose (1500 mg/kg/day in males and 500 mg/kg/day in females) correspond to approximately 2 and 14 times the adult human exposure for ezetimibe and total ezetimibe, respectively.

### *Simvastatin*

Initial carcinogenicity studies conducted in rats and mice with simvastatin employed doses ranging from 1 mg/kg/day to 25 mg/kg/day. No evidence of a treatment-related incidence of tumour types was found in mice in any tissue. A statistically significant ($p \leq 0.05$) increase in the incidence of thyroid follicular cell adenomas was observed in female rats receiving 25 mg/kg of simvastatin per day (16 times the maximum recommended human dose). This benign tumour type was limited to female rats; no similar changes were seen in male rats or in female rats at lower dosages (up to 5 mg/kg/day). These tumours are a secondary effect reflective of a simvastatin-mediated enhancement of thyroid hormone clearance in the female rat. No other statistically significant increased incidence of tumour types was identified in any tissues in rats receiving simvastatin.

Data from both of these studies indicated that squamous epithelial hyperplasia of the forestomach occurred at all dosage levels. These gastric changes are confined to an anatomical structure which is not found in man. Moreover, identical cells found in other locations (e.g., oesophagus and anorectal junction of the rat, mouse and dog) are unaffected.

Results of an additional 73 week carcinogenicity study in mice receiving simvastatin doses up to 400 mg/kg/day (250 times the maximum recommended human dose, based on a 50 kg person) exhibited increased incidences of hepatocellular adenomas and carcinomas, pulmonary adenomas and harderian gland adenomas. A no-effect dose of 25 mg/kg/day (16 times the maximum

recommended human dose) was established in this study and from the results of the initial 92 week carcinogenicity study in mice.

Results of an additional 106-week carcinogenicity study in rats receiving simvastatin doses ranging from 50 mg/kg/day to 100 mg/kg/day (31 to 63 times the maximum recommended human dose) exhibited a treatment-related increase in the incidence of hepatocellular neoplasms. The no-effect dose remains at 25 mg/kg/day (16 times the maximum recommended human dose) as established in the initial carcinogenicity study. An increase in the incidence of thyroid hyperplastic lesions was also observed; however, this is consistent with the previous finding that this is a species-specific response and has no implications for man.

Additional carcinogenicity studies have been conducted in mice at oral doses ranging from 1 to 400 mg/kg/day and in rats at doses of 1 to 100 mg/kg/day. Hepatocellular adenomas and carcinomas were observed in both sexes of both species at doses greater than 25 mg/kg/day. Plasma drug levels in rats at this no-effect dose level, expressed as the AUC for enzyme inhibitory activity, were 3 to 11 times greater than those in humans at the maximum recommended dose, whereas serum levels at the no-effect level in mice were similar to those in humans. Additional findings in mice were increased incidences of pulmonary adenomas at doses greater than 25 mg/kg/day, and of Harderian gland adenomas at 400 mg/kg/day. In rats, the incidence of thyroid follicular adenoma was increased in females at doses greater than 5 mg/kg/day and in males at doses greater than 25 mg/kg/day. These thyroid tumours were associated with focal cystic follicular hyperplasia, and may be a secondary effect reflective of a simvastatin-mediated enhancement of thyroid hormone clearance by the liver.

## Mutagenesis

### *Ezetimibe/simvastatin*

Ezetimibe alone or in combination with simvastatin did not cause gene mutation in bacteria or chromosomal damage in human peripheral lymphocytes or bone marrow cells in mice.

### *Ezetimibe*

Ezetimibe was not genotoxic in a series of *in vivo* and *in vitro* tests.

### *Simvastatin*

An extensive battery of *in vitro* and *in vivo* genetic toxicity tests have been conducted on both simvastatin and the corresponding open acid β-hydroxy-acid. These include assays for microbial mutagenesis, mammalian cell mutagenesis, single stranded DNA breakage and tests for chromosome aberrations. The results of these studies provided no evidence of an interaction between simvastatin or β-hydroxy-acid with genetic material at the highest soluble noncytotoxic concentrations tested in *in vitro* assay systems or at maximally tolerated doses tested *in vivo.*

## Reproduction

### *Ezetimibe*

Ezetimibe did not affect the fertility of male or female rats.

### *Simvastatin*

At maximally tolerated doses in both the rat and the rabbit, simvastatin had no effects on fertility or reproductive function.

## Development

### *Ezetimibe/simvastatin*

Concomitant administration of ezetimibe and simvastatin was not teratogenic in rats. In pregnant rabbits, a low incidence of skeletal malformations (fused caudal vertebrae, reduced number of caudal vertebrae) was observed when ezetimibe (1000 mg/kg; ≥ 146 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe) was administered with simvastatin (5 and 10 mg/kg).

Exposure to the pharmacologically active form of simvastatin was ≥ 246 times the human exposure at 10 mg daily) based on $AUC_{0\text{-}24hr}$.

***Ezetimibe***

Ezetimibe was not teratogenic in rats or rabbits and had no effect on prenatal or postnatal development.

***Simvastatin***

At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations and had no effects on neonatal development. However, in rats, an oral dose of 60 mg/kg/day of the hydroxy acid, pharmacologically active metabolite of simvastatin, resulted in decreased maternal body weight and an increased incidence of foetal resorptions and skeletal malformations compared with controls. Subsequent studies conducted at dosages of up to 60 mg/kg/day with this metabolite showed that these resorptions and skeletal malformations were consequences of maternal toxicity (forestomach lesions associated with maternal weight loss) specific to rodents and are highly unlikely to be due to a direct effect on the developing foetus. Although no studies have been conducted with simvastatin, maternal treatment of pregnant rats with a closely related HMG-CoA reductase inhibitor at dosages of 80 and 400 mg/kg/day (10 and 52-fold the maximum recommended therapeutic dose based on $mg/m^2$ body surface area) has been shown to reduce the foetal plasma levels of mevalonate.

# 6. Pharmaceutical Particulars

## *6.1 List of excipients*

Each Zimybe tablet also contains:

- lactose monohydrate,
- citric acid monohydrate,
- butylated hydroxyl anisole,
- ascorbic acid,
- croscarmellose sodium,
- hypromellose,
- sodium lauryl sulphate,
- microcrystalline cellulose and
- magnesium stearate.

## *6.2 Incompatibilities*

Not applicable.

## *6.3 Shelf life*

3 years.

## *6.4 Special precautions for storage*

Store at or below 25°C.

## *6.5 Nature and contents of container*

All strengths of Zimybe tablets are supplied in blister packs of 10 and 30 tablets.

Not all pack sizes may be marketed.

## *6.6 Special precautions for disposal*

Not applicable.

# 7. Medicines Schedule

Prescription Medicine

# 8. Sponsor Details

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Telephone 0800 168 169

# 9. Date of First Approval

26 June 2014

# 10. Date of Revision of the Text

7 February 2024

**Summary table of changes**

| Section | Summary of new information |
|---|---|
| Throughout | Editorial and formatting changes |
| 4.4 | Risk of statins inducing new onset or aggravating pre-existing myasthenia gravis or ocular myasthenia |
| 4.5 | Updated interaction between ticagrelor and simvastatin |
| 4.8 | Addition of severe cutaneous adverse reactions (SCARs), drug induced liver injury, myasthenia gravis and ocular myasthenia as post marketing adverse events<br><br>Updated ADR website |
| 2 & 6.1 | Updated allergen declaration |

Zimybe® is a Viatris company trade mark.