

## Name of Medicine

### VYTORIN®

*ezetimibe/simvastatin*

10/10 mg, 10/20 mg, 10/40 mg & 10/80 mg tablets

## Presentation

10/10 mg tablet: A white to off white, capsule shaped, biconvex compressed tablet marked 311 on one side. Dimensions are 8.48 mm x 4.24 mm.

10/20 mg tablet: A white to off white, capsule shaped, biconvex compressed tablet marked 312 on one side. Dimensions are 10.66 mm x 5.33 mm.

10/40 mg tablet: A white to off white, capsule shaped, biconvex compressed tablet marked 313 on one side. Dimensions are 13.86 mm x 5.98 mm.

10/80 mg tablet: A white to off white, capsule shaped, biconvex compressed tablet marked 315 on one side. Dimensions are 17.46 mm x 7.53 mm.

## Therapeutic Class

VYTORIN (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.

## Indications

### Primary Hypercholesterolaemia

VYTORIN 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)

VYTORIN 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).

## Dosage and Administration

The patient should be placed on a standard cholesterol-lowering diet before receiving VYTORIN and should continue on this diet during treatment with VYTORIN. The dosage should be individualised according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. VYTORIN 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 VYTORIN, lipid levels may be analysed after 2 or more weeks and dosage adjusted, if needed. The 10/80 mg dose of VYTORIN 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 Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

### **Dosage in Patients with Homozygous Familial Hypercholesterolaemia**

The recommended dosage for patients with homozygous familial hypercholesterolaemia is VYTORIN 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 Contraindications; Warnings and Precautions, *Myopathy/Rhabdomyolysis*). VYTORIN should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

### **Use in the Elderly**

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

### **Use in Paediatric (10 to 17 years of age) Patients**

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. Doses should be individualised according to the recommended goal of therapy. Children <10 years: Treatment with VYTORIN is not recommended.

### **Use in Hepatic Impairment**

No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6). Treatment with VYTORIN is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score >9) liver dysfunction. (See Warnings and Precautions, and Pharmacokinetics.)

### **Use in Renal Impairment**

No dosage adjustment is required for patients with moderate renal insufficiency. If treatment in patients with severe renal insufficiency (creatinine clearance  $\leq 30$  mL/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously (see Pharmacokinetics).

### **Concomitant Therapy**

Dosing of VYTORIN should occur either  $\geq 2$  hours before or  $\geq 4$  hours after administration of a bile acid sequestrant.

In patients taking amiodarone, verapamil, diltiazem or  $\geq 1$  g/day of niacin concomitantly with VYTORIN, the dose of VYTORIN should not exceed 10/20 mg/day (see Warnings and Precautions, *Myopathy/Rhabdomyolysis* and Interactions).

In patients taking amlodipine concomitantly with VYTORIN, the dose of VYTORIN should not exceed 10/40 mg/day (see Warnings and Precautions, *Myopathy/Rhabdomyolysis* and Interactions).

The safety and effectiveness of VYTORIN administered with fibrates have not been studied. Therefore, the combination of VYTORIN and fibrates should be avoided (see Warnings and Precautions, *Myopathy/Rhabdomyolysis* and Interactions).

## **Contraindications**

- Hypersensitivity to the active substances or to any of the excipients.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see Pregnancy and Nursing Mothers).
- Myopathy secondary to other lipid lowering agents.
- Concomitant administration of potent CYP3A4 inhibitors (eg. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*)).

- Concomitant administration of gemfibrozil, cyclosporin, or danazol (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

## Warnings and Precautions

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

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

In a clinical trial (SEARCH) 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 SEARCH, rhabdomyolysis was defined as a subset of myopathy with CK  $> 40 \times$  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 VYTORIN should only be used in patients at high risk for cardiovascular complications who have not achieve their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking VYTORIN 10/80 mg for whom an interacting agent is needed, a lower dose of VYTORIN or an alternative statin-ezetimibe regimen with less potential for drug-drug interactions should be used (see Contraindications; Dosage and Administrations).

All patients starting therapy with VYTORIN, or whose dose of VYTORIN is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. VYTORIN 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. Periodic CK determinations may be considered in patients starting therapy with VYTORIN 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 VYTORIN merit closer monitoring. Therapy with VYTORIN should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

### Drug Interactions

Because VYTORIN contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of VYTORIN 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, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin is unavoidable, therapy with VYTORIN should be suspended during the course of treatment (see Contraindications, Interactions).

***Gemfibrozil, cyclosporine or danazol:*** Concomitant use of these drugs with VYTORIN is contraindicated (see Contraindications, Interactions).

### **Other medicines**

***Amiodarone:*** In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone (See Dosage and Administrations, Interactions)

#### ***Calcium Channel Blockers:***

***Verapamil or diltiazem:*** Patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy.

The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medication with verapamil or diltiazem (see Dosage and Administrations; Interactions).

***Amlodipine:*** In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of VYTORIN should not exceed 10/40 mg daily in patients receiving concomitant medication with amlodipine (see Dosage and Administrations, Interactions).

***Moderate inhibitors of CYP3A4:*** Patients taking other medicines labeled as having a moderate inhibitor effect on CYP3A4 concomitantly with VYTORIN, particularly higher VYTORIN doses, may have an increased risk of myopathy.

***Other Fibrates:*** The safety and effectiveness of VYTORIN administered with fibrates have not been studied. Therefore, the concomitant use of VYTORIN and fibrates should be avoided. Concomitant use of gemfibrozil is contraindicated (see Contraindications; Interactions with other medicines).

***Fusidic acid:*** Patients on fusidic acid treated concomitantly with VYTORIN may have an increased risk of myopathy. Patients on fusidic acid and VYTORIN should be closely monitored. Temporary suspension of VYTORIN treatment may be considered (see Interactions, Other Medicine Interactions).

***Niacin (≥1 g/day):*** The dose of VYTORIN 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 an ongoing, double-blind, randomised cardiovascular outcomes trial conducted in China, the United Kingdom and Scandinavia, an interim analysis by the independent safety monitoring committee revealed that the incidence of myopathy among approximately 4700 UK/Scandinavian patients treated with either simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg co-administered with extended-release (ER) niacin/laropiprant 2 g/40 mg is similar to the overall incidence reported in the clinical trial database for simvastatin 40 mg (0.08%). However, in approximately 3900 Chinese patients in the same treatment arm, the incidence is higher than expected (approximately 0.9%). The risk of myopathy was not increased among 8600 Chinese, UK, or Scandinavian patients in the control arm (placebo plus simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg). There was no apparent contribution by ezetimibe to the increased incidence of myopathy.

Because the incidence of myopathy is higher in Chinese than in non-Chinese patients, caution should be used when treating Chinese patients with VYTORIN (particularly doses of 10/40 mg or higher) co-administered with lipid modifying doses ( $\geq 1$  g/day) of niacin or niacin-containing products. Because the risk of myopathy is dose-related, the use of VYTORIN 10/80 mg with lipid modifying doses ( $\geq 1$  g/day) of niacin or niacin-containing products is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy with co-administration in other Asian patients. (see Interactions, *Other medicine interactions*).

### **Anticoagulants**

If VYTORIN is added to warfarin, another coumarin anticoagulant, or flutidione, the International Normalised Ratio (INR) should be appropriately monitored (see Interactions).

### **Liver Enzymes**

In controlled co-administration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations ( $\geq 3$  X ULN) have been observed. (See Adverse Effects.)

It is recommended that LFTs be performed before treatment with VYTORIN begins and thereafter when clinically indicated. Patients titrated to the 10/80 mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80 mg dose, and periodically thereafter (e.g., 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 Warnings and Precautions, *Myopathy/ Rhabdomyolysis*).

VYTORIN 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 VYTORIN.

### **Hepatic Insufficiency**

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

### **Interstitial lung disease**

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

### **Pregnancy**

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

VYTORIN is contraindicated during pregnancy (see Animal Toxicology).

### **Simvastatin**

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

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

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

### Ezetimibe

No clinical data on exposed pregnancies are available for ezetimibe.

When ezetimibe was given with simvastatin, no teratogenic effects were observed in embryo-foetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed (see Animal Toxicology).

### **Nursing Mothers**

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether the active components of VYTORIN are excreted into human breast milk; therefore, women who are nursing should not take VYTORIN.

### **Paediatric Use**

Safety and effectiveness of VYTORIN 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. Adolescent patients treated with VYTORIN had an adverse experience profile similar to that of adult patients treated with VYTORIN. However elevations of CPK ( $\geq 10 \times \text{ULN}$ ) occurred in two patients (2%) treated with VYTORIN and in zero patients treated with simvastatin alone. No cases of myopathy were reported. **Doses greater than 10/40 mg/day have not been studied in this population.** In this 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. (See Dosage and Administration, and Adverse Effects.) VYTORIN has not been studied in patients younger than 10 years of age or in pre-menarchal girls.

### **Use In The Elderly**

Because advanced age ( $\geq 65$  years) is a predisposing factor for myopathy, VYTORIN should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients  $\geq 65$  years of age had an increased risk of myopathy compared to patients  $< 65$  years of age.

### **Animal Toxicology**

#### 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  $\text{LD}_{50}$  of simvastatin in mice is approximately 3.8 g/kg and in rats is approximately 5 g/kg.

#### Chronic Toxicology

#### **VYTORIN**

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*

In two-year studies conducted in mice and rats, ezetimibe was not carcinogenic.

### *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 ano-rectal 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.

### Mutagenesis

#### *VYTORIN*

Combination of ezetimibe with simvastatin was not genotoxic in a series of *in vitro* and *in vivo* assays.

#### *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  $\beta$ -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  $\beta$ -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

#### *VYTORIN*

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;  $\geq 146$  times the human exposure at 10 mg daily based on  $AUC_{0-24hr}$  for total ezetimibe) was administered with simvastatin (5 and 10

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

#### *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.

#### **Effects on the Ability to Drive and Use Machinery**

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 VYTORIN may affect some patients' ability to drive or operate machinery. Individual responses to VYTORIN may vary. (See Adverse Effects.)

### **Adverse Effects**

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

The following common ( $\geq 1/100$ ,  $< 1/10$ ) or uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); medicine-related adverse experiences were reported in patients taking VYTORIN (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 ( $\geq 1/100$ ,  $< 1/10$ ) or uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); medicine-related adverse experiences were reported in patients taking VYTORIN (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), the safety and tolerability profile of the group treated with VYTORIN was similar to that of adult patients treated with VYTORIN (see Warnings and Precautions, *Paediatric Use*).

**Post-marketing Experience**

The following additional adverse reactions have been reported in post-marketing use with VYTORIN or during clinical studies or post-marketing use with one of the individual components. The adverse reactions reported for VYTORIN are consistent with those previously reported with ezetimibe and/or simvastatin.

*Investigations:* liver function test abnormal

*Blood and lymphatic system disorders:* thrombocytopenia; anaemia

*Nervous system disorders:* peripheral neuropathy; memory impairment

*Respiratory, thoracic and mediastinal disorders:* cough; interstitial lung disease

*Gastrointestinal disorders:* constipation; pancreatitis; gastritis

*Skin and subcutaneous tissue disorders:* alopecia; hypersensitivity reactions, including rash, urticaria, anaphylaxis, angioedema; erythema multiforme

*Musculoskeletal and connective tissue disorders:* muscle cramps; myopathy/rhabdomyolysis (see Warnings and Precautions)

*Metabolism and nutrition disorders:* decreased appetite

*Vascular disorders:* hot flush; hypertension

*General disorders and administration site conditions:* pain

*Hepatobiliary disorders:* hepatitis/jaundice; hepatic failure; cholelithiasis; cholecystitis

*Reproductive system and breast disorders:* erectile dysfunction

*Psychiatric disorders:* depression

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

The following adverse events have been reported with some statins:

sleep disturbances, including insomnia and nightmares

memory loss

sexual dysfunction

depression

exceptional cases of interstitial lung disease, especially with long term therapy

### **Laboratory Test Findings**

In controlled clinical co-administration trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST  $\geq 3$  X ULN, consecutive) was 1.7% for patients treated with VYTORIN. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. (See Warnings and Precautions.)

Clinically important elevations of CK ( $\geq 10$  X ULN) were seen in 0.2% of the patients treated with VYTORIN.

In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n = 248), elevations of CPK ( $\geq 10$  X ULN) occurred in two patients (2%) treated with VYTORIN and in zero patients treated with simvastatin alone. No cases of myopathy were reported.

### **Interactions**

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

VYTORIN is bioequivalent to co-administered ezetimibe and simvastatin.

### **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 VYTORIN:

Concomitant use with medicines labeled as having a potent inhibitory effect on CYP3A4 (eg. itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone) is contraindicated. (see Contraindications, Warnings and Precautions, *Myopathy/Rhabdomyolysis, Interactions*).

**Gemfibrozil, cyclosporine or danazol:** (see Contraindications; Warnings and Precautions, *Myopathy/Rhabdomyolysis, Interactions*).

### **Other Medicine Interactions**

**Amiodarone:** The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with VYTORIN (see Dosage and Administrations, Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

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

**Calcium channel blockers:** The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see Dosage and Administrations; Warnings and Precautions, *Myopathy/Rhabdomyolysis, Interactions*).

**Moderate inhibitors of CYP3A4:** Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with VYTORIN, particularly higher VYTORIN doses, may have an increased risk of myopathy.\*

**Fusidic Acid:** Patients on fusidic acid treated concomitantly with VYTORIN may have an increased risk of myopathy (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

**Fibrates:** Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5 and 1.7 fold, respectively; however, these increases are not considered clinically significant. The safety and effectiveness of VYTORIN 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 Animal Toxicology). Although the relevance of this preclinical finding to humans is unknown, co-administration of VYTORIN with fibrates is not recommended until use in patients is studied.

**Niacin:** In a study of 15 healthy adults, concomitant VYTORIN (10/20 mg daily for 7 days) caused a small increase in the mean AUCs of niacin (22%) and nicotinuric acid (19%) administered as NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5 days following a low-fat breakfast). In the same study, concomitant NIASPAN slightly increased the mean AUCs of ezetimibe (9%), total ezetimibe (26%), simvastatin (20%) and simvastatin acid (35%). These increases are not considered clinically significant. (See Warnings and Precautions, *Myopathy/Rhabdomyolysis*.)

**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 such patients taking this combination is advised.

**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, very large quantities (over 1 litre daily) significantly increase the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided while taking VYTORIN (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

### **Anticoagulants**

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International 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 VYTORIN 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 VYTORIN 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) had no significant effect on bioavailability of warfarin and prothrombin time in a 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 fludione. Most of these patients were also on other medications (see Warnings and Precautions).

The effect of VYTORIN 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.

### **Cyclosporine**

In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, 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 m<sup>2</sup>) who was receiving multiple medications, including cyclosporine, 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 cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of cyclosporine alone (see Warnings and Precautions).

## **Overdosage**

### **VYTORIN**

No specific treatment of overdosage with VYTORIN 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<sub>50</sub> 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 27 patients with homozygous sitosterolaemia 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.

## **Actions**

### **VYTORIN**

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. VYTORIN contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. VYTORIN 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 [<sup>14</sup>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.

## Pharmacokinetics

### 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  $\beta$ -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  $\beta$ -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  $\beta$ -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.

### Metabolism

#### 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  $\beta$ -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  $\beta$ -hydroxy-acid metabolite, its half-life averaged 1.9 hours.

## **Elimination**

### Ezetimibe

Following oral administration of  $^{14}\text{C}$ -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  $\beta$ -hydroxy-acid metabolite an average of only 0.3% of the IV dose was excreted in urine as inhibitors.

## **Characteristics in Patients**

### 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.

### Geriatric Patients

Plasma concentrations for total ezetimibe are about 2 fold higher in the elderly ( $\geq 65$  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.

### 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 Warnings and Precautions).

## Renal Insufficiency

### *Ezetimibe*

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl  $\leq$ 30 mL/min/1.73 m<sup>2</sup>), 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 cyclosporine) had a 12 fold greater exposure to total ezetimibe.

### *Simvastatin*

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.

## **Pharmaceutical Precautions**

Store up to 25°C, usual climatic temperature excursions permitted. Keep container tightly closed.

## **Medicine Classification**

Prescription Medicine

## **Package Quantities**

VYTORIN tablets are available in packs of 30 tablets.

## **Further Information**

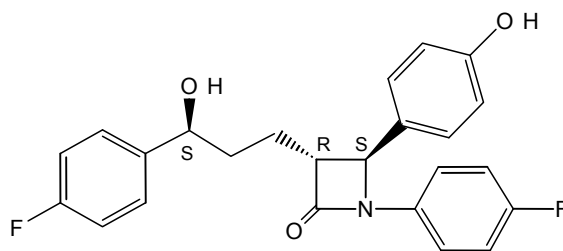
### **Chemistry**

VYTORIN contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

### Ezetimibe

The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is C<sub>24</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>3</sub> and its molecular weight is 409.4.

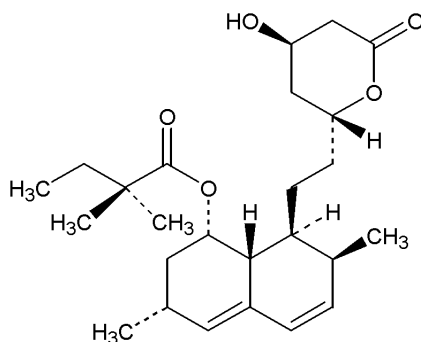
Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Its structural formula is:



### Simvastatin

Simvastatin, an inactive lactone, is hydrolysed to the corresponding  $\beta$ -hydroxy-acid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1 $\alpha$ ,3 $\alpha$ ,7 $\beta$ ,8 $\beta$  (2S\*,4S\*),-8a $\beta$ ]]. The empirical formula of simvastatin is C<sub>25</sub>H<sub>38</sub>O<sub>5</sub> and its molecular weight is 418.57.

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Its structural formula is:



### Inactive Ingredients

Each tablet contains the following inactive ingredients: butylated hydroxyanisole, citric acid monohydrate, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and propyl gallate.

### **Name and Address**

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### **Date of Preparation**

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