VYTORIN™ Tablet

Ezetimibe/Simvastatin

COMPOSITION

Each tablet of VYTORIN contains 10 mg of ezetimibe and 10 mg of simvastatin (VYTORIN 10/10), 20 mg of simvastatin (VYTORIN 10/20).

Clinical testing has been conducted over the dose range 10 mg ezetimibe/10 mg simvastatin to 10 mg ezetimibe/80 mg simvastatin.

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.

MECHANISM OF 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-PickC1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

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Ezetimibe localizes 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 hypercholesterolemic 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 hydrolyzed in the liver to the corresponding active β-hydroxyacid form which has a potent activity in inhibiting HMG-CoA reductase (3 hydroxy - 3 methylglutaryl CoA reductase). This enzyme catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

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

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

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

DISTRIBUTION

Ezetimibe

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

Simvastatin

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

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

METABOLISM

Ezetimibe

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

Simvastatin

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

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

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

ELIMINATION

Ezetimibe

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces 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 feces within 96 hours. The amount recovered in the

feces represents absorbed drug equivalents excreted in bile as well as unabsorbed drug. Following an intravenous injection of the β-hydroxyacid metabolite an average of only 0.3% of the IV dose was excreted in urine as inhibitors.

Characteristics in Patients (Special Populations)

Pediatric 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 pediatric population <10 years of age are not available. Clinical experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH.

Geriatric Patients

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

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 (WARNING AND PRECAUTION).

Renal Insufficiency

Ezetimibe

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 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.

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.

ANIMAL PHARMACOLOGY

Ezetimibe

The hypocholesterolemic effect of ezetimibe was evaluated in Rhesus monkeys, a model for the human metabolism of cholesterol, as well as in dogs. Rhesus monkeys were fed a cholesterol-containing diet that mimics a human Western diet. Ezetimibe was found to have an ED_{50} of 0.0005 mg/kg/day for inhibiting the rise in plasma cholesterol levels (ED_{100} = 0.003 mg/kg/day). The ED_{50} in dogs was found to be 0.007 mg/kg/day. These results are consistent with ezetimibe being an extremely potent cholesterol absorption inhibitor.

In dogs given ezetimibe (≥0.03 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 3-fold. However, a dose of 300 mg/kg/day administered

to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a normal or cholesterol rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively. The relevance of these preclinical findings to humans is unknown.

Simvastatin

Simvastatin is a gamma-lactone obtained by chemical modification of lovastatin. Hydrolysis of the lactone by either chemical or enzymatic means results in the dihydroxy open acid designated as β-hydroxyacid. The open acid is the active form of the compound. It is a competitive inhibitor of HMG-CoA reductase, a key rate-limiting enzyme in the cholesterol biosynthetic pathway. The Ki of inhibition of a solubilized HMG-CoA reductase preparation obtained from rat liver microsomes is approximately 1 X 10^{-10}M.

Two systems have been utilized to demonstrate that simvastatin is an inhibitor of cholesterol synthesis; mammalian cells grown in culture and *in vivo* in the rat. The IC_{50} values for inhibition of sterol synthesis in cultured animal cells by simvastatin, as determined by measuring the incorporation of ^{14}C-acetate into ^{14}C-sterol, are 19.3 nM for mouse L-M cells, 13.3 nM for the rat hepatoma cell line, H4IIE, and 15.6 nM for the human hepatoma cell line, Hep-G2. These results demonstrate that simvastatin is active against the human enzyme as well as the rodent one.

The inhibition of incorporation of ^{14}C-acetate into ^{14}C-cholesterol in rats has been used to assess the *in vivo* effectiveness of simvastatin. Simvastatin is an orally active inhibitor of cholesterol synthesis with an ID_{50} value less than 0.15 to 0.2 mg/kg and 87% inhibition at 2.4 mg/kg by one hour after an oral dose of the drug.

Studies have been carried out in the dog in order to assess the effects of simvastatin on serum total lipoprotein cholesterol. This animal model has been shown to respond to HMG-CoA reductase inhibitors with respect to lowering of circulating cholesterol as opposed to rats, which show no sustained effects of these agents on cholesterol levels.

In the dog, simvastatin is a potent, orally active agent that lowers circulating cholesterol. This occurs in the presence or absence of the bile acid sequestrant, cholestyramine.

In dogs treated with 12 gm per day of cholestyramine, cholesterol is decreased by an average of 35%. Treatment of these dogs with 1 and 2 mg/kg/day of simvastatin results in an additional 29.1% and 37.6% decrease, respectively, from the baseline established with cholestyramine. Similarly, in chow-fed dogs, cholesterol is decreased 26.2% by treatment with 8 mg/kg/day of simvastatin. The effects of simvastatin are primarily on LDL-C in spite of the fact that approximately 70-80% of circulating cholesterol in the dog is in the form of HDL. In the cholestyramine-primed dogs, LDL-C decreased by 57-72% with a 19-38% decrease in HDL.

Similarly, LDL-C decreased by 62% in chow-fed dogs after treatment with 8 mg/kg/day of simvastatin with a slight decrease in HDL levels that did not reach significance.

Ancillary pharmacology studies to assess effects on organ systems and biological parameters were conducted with β-hydroxyacid. No major changes were seen. Minor effects were noted on acid secretion and respiratory parameters in dogs.

In conclusion, simvastatin is a competitive inhibitor of the key cholesterol biosynthetic enzyme, HMG-CoA reductase. This inhibition is manifested in cultured animal cells and *in vivo* in the rat by a block in cholesterol synthesis. In the dog, an animal model that is responsive to HMG-CoA reductase inhibitors, simvastatin is a highly effective agent for lowering circulating total-C and LDL-C. Simvastatin is free of significant effects on ancillary pharmacological parameters.

INDICATIONS:

Primary Hypercholesterolemia

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 patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

VYTORIN is indicated for the reduction of elevated total-C and LDL-C levels in 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 individualized 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 10/40 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 analyzed after 2 or more weeks and dosage adjusted, if needed.

Dosage in Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is VYTORIN 10/40 mg/day in the evening. 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 *Characteristics in Patients [Special Populations]*).

Use in Pediatric Patients

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 WARNING AND PRECAUTION and *Characteristics in Patients [Special Populations]*.)

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 ≤ 30 mL/min) is deemed necessary, dosages above 10/10 mg/day should be implemented cautiously. (See *Characteristics in Patients [Special Populations]*.)

Coadministration with other medicines

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

In patients taking amiodarone, verapamil, diltiazem concomitantly with VYTORIN, the dose of VYTORIN should not exceed 10/20 mg/day (see WARNING AND PRECAUTION, *Myopathy /Rhabdomyolysis* and DRUG INTERACTIONS).

In patients taking amlodipine concomitantly with VYTORIN, the dose of VYTORIN should not exceed 10/20 mg/day (see WARNING AND PRECAUTION, *Myopathy /Rhabdomyolysis* and DRUG INTERACTIONS).

WARNING AND PRECAUTION

Clinical testing has been conducted over the dose range 10 mg ezetimibe/10 mg simvastatin to 10 mg ezetimibe/80 mg simvastatin.

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 10X 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 DRUG INTERACTIONS). Predisposing factors for myopathy include advanced age (≥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 in which patients with a history of myocardial infarction were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based 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 achieved 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 DOSAGE AND ADMINISTRATION, and CONTRAINDICATIONS).

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 (see SIDE EFFECTS). 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.

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

Drug Interactions

- Because VYTORIN contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of VYTORIN with the following drugs:

  Contraindicated Drugs

  - **Potent inhibitors of CYP3A4:** Concomitant use with medicines labeled 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 drugs containing cobicistat)** is contraindicated. If short term treatment with potent

CYP3A4 inhibitors is unavoidable, therapy with VYTORIN should be suspended during the course of treatment. (see CONTRAINDICATIONS and DRUG INTERACTIONS).

- **Gemfibrozil, cyclosporine, or danazol:** Concomitant use of these drugs with VYTORIN is contraindicated (see CONTRAINDICATIONS, and DRUG INTERACTIONS)

Other Drugs

- **Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis (see DRUG INTERACTIONS, *Other drug interactions*). Co-administration with fusidic acid is not recommended. In patients where the use of systemic fusidic acid is considered essential, VYTORIN should be discontinued throughout the duration of fusidic acid treatment. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of VYTORIN and fusidic acid should only be considered on a case-by-case basis under close medical supervision.

- **Amiodarone.** In 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 DRUG 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 DRUG INTERACTIONS, *Other drug 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 10/20 mg daily in patients receiving concomitant medication with amlodipine.

- **Lomitapide:** The dose of VYTORIN should not exceed 10/40 mg daily in patients with HoFH receiving concomitant medication with lomitapide (see DRUG 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. When coadministering VYTORIN with a moderate inhibitor of CYP3A4, a dose adjustment of VYTORIN may be necessary.

- **Inhibitor 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 Vytorin may be necessary. Coadministration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of Vytorin should not exceed 10/20 mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir (see DRUG INTERACTIONS. Other drug interactions).**

- **Other Fibrates:** The safety and effectiveness of VYTORIN administered with fibrates, except fenofibrate, have not been studied. **Therefore, the concomitant use of VYTORIN and fibrates, except fenofibrate, should be avoided. Concomitant use of gemfibrozil is contraindicated (see CONTRAINDICATIONS).**

- **Niacin (≥1 g/day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered 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 coadministered 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, coadministration of VYTORIN with lipid-modifying doses (≥1 g/day) of niacin is not recommended in Asian patients.** (See DRUG INTERACTIONS.)

- **Daptomycin:** Reports of myophaty and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors coadministered with daptomycin. Cautions 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 VYTORIN temporarily in patients taking daptomycin (see. DRUG INTERACTIONS).

- **Anticoagulants:** If VYTORIN is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see DRUG INTERACTIONS).

Liver Enzymes

In controlled coadministration trials in patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥3 X ULN) have been observed. (See SIDE EFFECTS.)

It is recommended that LFTs be performed before treatment with VYTORIN begins and thereafter when clinically indicated. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 X ULN and are persistent, the drug should be discontinued. Note that ALT may emanate from muscle,

therefore ALT rising with CK may indicate myopathy (see WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis*).

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

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.

Information for Patients

Patients should be advised about substances they should not take concomitantly with VYTORIN and be advised to report promptly unexplained muscle pain, tenderness or weakness.

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 *Characteristics in Patients [Special Populations]*).

PREGNANCY

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

VYTORIN

VYTORIN is contraindicated during pregnancy.

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 fetal 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-fetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed.

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

Pediatric use

VYTORIN

There are insufficient data for the safe and effective use of VYTORIN in pediatric patients (see Ezetimibe and Simvastatin below)

Ezetimibe

The pharmacokinetics of ezetimibe in adolescent (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with ezetimibe in pediatric population is limited to 4 patients (9 to 17 years) with homozygous sitosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (< 10 years) is not recommended.

Simvastatin

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. Doses greater than 40 mg have not been studied in this population. 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. Adolescent females should be conseled on appropiate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and WARNING AND PRECAUTION, Pregnancy). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

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 VYTORIN may affect some patient's ability to drive or operate machinery. Individual responses to VYTORIN may vary. (See SIDE EFFECTS.)

CONTRA INDICATIONS

- 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, Nursing mothers).
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin nefazodone and drugs

containing cobicistat) (see WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis* and DRUG INTERACTIONS).

- Concomitant administration of gemfibrozil, cyclosporine, or danazol (see WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis* and DRUG INTERACTIONS*)*.

DRUG INTERACTIONS

VYTORIN

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin.

VYTORIN is bioequivalent to coadministered ezetimibe and simvastatin.

Multiple mechanism 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 drugs

Concomitant use of the following drugs is contraindicated:

Potent Inhibitors of CYP3A4

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of the simvastatin component of VYTORIN: Concomitant use of drugs labeled as having a

potent inhibitory effect on CYP3A4 (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone or drugs containing cobicistat) is contraindicated. (See CONTRAINDICATIONS, WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis*)

Gemfibrozil, Cyclosporine, or Danazol (see CONTRAINDICATIONS, and WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis*).

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. (See CONTRAINDICATIONS, and WARNING and PRECAUTION, *Myopathy/Rhabdomyolysis*.)

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 m2) 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 CONTRAINDICATIONS, and WARNING PRECAUTION, *Myopathy/Rhabdomyolysis*)

Other drug interactions

Other Fibrates: The safety and effectiveness of VYTORIN administered with fibrates, except fenofibrate, have not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. Coadministration of ezetimibe with other fibrates has not been studied. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile (see ANIMAL PHARMACOLOGY). Although the relevance of this

preclinical finding to humans is unknown, coadministration of VYTORIN with fibrates, other than fenofibrate, is not recommended until use in patients is studied.

Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid (see. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with VYTORIN (see WARNING AND PRECAUTION, *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 ADMINISTRATION, and WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis*).

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide *(*see DOSAGE AND ADMINISTRATION and PRECAUTIONS, *Myopathy/Rhabdomyolysis).*

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. (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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 CONTRAINDICATIONS; PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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 coadministering simvastatin with an inhibitor of BCRP, a dose adjustment of Vytorin may be necessary (see DOSAGE AND ADMINISTRATION, PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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%). Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day) of niacin (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

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

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMC-CoA reductase inhibitors and daptomycin (see. PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Other interactions

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolized 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 during VYTORIN therapy (see WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis*).

Anticoagulants

In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. 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 Normalized Ratio in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications (see WARNING AND PRECAUTION).

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.

SIDE EFFECTS

VYTORIN (or coadministration 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 (≥1/100, <1/10) or uncommon (≥1/1000, <1/100); drug-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; edema peripheral

Psychiatric disorders:
Uncommon: sleep disorder

The following common (≥1/100, <1/10) or uncommon (≥1/1000, <1/100); drug-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; diarrhea; 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; edema peripheral

Psychiatric disorders:

Uncommon: insomnia

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: thrombocytopaenia; 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, angio-edema; erythema multiforme

Musculoskeletal and connective tissue disorders: muscle cramps; myopathy/rhabdomyolysis (see WARNING AND PRECAUTION, *Myopathy/Rhabdomyolysis*)

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 persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents (see PRECAUTIONS, *Myopathy/Rhabdomyolysis)*.

Metabolism and nutrition disorders: decreased appetite

Vascular disorders: hot flush; hypertension

General disorders and administration site conditions: pain

Hepato-biliary 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, thrombocytopenia, eosinophilia, ESR increased, arthritis and arthralgia, urticaria, photosensitivity, fever, flushing, dyspnea and malaise.

There have been rare postmarketing 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 nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Laboratory Values

In controlled clinical coadministration 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 VYTORIN. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (See WARNING AND PRECAUTION).

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

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

Concomitant Lipid-Lowering Therapy

In controlled clinical trial studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine.

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. Coadministration of ezetimibe (1000 mg/kg) and simvastatin (1000 mg/kg) was well-tolerated in acute, oral toxicity studies in mice and rats. No clinical signs of toxicity were observed in these animals. The estimated oral LD_{50} for both species was ezetimibe ≥1000 mg/kg/simvastatin ≥1000 mg/kg.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Simvastatin

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

The dialyzability of simvastatin and its metabolites in man is not known at present.

STORAGE

Store up to 30°C, usual climatic temperature excursions permitted. Keep container tightly closed.

PRESENTATION

VYTORIN™ 10/10 : Box, 3 blister @ 10 tablet; Reg. No.: DKL1906609510A1

VYTORIN™ 10/20 : Box, 3 blister @ 10 tablet; Reg. No.: DKL1906609510B1

HARUS DENGAN RESEP DOKTER/ ON MEDICAL PRESCRIPTION ONLY

Manufactured by:

DISETUJUI OLEH BPOM : 14/06/2021

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