For the use only of a Registered Medical Practitioners or a Hospital or a Laboratory

Ezzicad™ S

EZZICAD S 10/10 (EZETIMIBE 10MG/ SIMVASTATIN 10MG) TABLETS
EZZICAD S 10/20 (EZETIMIBE 10MG/ SIMVASTATIN 20MG) TABLETS
EZZICAD S 10/40 (EZETIMIBE 10MG/ SIMVASTATIN 40MG) TABLETS

I. THERAPEUTIC CLASS

EZZICAD S is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

ATC code: C10BA02

II. COMPOSITION

EZZICAD S is available for oral use as tablets containing 10 mg of ezetimibe, and 10 mg of simvastatin (Ezzicad S 10/10), 20 mg of simvastatin (Ezzicad S 10/20) or 40 mg of simvastatin (Ezzicad S 10/40).

III. CLINICAL PHARMACOLOGY

IIIa. *Mechanism of Action*

EZZICAD S

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. EZZICAD S contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. EZZICAD S 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 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 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%.

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

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.

IIIb. *Pharmacokinetics*

IIIb-1. *Absorption*

Ezetimibe

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

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

IIIb-2. *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.

IIIb-3. *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

IIIb-4. *Elimination*

Ezetimibe

Following oral administration of 14C-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.

IIIb-5. *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.

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

In a study, 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

Renal Insufficiency

Ezetimibe

In a study, patients with severe renal disease (n=8; mean CrCl≥ 30 mL/min/1.73 m2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9).

An additional patient in the same 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.

IIIb-6. *Drug 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.

IV. INDICATIONS

Prevention of Cardiovascular Events

EZZICAD S is indicated to reduce the risk of cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, or need for revascularization), in patients with coronary heart disease (CHD) and history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Primary Hypercholesterolemia

EZZICAD S 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

EZZICAD S 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).

V. DOSAGE AND ADMINISTRATION

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

Patients with Primary Hypercholesterolemia

In patients with primary hyperlipidemia or mixed hyperlipidemia, the dosage range is 10/10 mg/day through 10/80 mg/day (NOTE: EZZICAD S 10/80mg not available in Malaysia). 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 EZZICAD S, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed. The 10/80 mg dose (NOTE: EZZICAD S 10/80mg not available in Malaysia) 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.

For patients who are currently on both simvastatin and ezetimibe, no dosage adjustment is required when switching to EZZICAD S.

Patients with Coronary Heart Disease

In a published cardiovascular events risk reduction study (IMPROVE-IT), the starting dose was 10/40 mg once a day in the evening. The 10/80-mg dose (NOTE: EZZICAD S 10/80mg not available in Malaysia) is only recommended when the benefits are expected to outweigh the potential risks.

Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage for patients with homozygous familial hypercholesterolemia is EZZICAD S 10/40 mg/day or 10/80 mg/day in the evening. The 10/80-mg dose (NOTE: EZZICAD S 10/80mg not available in Malaysia) is only recommended when the benefits are expected to outweigh the potential risks. EZZICAD S should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

In patients taking lomitapide concomitantly with EZZICAD S, the dose of EZZICAD S should not exceed 10/40 mg/day.

Use in the Elderly

No dosage adjustment is required for elderly patients.

Use in Pediatric Patients

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

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.

Co-administration with other medicines

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

In patients taking amiodarone, verapamil, diltiazem, or products containing elbasvir or grazoprevir concomitantly with EZZICAD S, the dose of EZZICAD S should not exceed 10/20 mg/day.

In patients taking amlodipine concomitantly with EZZICAD S, the dose of EZZICAD S should not exceed 10/40 mg/day.

The safety and effectiveness of EZZICAD S administered with fibrates have not been studied. Therefore, the combination of EZZICAD S and fibrates should be avoided.

VI. 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)
- 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).
- Concomitant administration of gemfibrozil, cyclosporine, or danazol.

VII. 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 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. 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.

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 Ezetimibe & Simvastatin tablets (NOTE: EZZICAD S 10/80mg is not available in Malaysia) should only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking Ezetimibe & Simvastatin tablets 10/80 mg for whom an interacting agent is needed, a lower dose of Ezetimibe & Simvastatin tablets or an alternative statin-ezetimibe regimen with less potential for drug-drug interactions should be used.

All patients starting therapy with EZZICAD S , or whose dose of EZZICAD S is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. EZZICAD S 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 Ezetimibe & Simvastatin tablets or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 10/80 mg dose (NOTE: EZZICAD S 10/80mg not available in Malaysia). 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 EZZICAD S merit closer monitoring. Therapy with EZZICAD S should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

Drug Interactions

- **Because EZZICAD S contains simvastatin, the risk of myopathy/rhabdomyolysis is increased by concomitant use of EZZICAD S 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 EZZICAD S should be suspended during the course of treatment.
- **Gemfibrozil, cyclosporine, or danazol:** Concomitant use of these drugs with EZZICAD S is contraindicated.

Other Drugs

- **Fusidic acid:** Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy/rhabdomyolysis. Co-administration with fusidic acid is not recommended. In patients where the use of systemic fusidic acid is considered essential, EZZICAD S 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 EZZICAD S and fusidic acid should only be considered on a case-by-case basis under close medical supervision.
- **Amiodarone:** Myopathy was reported in patients receiving simvastatin 80 mg and amiodarone. **The**

dose of EZZICAD S should not exceed 10/20 mg daily in patients receiving concomitant medication with amiodarone.

- **Calcium channel blockers**
- **Verapamil or diltiazem:** Patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. **The dose of EZZICAD S should not exceed 10/20 mg daily in patients receiving concomitant medication with verapamil or diltiazem.**
- **Amlodipine:** Patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. **The dose of EZZICAD S should not exceed 10/40 mg daily in patients receiving concomitant medication with amlodipine.**
- **Lomitapide: The dose of EZZICAD S should not exceed 10/40 mg daily in patients with HoFH receiving concomitant medication with lomitapide.**
- **Moderate inhibitors of CYP3A4:** Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with EZZICAD S, particularly higher EZZICAD S doses, may have an increased risk of myopathy. When coadministering EZZICAD S with a moderate inhibitor of CYP3A4, a dose adjustment of EZZICAD S may be necessary.
- **Inhibitors of Breast Cancer Resistant Protein (BCRP):** Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of simvastatin and an increased risk of myopathy; therefore, a dose adjustment of Ezetimibe & Simvastatin tablets may be necessary. Coadministration of elbasvir and grazoprevir with simvastatin has not been studied; however, **the dose of EZZICAD S should not exceed 10/20mg daily in patients receiving concomitant medication with products containing elbasvir or grazoprevir.**
- **Other Fibrates:** The safety and effectiveness of EZZICAD S administered with fibrates, have not been studied. Concurrent use of fibrates may cause severe myositis and myoglobinuria. **Therefore, the concomitant use of EZZICAD S and fibrates, should be avoided. Concomitant use of gemfibrozil is contraindicated.**
- **Niacin (> 1 g/day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day) of niacin. As there was no incremental benefit on cardiovascular outcomes with the addition of lipid-modifying doses (≥ 1 g/day) of niacin, the benefit of the combined use of simvastatin with niacin should be carefully weighed against the potential risks of the combination. And an incidence of myopathy is known to be higher in Chinese than in non-Chinese patients, **coadministration of EZZICAD S with lipid-modifying doses (≥ 1 g/day) of niacin is not recommended in Asian patients.**
- **Daptomycin:** Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors coadministered with daptomycin. Caution should be used when prescribing HMG CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to suspending EZZICAD S temporarily in patients taking daptomycin.
- **Anticoagulants:** If EZZICAD S are added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored.

Myasthenia Gravis/ Ocular Myasthenia
In few cases, statins have been reported to include new onset or aggravate pre-existing myasthenia gravis or ocular myasthenia. EZZICAD S should be discontinued in case these conditions occur. There have been reports of recurrences of these conditions when the same or a different statin was (re-) administered.

Liver Enzymes
In patients receiving ezetimibe with simvastatin, consecutive transaminase elevations (≥ 3 X ULN) have been observed.
It is recommended that LFTs be performed before treatment with EZZICAD S 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.
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 EZZICAD S, promptly interrupt therapy. If an alternate etiology is not found do not restart EZZICAD S.
EZZICAD S 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 EZZICAD S.

Hepatic Insufficiency
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, EZZICAD S are not recommended in these patients.

VIII. PRECNANCY
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.
EZZICAD S 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.
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, EZZICAD S should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with EZZICAD S should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

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

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

X. USE IN THE ELDERLY
Because advanced age (≥ 65 years) is a predisposing factor for myopathy, EZZICAD S should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients <65 years of age.

XI. DRUG INTERACTIONS
EZZICAD S
No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with simvastatin.
EZZICAD S is bioequivalent to co-administered ezetimibe and simvastatin.
Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g. OATP1B1) 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
Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of the simvastatin component of EZZICAD S. 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 or nefazodone) is contraindicated. If treatment with potent CYP3A4 inhibitors is unavoidable, therapy with simvastatin should be suspended during the course of treatment.
Gemfibrozil, cyclosporine or danazol:
Concomitant use of these drugs with simvastatin is contraindicated.

Other drug interactions
Other Fibrates: The safety and effectiveness of EZZICAD S administered with fibrates have not been studied.
Simvastatin - Fibrates can cause myopathy when given alone. Severe myositis with myoglobinuria has been reported with concomitant use of statins and fibrates. Therefore, the concomitant use of EZZICAD S and fibrates, should be avoided. Concomitant use of gemfibrozil is contraindicated.
The dose of simvastatin should not exceed 10 mg daily in patients receiving concomitant medication with fibrates other than gemfibrozil or fenofibrate. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDLC may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring.
Ezetimibe Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. Co-administration of ezetimibe with other fibrates has not been studied. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of EZZICAD S with fibrates, is not recommended until such time as it is studied.
Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid.
Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with EZZICAD S.
In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone.
Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding EZZICAD S 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.

- Verapamil or diltiazem: In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. The dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem.
- Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine.

Lomitapide: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of lomitapide.
Moderate Inhibitors of CYP3A4: Patients taking other medicines labeled as having a moderate inhibitory effect on CYP3A4 concomitantly with EZZICAD S, particularly higher EZZICAD S doses may have an increased risk of myopathy.
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.
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 EZZICAD S may be necessary.
Niacin: Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥ 1 g/day) of niacin).
The dose of simvastatin should not exceed 40mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥ 1g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥ 1 g/day) of niacin.
Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and EZZICAD S 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 HMG-CoA reductase inhibitors and daptomycin.

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 EZZICAD S therapy.

Anticoagulants
In patients taking coumarin anticoagulants, prothrombin time should be determined before starting EZZICAD S 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 EZZICAD S 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. There have been post-marketing reports of increased International Normalized Ratio in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications.
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.

XII. SIDE EFFECTS
EZZICAD S is generally well tolerated.
The following (≥1/100, <1/10) or uncommon (≥1/1000, <1/100); drug-related adverse experiences were reported in patients taking Ezetimibe & Simvastatin tablets:
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 disorders
The following common (≥ 1/100, <1/10) or uncommon (≥ 1/1000, <1/100); drug-related experiences were reported in patients taking Ezetimibe & Simvastatin Tablets and at a greater incidence than statins administered alone;
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; gastroesophagealreflux disease; vomiting
Skin and subcutaneous tissue disorders;
Uncommon; pruritus; rash; urticarial
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
Patients with Coronary Heart Disease
The incidence of myopathy 0.2% for Ezetimibe & Simvastatin and 0.1% for Simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN or two consecutive observations of CK ≥ 5 and < 10 times ULN. The incidence of rhabdomyolysis was 0.1% for Ezetimibe & Simvastatin and 0.2% for Simvastatin , where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥ 10 times ULN with evidence of renal injury; ≥ 5 X ULN and <10 X ULN on two consecutive occasions with evidence of renal injury or CK ≥ 10,000 IU/L without evidence of renal injury). The incidence of consecutive elevations of transaminases (≥ 3 X ULN) was 2.5% for Ezetimibe & Simvastatin and 23% for simvastatin.
Others (Rare) In Association With Statin Use:
There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).
Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.
Musculoskeletal disorders:
Frequency not known: Immune-mediated necrotizing myopathy

XIII. OVERDOSAGE
EZZICAD S
No specific treatment of overdosage with EZZICAD S can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed.

XIV. STORAGE
Store below 30˚C

XV. SHELF LIFE
24 months

XVI. PHYSICAL APPEARANCE & AVAILABILITY

EZZICAD S 10/10	White to off white capsule shaped uncoated tablets debossed with "G" on one side and "321" on other side
EZZICAD S 10/20	White to off white capsule shaped uncoated tablets debossed with "G" on one side and "322" on other side.
EZZICAD S 10/40	White to off white capsule shaped uncoated tablets debossed with "G" on one side and "323" on other side

10 tablets in a Alu-Alu blister pack, 3 such blisters packed in carton along with a leaflet.

XVII. MANUFACTURER
Glenmark Pharmaceuticals Limited
Plot No. 2, Phase II, Pharma Zone, SEZ, Dist. Dhar, Pithampur, 454775,
Madhya Pradesh, INDIA

XVIII. PRODUCT REGISTRATION HOLDER
Glenmark Pharmaceuticals (Malaysia) Sdn Bhd
D-31-02, Menara Suezcap 1, No.2, Jalan Kerinchi, 59200 Kuala Lumpur, Malaysia

XIX. PRODUCT REGISTRATION NO.
EzzicADS 10/10: MAL24056062AZ
EZZICAD S 10/20: MAL24056063AZ
EZZICAD S 10/40: MAL24056061AZ

XIX. DATE OF REVISION
03/05/2024

PE00000 **MY**

ICONGRAPHICS CODE:

PANTONE SHADE

PANTONE BLACK PROCESS C

Supersedes Artwork Code

PHARMACODE:

800 mm

120 mm