UNILAB

Ezetimibe

Exelzio®

10 mg Tablet

Lipid Modifying Agent

℞

FORMULATION

Each tablet contains:

Ezetimibe ..... 10 mg

PRODUCT DESCRIPTION

Ezetimibe (Exelzio®) 10 mg Tablet: White to off white, capsule-shaped tablet with beveled edges

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ezetimibe is a lipid-lowering compound that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Ezetimibe has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., HMG-CoA reductase inhibitors [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 in the intestinal uptake of cholesterol and phytosterols.

Ezetimibe does not inhibit cholesterol synthesis in the liver, or increase bile acid excretion. Instead, 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. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood; this distinct mechanism is complementary to that of statins and of fenofibrate.

Ezetimibe decreases total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein (non-HDL-C) and increases high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolemia. Administration of ezetimibe with a statin is effective in improving serum total-C, LDL-C, Apo B, non-HDL-C, TG, and HDL-C beyond either treatment alone. Administration of ezetimibe with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia as compared to either treatment alone. In addition to reducing lipoprotein concentrations, ezetimibe has also been shown to decrease concentrations of noncholesterol sterols, including sitosterol and campesterol.

Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease (CHD) and acute coronary syndrome (ACS) event history. Ezetimibe in combination with simvastatin has also been shown to reduce the risk of major cardiovascular events (cardiac death or nonfatal myocardial infarction, stroke, or any revascularization procedure) in patients with chronic kidney disease.

PHARMACOKINETICS

Ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide) after oral administration. Mean maximum plasma concentrations (Cmax) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. Food had no effect on the oral bioavailability of ezetimibe when administered as 10 mg tablet. Ezetimibe can be administered with or without food.

Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Ezetimibe is metabolized primarily in the small intestine and liver via glucuronide conjugation with subsequent biliary excretion. 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.

Approximately 78% of the dose is excreted in the feces predominantly as ezetimibe, with 11% found in the urine mainly as ezetimibe-glucuronide. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Special Populations:

Hepatic Impairment: In patients with mild hepatic impairment (Child-Pugh score 5 or 6), the mean area under the curve (AUC) for total ezetimibe (after a single 10 mg dose of ezetimibe) was increased approximately 1.7-fold compared to healthy subjects. In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe(after multiple doses of 10 mg daily) was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects.

Renal Impairment: In patients with severe renal impairment, the mean AUC for total ezetimibe was increased approximately 1.5-fold (after a single 10 mg dose of ezetimibe) compared to healthy subjects.

INDICATIONS

Primary Hypercholesterolemia

Ezetimibe is indicated:

- As adjunct to diet, administered alone or with statin, to decrease elevated total-C, LDL-C, Apo B, TG, and non-HDL-C and to increase HDL-C in adult and adolescent (10 to 17 years old) patients with primary (heterozygous familial and non-familial) hypercholesterolemia
- As adjunct to diet, administered with fenofibrate, to decrease elevated total-C, LDL-C, Apo B, and non-HDL-C in adult patients with mixed hyperlipidemia

Prevention of Cardiovascular Events

- 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 a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin

Prevention of Major Cardiovascular Events in Chronic Kidney Disease

- To reduce the risk of major cardiovascular events (cardiac death or nonfatal myocardial infarction, stroke, or any revascularization procedure) in patients with chronic kidney disease when administered concomitantly with simvastatin

Homozygous Familial Hypercholesterolemia (HoFH)

- As adjunct to diet, administered with a statin, to decrease elevated total-C and LDL-C levels in adult and adolescent (10 to 17 years old) patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Homozygous Sitosterolemia (Phytosterolemia)

- As adjunct to diet to decrease elevated sitosterol and campesterol levels in adult and adolescent (10 to 17 years old) patients with homozygous familial sitosterolemia

DOSAGE AND MODE OF ADMINISTRATION

General Dosing Recommendations:

- Lipid modifying agents such as ezetimibe should be used in conjunction with appropriate diet and exercise.
- May be taken any time of the day, with or without food

INDICATIONS	RECOMMENDED ORAL EZETIMIBE DOSE
Primary (heterozygous familial and non-familial) hypercholesterolemia	Adults and adolescents (10 to 17 years old): 10 mg once a day, used alone or with a statin
Mixed hyperlipidemia	Adults: 10 mg once a day, used with fenofibrate
Prevention of Cardiovascular Events	Adults: 10 mg once a day, used with a statin •Ezetimibe may be administered with a statin with proven cardiovascular benefit for incremental cardiovascular event reduction.
Prevention of Major Cardiovascular Events in Chronic Kidney Disease	*Combination therapy with simvastatin:* Adults: ezetimibe 10 mg and simvastatin 20 mg, once a day in the evening •Doses of simvastatin exceeding 20 mg should be used with caution and closely monitored in patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 m^2.
Homozygous Familial Hypercholesterolemia (HoFH)	Adults and adolescents (10 to 17 years old): 10 mg once a day, used with a statin •May also receive adjunctive treatments (e.g., LDL apheresis)
Homozygous Sitosterolemia (Phytosterolemia)	Adults and adolescents (10 to 17 years old): 10 mg once a day
Or, as prescribed by a physician	

Special Dosing Instructions

SPECIAL POPULATIONS	RECOMMENDED ORAL EZETIMIBE DOSE
Dosage in Pediatric Patients (10 to 17 years old)	*Monotherapy:* No dosage adjustment is necessary in pediatric patients 10 to 17 years old *Combination therapy with a statin:* When ezetimibe is administered with a statin, the dosage instructions for the statin in children should be followed. Ezetimibe coadministered with doses of simvastatin greater than 40 mg/day has not been studied in pediatric patients 10 to 17 years old and is not recommended.
Concomitant Lipid-Lowering Therapy	Ezetimibe may be administered with a statin (in patients with primary hypercholesterolemia) or with fenofibrate (in patients with mixed hyperlipidemia) for incremental effect. The daily dose of ezetimibe may be taken at the same time as the statin or fenofibrate, according to the dosing recommendations for the respective medications.
Coadministration with Bile Acid Sequestrant	Ezetimibe should be administered ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.
Dosage in Patients with Hepatic Impairment	No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Ezetimibe is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score > 9) hepatic impairment.
Dosage in Patients with Renal Impairment	*Monotherapy:* No dosage adjustment is necessary in patients with renal impairment *Combination therapy with a statin:* No dosage adjustment of ezetimibe or simvastatin is necessary in patients with mild renal impairment (estimated glomerular filtration rate ≥60 mL/min/1.73 m^2)
Dosage in the Elderly	No dosage adjustment is necessary in geriatric patients

CONTRAINDICATIONS

- Hypersensitivity to any component of the product
- When ezetimibe is to be administered with a statin or with fenofibrate, the contraindications to that medication should be reviewed before starting concomitant therapy.
- The combination of ezetimibe with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.
- The combination of ezetimibe with fenofibrate is contraindicated in patients with gallbladder disease.
- **All statins and fenofibrate are contraindicated in pregnant and breastfeeding women. When ezetimibe is administered with a statin or with fenofibrate in a woman of childbearing potential, refer to the package insert for that particular medication.**

WARNINGS AND PRECAUTIONS

Use with Statins or Fenofibrate

Concomitant administration of ezetimibe with a specific statin or fenofibrate should be in accordance with the package insert for that medication.

When ezetimibe is initiated in a patient already taking a statin or fenofibrate, liver function tests should be considered at initiation of ezetimibe therapy, and then as indicated.

When ezetimibe is initiated at the same time as a statin or fenofibrate, liver function tests should be performed at initiation of therapy and according to the recommendations of that medication.

Liver Enzymes

In controlled monotherapy studies, the incidence of consecutive elevations (≥3 times the upper limit of normal [ULN]) in serum transaminases was similar between ezetimibe (0.5%) and placebo (0.3%). In controlled combination studies in patients receiving ezetimibe with a statin, the incidence of consecutive transaminase elevations (≥3 X ULN) was 1.3% compared to 0.4% in patients on statin monotherapy. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

When ezetimibe is coadministered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin. Should an increase in ALT or AST (≥3 X ULN) persist; consider withdrawal of ezetimibe and/or the statin.

Musculoskeletal Effects

In clinical studies, the incidence of myopathy or rhabdomyolysis appears to be similar among patients receiving ezetimibe, statin monotherapy, or placebo. However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical studies, the incidence of creatine phosphokinase

(CPK) >10 X ULN was 0.2% for ezetimibe compared to 0.1% for placebo, and 0.1% for ezetimibe coadministered with a statin compared to 0.4% for statins alone. Risk for skeletal muscle toxicity increases with higher doses of statin, advanced age (>65 years old), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs.

During postmarketing period, there were cases of myalgia. myopathy and/or rhabdomyolysis reported with ezetimibe. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported with ezetimibe monotherapy and with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates. Ezetimibe and any statin or fibrate that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of muscle symptoms and a CPK level >10 X ULN indicates myopathy.

Hepatic Impairment

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, ezetimibe is not recommended in these patients.

Fibrates

The coadministration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, coadministration of ezetimibe and fibrates (other than fenofibrate) is not recommended (see **Interactions with Other Medicaments**).

Fibrates may increase cholesterol excretion from the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. With the potential for cholelithiasis, and the higher incidence of cholecystectomies in patients administered ezetimibe and fenofibrate in a clinical study, coadministration of ezetimibe and fenofibrate is not recommended in patients with pre-existing gallbladder disease (see I**nteractions with Other Medicaments** and **Contraindications**).

Ciclosporin

Caution should be exercised when initiating ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ezetimibe and ciclosporin (see I**nteractions with Other Medicaments**).

Effects on Ability to Drive and Use Machines

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

INTERACTIONS WITH OTHER MEDICAMENTS

Ciclosporin: Concomitant use of ezetimibe and ciclosporin increased exposure to both drugs. The degree of increase in ezetimibe exposure may be greater in patients with severe renal impairment. In patients treated with ciclosporin, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. Ciclosporin concentrations should be monitored in patients receiving ezetimibe and ciclosporin.

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

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. Reduced LDL-C lowering effect may occur as a result of this interaction. Ezetimibe should be administered at least 2 hours before of at least 4 hours after the administration of the bile acid sequestrant.

Fibrates: The efficacy and safety of coadministration of ezetimibe with fibrates other than fenofibrate have not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. Coadministration of ezetimibe with fibrates other than fenofibrate is not recommended.

Fenofibrate: Concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

Gemfibrozil: Concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

Statins: No clinically significant pharmacokinetic interactions were observed when ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Coumarin Anticoagulants: Concomitant administration of ezetimibe had no significant effect on bioavailability of warfarin and prothrombin time. If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored.

Drugs Affecting the Cytochrome P450 (CYP) System: No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized via CYP 1A2, 2D6, 2C8, 2C9, and 3A4 isoenzymes, or N-acetyltransferase.

Others: Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during coadministration. Cimetidine had no significant effect on the bioavailability of ezetimibe.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

All statins and fenofibrate are contraindicated in pregnant women. When ezetimibe is administered with a statin or fenofibrate in a woman of childbearing potential, refer to the package insert for that particular medication (see **Contraindications**).

Lactation: It is not known whether ezetimibe is excreted into human milk. However, ezetimibe is distributed into milk in rats. Ezetimibe should not be used in breastfeeding women unless the potential benefit justifies the potential risk to the infant.

All statins and fenofibrate are contraindicated in breastfeeding women. When ezetimibe is administered with a statin or fenofibrate in a breastfeeding woman, refer to the package insert for that particular medication (see **Contraindications**).

Children: Ezetimibe is not recommended in pediatric patients below 10 years of age. There are limited data on the efficacy and safety of ezetimibe in pediatric patients 6 to 10 years of age.

Elderly: There were no age-related differences in the efficacy or safety profile of ezetimibe, however, greater sensitivity of some older individuals cannot be ruled out.

UNDESIRABLE EFFECTS

The most frequently reported adverse events with ezetimibe include upper respiratory tract infection, headache, myalgia, and back pain.

Ezetimibe Monotherapy

Infections and infestations: Influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection, viral infection

Blood and lymphatic system disorders: Thrombocytopenia

Immune system disorders: Hypersensitivity reactions, including anaphylaxis, angioedema, rash and urticaria; panniculitis

Metabolism and nutrition disorders: Decreased appetite

Psychiatric disorders: Depression

Nervous system disorders: Dizziness, headache, paresthesia

Cardiac disorders: Palpitation

Vascular disorders: Hot flush, hypertension

Respiratory, thoracic and mediastinal disorders: Cough, dyspnea

Gastrointestinal disorders: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gastroesophageal reflux disease, nausea, pancreatitis

Hepatobiliary disorders: Cholecystitis, cholelithiasis, hepatitis

Skin and subcutaneous tissue disorders: Erythema multiforme

Musculoskeletal and connective tissue disorders: Arthralgia, asthenia, back pain, muscle spasms, myalgia, myopathy/rhabdomyolysis, neck pain, pain in extremity

General disorders and administration site conditions: Arm pain, chest pain, fatigue pain

Investigations: Increased ALT and/or AST, blood CPK, gamma-glutamyltransferase; abnormal liver function test

When ezetimibe is to be administered with a statin or fenofibrate, please also refer to the package insert for that particular medication for its adverse effects.

Ezetimibe + Statin Combination Therapy

Infections and infestations: Influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection

Nervous system disorders: Dizziness, headache, paresthesia

Gastrointestinal disorders: Abdominal pain, diarrhea, dry mouth, gastritis, pancreatitis

Hepatobiliary disorders: Hepatitis

Skin and subcutaneous tissue disorders: Pruritus, rash, urticaria

Musculoskeletal and connective tissue disorders: Arthralgia, back pain, muscular weakness, myalgia, myopathy/rhabdomyolysis, pain in extremity

General disorders and administration site conditions: Asthenia, chest pain, fatigue, peripheral edema

Investigations: Increased ALT and/or AST

Ezetimibe + Fenofibrate Combination Therapy

Gastrointestinal disorders: Abdominal pain

Hepatobiliary disorders: Cholelithiasis

Investigations: Increased ALT and/or AST

Surgical and medical procedures: In a combination study, higher incidence rate of cholecystectomy was observed in patents receiving ezetimibe with fenofibrate.

OVERDOSE AND TREATMENT

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

There have been a few cases of overdosage reported with ezetimibe. Most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

STORAGE CONDITIONS

Store at temperatures not exceeding 30°C.
Keep the product out of reach and sight of children.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

AVAILABILITY

Ezetimibe (Exelzio®) 10 mg Tablet, in Alu/Alu Blister Pack x 10's (Box of 30's)
DRP-12893

Manufactured by KRKA, d.d., Novo mesto
Šmarješka cesta 6, Novo mesto. 8501, Slovenia
Imported and Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

DATE OF FIRST AUTHORIZATION: October 2022
DATE OF LAST REVISION: August 2024

Reg. IPOPHIL

THE185006IN01

Trusted Quality Healthcare

UNILAB Consumer Care
8-UNILAB-1
8-864522-1
Provincial Toll Free: +1-800-10-864522-1
E-mail: info@unilab.com.ph
Website: www.unilab.com.ph