

Professional Information for Medicines for Human Use

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

EZOTAK (tablets)

2. QUALITATIVE AND QUANTITIVE COMPOSITION:

EZOTAK:

Each tablet contains 10 mg ezetimibe.

Contains sugar: 62 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white, uncoated, capsule shaped beveled edge tablets debossed with "E Z" on one side and "10" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hypercholesterolaemia

EZOTAK administered with an HMG-CoA reductase inhibitor (statin) or alone, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C), in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

EZOTAK administered with a statin is indicated for the reduction of elevated total-C and LDL-C levels in patients with Homozygous Familial Hypercholesterolaemia (HoFH).

4.2 Posology and method of administration

The patient should be on an appropriate lipid-lowering diet and weight loss programme where indicated and should continue on this diet during treatment with **EZOTAK**.

The recommended dose of **EZOTAK** is 10 mg once (daily, used alone, with a statin. or with fenofibrate).

EZOTAK can be administered at any time of the day, with or without food.

Use in the Elderly

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

Use in Paediatric Patients

Children 10 years of age or older: No dosage adjustment is required (see section 5.2).

Children under 10 years of age: No clinical data on safety and efficacy are available; therefore, treatment with **EZOTAK** is contraindicated.

Use in Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with **EZOTAK** is contraindicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction due to unknown effects (see section 4.3).

Concomitant use with bile acid sequestrants

Dosing of **EZOTAK** should occur either 2 or more hours before or 4 or more hours after administration of a bile acid sequestrant.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to ezetimibe or to any of the excipients of **EZOTAK** (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Moderate to severe hepatic impairment (Child Pugh score ≥ 7).
- Children below the age of 10 years.
- **EZOTAK** co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

4.4 Special warnings and precautions for use

When **EZOTAK** is to be administered with a statin, please refer to the professional information for that particular medicine.

Liver enzymes

In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥ 3 × the upper limit of normal [ULN]) have been observed. When **EZOTAK** is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin (see section 4.8).

Skeletal muscle

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level > 10 times the ULN, **EZOTAK**, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with **EZOTAK** should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness (see section 4.8).

Hepatic impairment

Due to the unknown effects of the increased exposure to **EZOTAK** in patients with moderate or severe hepatic impairment, **EZOTAK** is not recommended (see section 4.3 and 5.2).

Paediatric population

The safety and efficacy of **EZOTAK** co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age.

The safety and efficacy of **EZOTAK** co-administered with simvastatin have not been studied in paediatric patients < 10 years of age (see sections 4.2).

The long-term efficacy of therapy with **EZOTAK** in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates

The safety and efficacy of **EZOTAK** administered with fibrates have not been established. The co-administration of **EZOTAK** with fibrates other than fenofibrate has not been studied.

Fenofibrate

If cholelithiasis is suspected in a patient receiving **EZOTAK** and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see sections 4.5 and 4.8).

Alternative lipid-lowering therapy should be considered.

Ciclosporin

Caution should be exercised when initiating **EZOTAK** in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving **EZOTAK** and ciclosporin (see section 4.5).

Anticoagulants

If **EZOTAK** is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Lactose monohydrate

EZOTAK contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take **EZOTAK**.

4.5 Interaction with other medicines and other forms of interaction

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

In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam, during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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.

Cholestyramine

Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates

In patients receiving fenofibrate and ezetimibe, medical practitioners should be aware of the possible risk of cholelithiasis and gallbladder disease (see sections 4.4 and 4.8).

If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).

Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1,5 and 1,7-fold respectively).

Co-administration of ezetimibe with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile but not in all species (see section 5.3). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Statins

No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.

Ciclosporin

In a study of eight post-renal transplant patients with creatinine clearance of > 50 ml/min on a stable dose of ciclosporin, 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, receiving ezetimibe alone, from another study (n = 17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medications, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. 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 ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ezetimibe and ciclosporin (see section 4.4).

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. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

EZOTAK is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

No clinical data are available on the use of **EZOTAK** during pregnancy.

Lactation

EZOTAK should not be used during lactation. Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Fertility

No clinical trial data are available on the effects of ezetimibe on human fertility. **EZOTAK** had no effect on the fertility of male or female.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

EZOTAK when administered alone

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Infections and infestations	Viral infections, pharyngitis, sinusitis	Frequent
Metabolism and nutrition disorders	Decreased appetite	Less frequent
Vascular disorders	Hot flush, hypertension	Less frequent
Respiratory, thoracic and mediastinal disorders	Cough	Frequent
Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence	Frequent
	Dyspepsia, gastroesophageal reflux disease, nausea	Less frequent
Musculoskeletal, connective tissue and bone disorders	Arthralgia, back pain	Frequent
	Muscle spasms, neck pain	Less frequent
General disorders and administration site conditions	Headache, fatigue	Frequent
	Chest pain, pain	Less frequent
Investigations	Increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), increased blood creatine phosphokinase, increased gamma-glutamyl transferase, abnormal liver function test	Less frequent

EZOTAK when administered with a statin

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Infections and infestations	Pharyngitis, sinusitis, upper respiratory tract infection	Frequent
Nervous system disorders	Headache, dizziness	Frequent
	Paraesthesia	Less frequent
Gastrointestinal disorders	Abdominal pain, constipation, diarrhoea, flatulence, nausea	Frequent
	Dry mouth, gastritis	Less frequent
Skin and subcutaneous tissue disorders	Pruritus, rash, urticaria	Less frequent
Musculoskeletal, connective tissue and bone disorders	Myalgia, arthralgia, back pain	Frequent
	Muscular weakness, pain in extremity	Less frequent
General disorders and administration site conditions	Chest pain, fatigue	Frequent
	Asthenia, peripheral oedema	Less frequent
Investigations	Increased ALT and/or AST	Frequent

Less frequent side effects

- decreased appetite;
- hot flush;
- high blood pressure;
- indigestion, dry mouth, heartburn;
- muscle spasms, neck pain, hand or foot pain;
- increased blood creatinine phosphokinase or gamma-glutamyl transferase levels when blood tests are done;
- tingling or numbness of your hands and feet (pins and needles);
- weakness or lack of energy.

Frequency unknown side effects

- feeling depressed;
- shortness of breath (dyspnoea);
- raised red rash, sometimes with target-shaped lesions (erythema multiforme).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of **EZOTAK**.

5. HOW TO STORE EZOTAK

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What EZOTAK contains:

Each tablet contains 10 mg ezetimibe.

The active substance is Ezetimibe.

The other ingredients of **EZOTAK** are cellulose microcrystalline, croscarmellose sodium, crospovidone, hypromellose, lactose monohydrate, magnesium stearate and sodium lauryl sulfate.

What EZOTAK looks like and contents of the pack

EZOTAK:

White to off-white, uncoated, capsule shaped beveled edge tablets debossed with "E Z" on one side and "10" on other side.

Blister pack:

Cold form 3 layer laminate film – Aluminium foil blister pack:

Blister pack comprises of cold form laminate (25 micron OPA/45 micron Al foil/60 micron PVC) as the forming material and 25 micron aluminum foil with 7 g/m² heat seal lacquer as the lidding material.

PVC/PVdC film - Aluminium foil blister pack:

Blister pack comprises of PVC film 250 micron clear, coated with 120 GSM PVdC as the forming material and 25 micron aluminum foil with 7 g/m² heat seal lacquer as the lidding material.

Pack size: 30's - Each carton contains 3 blisters of 10 tablets each.

HDPE container:

60 ml HDPE container with 33 mm neck finish closed with 33 mm – 400 child resistant closure with wad having TEKNIPLEX HS 123 induction sealing liner induction sealing liner.

Pack size: 30's – Each HDPE container contains 30 tablets.

Holder of Registration

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Registration number:

52/7.5/0279

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17 August 2021

S4

PATIENT INFORMATION LEAFLET

EZOTAK 10 mg (tablet)

Ezetimibe

Contains Sugar: lactose monohydrate 62 mg

Read all of this leaflet carefully before you start taking EZOTAK.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **EZOTAK** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What **EZOTAK** is and what it is used for
2. What you need to know before you take **EZOTAK**
3. How to take **EZOTAK**
4. Possible side effects
5. How to store **EZOTAK**
6. Contents of the pack and other information

1. WHAT EZOTAK IS AND WHAT IS USED FOR

EZOTAK is a medicine used to lower levels of total cholesterol, "bad" cholesterol (LDL cholesterol) and fatty substances called triglycerides in the blood. Additionally, **EZOTAK** raises levels of "good" cholesterol (HDL cholesterol). **EZOTAK** works by reducing the cholesterol absorbed in your digestive tract.

EZOTAK is used for patients who cannot control their cholesterol levels by diet alone. You should however stay on a cholesterol-lowering diet while taking **EZOTAK**.

EZOTAK adds to the cholesterol-lowering effect of statins, a group of medicines that reduce the cholesterol your body makes by itself.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE EZOTAK

Do not take EZOTAK:

- If you are allergic to ezetimibe or any of the ingredients of **EZOTAK** (see What **EZOTAK** contains).
- If you are pregnant or breastfeeding (see pregnancy and breastfeeding).
- If you have moderate to severe liver problems.
- **EZOTAK** co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

EZOTAK is not recommended in children under the age of 10 years.

Warnings and precautions

Tell your doctor before taking **EZOTAK**:

Take special care with **EZOTAK**:

- If you experience any unexplained muscle pain, tenderness or muscle weakness. Contact your doctor immediately.
- If you are already taking other medicines to lower your cholesterol levels in the blood.
- If you are taking warfarin tablets used to prevent blood clots or any other anti-clotting medicine.

Your doctor should do a blood test before you start taking **EZOTAK** with a statin. This is to check how well your liver is working.

Your doctor may also want you to do blood tests to check how well your liver is working after you start taking **EZOTAK** with a statin.

Do not give **EZOTAK** to children below 10 years, as safety and efficacy have not been established.

Taking other medicines with EZOTAK:

Always tell your health care provider if you are taking any other medicine. (This includes complementary or traditional medicines).

Tell your doctor or pharmacist if you are currently using:

- cholestyramine (used to lower cholesterol), because it affects the way **EZOTAK** works;
- fibrates (medicines used to lower cholesterol);
- ciclosporin (used to prevent organ rejection after a transplant);
- Medicines to prevent blood clots, such as warfarin (anticoagulants).

Always tell your healthcare professional if you are taking any other medicine (This included complementary and traditional medicines).

Taking EZOTAK with food and drink:

See section 3.

Pregnancy and breastfeeding:

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking **EZOTAK**.

Do not take **EZOTAK** if you are pregnant or breastfeeding.

Driving and using machinery:

EZOTAK can cause side effects, such as dizziness. Do not drive a vehicle, operate machinery, or do anything else that requires your attention until you know how **EZOTAK** affects you.

EZOTAK contains lactose:

If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before taking **EZOTAK**.

3. HOW TO TAKE EZOTAK

Do not share medicines prescribed for you with any other person.

Always take exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Before you start taking **EZOTAK**, you should be on a diet to reduce your cholesterol,

You should stay on this diet whilst taking **EZOTAK**.

Adults and children (10 years of age and older):

The usual dose is one **EZOTAK** tablet once a day.

Take **EZOTAK** at any time of the day. You can take **EZOTAK** with or without food.

If your doctor has prescribed **EZOTAK** along with any other medicine containing bile acid sequestrant, you should take **EZOTAK** at least 2 hours before or 4 hours after taking the bile acid sequestrant.

Your doctor will tell you how long your treatment with **EZOTAK** will last. Do not stop treatment early because this may reoccurrence of your condition.
If you have the impression that the effect of **EZOTAK** is too strong or too weak, tell your doctor or pharmacist.

If you take more EZOTAK than you should:

Take this leaflet and the rest of the remaining **EZOTAK** with you so the doctor will know what you have taken.

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take EZOTAK:

Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

EZOTAK can have side effects.

Not all side effects reported for **EZOTAK** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **EZOTAK**, please consult your health care provider for advice.

If any of the following happens, stop taking **EZOTAK** and tell your doctor immediately or go to the casualty department at your nearest hospital:

- swelling of your hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing;
- rash, hives or itching;
- fainting.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **EZOTAK**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- chest pain;
- bleeding or bruising more easily than normal;
- myopathy (unexplained muscle pain, tenderness or weakness, stiffness or cramping);
- inflammation of pancreas (nausea, vomiting, fever, pain of your stomach area that radiates to your back, increased heart rate);
- rhabdomyolysis (temporary paralysis or weakness of muscles);
- yellowing of your skin and eyes, dark urine, and tiredness which may be symptoms of liver problems;
- inflammation of your gallbladder or gallstones (persistent pain in the abdominal area, fever, nausea and vomiting, sweating, loss of appetite).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following

Frequent side effects

- viral infections, infections of the sinuses (runny nose, nasal congestion);
- upper respiratory tract infection (sneezing, runny nose, scratchy or sore throat, fever);
- cough;
- abdominal pain, diarrhoea, flatulence (wind), constipation, nausea (feeling sick);
- joint pain, back pain, muscle pain;
- headache, dizziness;
- feeling tired;
- elevations in liver function when blood tests are done [increased alanine transaminases (ALT) and/or aspartate transaminase (AST)].

DETACH BEFORE DISPENSING

EZOTAK when administered with fenofibrate

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Gastrointestinal disorders	Abdominal pain	Frequent

Post-marketing data

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Blood and the lymphatic system disorders	Thrombocytopenia	Frequency unknown
Immune system disorders	Hypersensitivity reactions (anaphylaxis, rash, urticaria, angioedema)	Frequency unknown
Psychiatric disorders	Depression	Frequency unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Frequency unknown
Gastrointestinal disorders	Pancreatitis	Frequency unknown
Hepatobiliary disorders	Hepatitis, cholelithiasis, cholecystitis	Frequency unknown
Skin and subcutaneous tissue disorders	Erythema multiforme	Frequency unknown
Musculoskeletal, connective tissue and bone disorders	Myopathy/rhabdomyolysis	Frequency unknown

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **'6.04 Adverse Drug Reactions Reporting Form'.** Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9 Overdosage

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

In the event of an overdose, symptomatic and supportive measures should be employed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.5 Serum-cholesterol reducers.

Pharmacotherapeutic group: Other lipid modifying agents, ATC code: C10A X09

Mechanism of action:

Ezetimibe inhibit the intestinal absorption of cholesterol and related plant sterols.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption.

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.

Paediatric population

The safety and efficacy of ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. The safety and efficacy of ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age.

The long-term efficacy of therapy with ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

5.2 Pharmacokinetics

Absorption

After oral administration, ezetimibe is 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. **EZOTAK** can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are bound 99,7% and 88 to 92% to human plasma proteins, respectively.

Biotransformation

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

Elimination

Following oral administration of 14C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Special populations

Paediatric Patients

The absorption and metabolism of ezetimibe are similar between children 10 years of age or older and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population less than 10 years of age are not available.

Elderly

Plasma concentrations for total ezetimibe are about 2 fold higher in the elderly (65 years or older) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

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. No dosage adjustment is necessary for patients with mild hepatic insufficiency. 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. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score greater than 9) hepatic insufficiency, **EZOTAK** is contraindicated in these patients (see section 4.4).

Renal Insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (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 This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

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

Gender

Plasma concentrations for total ezetimibe are slightly higher (less than 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

5.3. Preclinical safety data

No further information of relevance available.

6 Pharmaceutical particulars

6.1 List of excipients

The other ingredients of **EZOTAK** are cellulose microcrystalline, croscarmellose sodium, crospovidone, hypromellose, lactose monohydrate, magnesium stearate and sodium lauryl sulfate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25 °C.

Do not remove blister from carton until required for use.

6.5 Nature and contents of container

Blister pack:

Cold form 3-layer laminate film - Aluminium foil blister pack:

Blister pack comprises of cold form laminate (25 micron OPA/45 micron Al foil/60 micron PVC) as the forming material and 25 micron aluminum foil with 7 g/m^2 heat seal lacquer as the lidding material.

PVC/PVdC film - Aluminium foil blister pack:

Blister pack comprises of PVC film 250 micron clear, coated with 120 GSM PVdC as the forming material and 25 micron aluminum foil with 7 g/m^2 heat seal lacquer as the lidding material.

Pack size: 30's - Each carton contains 3 blisters of 10 tablets each.

HDPE container:

60 ml HDPE container with 33 mm neck finish closed with 33 mm – 400 child resistant closure with wad having TEKNIPLEX HS 123 induction sealing liner induction sealing liner.

Pack size: 30's – Each HDPE container contains 30 tablets.

6.6 Special precautions for disposal and other handling

Procedures for safe handling of cytotoxic drugs should be followed.

7 Holder of certificate of registration

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8 Registration number

52/7.5/0279

9 Date of first authorisation/renewal of the authorisation

17 August 2021

P1537462

DETACH BEFORE DISPENSING

Minder gereelde newe-effekte

- verminderde eetlus;
- warm gloede;
- hoë bloeddruk;
- slegte spysvertering, droë mond, sooibrand;
- spierspasmas, nekpyn, hand- of voetpyn;
- verhoogde bloedkreatinienfosfokinase of -gamma-glutamiel transferase vlakke wanneer bloedtoetse gedoen word;
- tinteling of gevoelloosheid van u hande en voete (spelde en naalde);
- swakheid of gebrek aan energie.

Frekwensie van newe-effekte onbekend

- voel depressief;
- kortasem (dispnee);
- verhoogde rooi uitslag, soms met teikenvormige letsels (multivorme eriteem).

Indien u enige newe-effekte opmerk wat nie in hierdie pamflet genoem word nie, lig asseblief u dokter of apteker in.

Aanmelding van newe-effekte

Indien u newe-effekte ervaar, praat met u dokter, apteker of verpleegster. Dit sluit enige moontlike newe-effekte in wat nie in hierdie pamflet gelys is nie. U kan ook newe-effekte aanmeld aan SAHPRA via die "**6. 04 Adverse Drug Reaction Reporting Form**", wat aanlyn gevind word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte aan te meld, kan u meer inligting verskaf oor die veiligheid van **EZOTAK**.

5. HOE OM EZOTAK TE BERG

Berg teen of benede 25 °C.

Hou die stulpstroke in die karton tot benodig vir gebruik.

BERG ALLE MEDISYNE BUITE BEREIK VAN KINDERS

Neem alle ongebruikte medisyne terug na u apteker.
Moenie ongebruikte medisyne in dreine of rioolstelsels (bv. toilette) weggooi nie.

6. INHOUD VAN DIE VERPAKKING EN ANDER INLIGTING

Wat EZOTAK bevat:

Elke tablet bevat 10 mg ezetimibe.

Die aktiewe bestanddeel is Ezetimibe.

Die ander bestanddele van **EZOTAK** is mikrokristallyne sellulose, natriumkroskarmellose, krospovidoon, hipromellose, laktosemonohidraat, magnesiumstearaat en natriumlaurielsulfaat.

Hoe EZOTAK lyk en inhoud van die verpakking

EZOTAK:

Wit tot naaswit, onbedekte, kapsulevormige, skuinsrand tablette gebosseleer met "EZ" aan die een kant en "10" aan die ander kant.

Stulpverpakking:

Koudvormige 3-laag gelamineerde film – Aluminiumfoelie stulpverpakking:

Die stulpverpakking bestaan uit koudvormige laminaat (25 mikron OPA/45 mikron Al foelie/60 mikron PVC) as die vormingsmateriaal en 25 mikron aluminiumfoelie met 7 g/m^2 hitte seëllak as die dekselmateriaal.

PVC/PVdC film – Aluminiumfoelie stulpverpakking:

Die stulpverpakking bestaan uit PVC-film 250 mikron helder, bedek met 120 GSM PVdC as die vormingsmateriaal en 25 mikron aluminiumfoelie met 7 g/m^2 hitte seëllak as die dekselmateriaal.

Verpakkingsgrootte: 30's – Elke karton bevat 3 stulpstroke met 10 tablette elk.

HDPE-houer:

60 ml HDPE-houer met 33 mm nekafwerking gesluit met 33 mm – 400 kindweerstandige sluiting met watte en TEKNIPLEX HS 123 induksie seëlvoering.

Verpakkingsgrootte: 30's – Elke HDPE-houer bevat 30 tablette.

Houer van Registrasie

AUROGEN SA (Edms.) Bpk
Woodhill Office Park, Gebou 1
Philip Engelbrechtlaan 53
Meyersdal. Uitbr. 12
1448, Johannesburg
Suid-Afrika

Registrasienommer:

52/7.5/0279

Hierdie pamflet is laas hersien in:

17 Augustus 2021

PASIËNTINLIGTINGSPAMFLET

EZOTAK 10 mg (tablet)

Ezetimibe

Bevat Suiker: laktosemonohidraat 62 mg

Lees hierdie hele pamlet sorgvuldig deur voordat u EZOTAK begin neem.

- Hou hierdie pamflet. U moet dit dalk weer lees.
- Indien u verdere vrae het, vra asseblief u dokter of apteker.
- **EZOTAK** is vir u persoonlik voorgeskryf en u moet nie u medisyne met ander mense deel nie.
- Dit kan skadelik vir hulle wees, selfs al het hulle dieselfde simptome as u.

Wat is in hierdie pamflet

1. Wat **EZOTAK** is en waarvoor dit gebruik word
2. Wat u moet weet voordat u **EZOTAK** neem
3. Hoe om **EZOTAK** te neem
4. Moontlike newe-effekte
5. Hoe om **EZOTAK** te berg
6. Inhoud van die verpakking en ander inligting

1. WAT EZOTAK IS EN WAARVOOR DIT GEBRUIK WORD

EZOTAK is 'n medisyne wat gebruik word vir die verlaging van totale cholesterol, "slegte" cholesterol (LDL cholesterol) en vetterige stowwe, genaamd trigliserieds, in die bloed. Daarbenewens, verhoog **EZOTAK** die vlakke van "goeie" cholesterol (HDL cholesterol). **EZOTAK** werk deur die cholesterol te verlaag wat in u spysverteringstelsel geabsorbeer word.

EZOTAK word gebruik vir pasiënte wat nie hul cholesterolvlakke deur dieet alleen kan beheer nie. U moet egter op 'n cholesterolverlagende dieet bly terwyl u **EZOTAK** neem.

EZOTAK dra by tot die cholesterolverlagende effek van statiene, 'n groep medisyne wat die cholesterol verminder wat u liggaam self produseer.

2. WAT U MOET WEET VOORDAT U EZOTAK NEEM

Moenie EZOTAK neem nie:

- Indien u allergies is vir ezetimibe of enige van die bestanddele van **EZOTAK** (sien Wat **EZOTAK** bevat).
- Indien u swanger is of borsvoed (sien swangerskap en borsvoeding).
- Indien u matige of ernstige lewerprobleme het.
- **EZOTAK** saam met 'n statien is teenaangedui by pasiënte met aktiewe lewersiekte of onverklaarbare volgehoue verhogings in serumtransaminases.

EZOTAK word nie aanbeveel vir kinders onder die ouderdom van 10 jaar nie.

Waarskuwings en voorsorgmaatreëls:

Vertel u dokter voordat u **EZOTAK** neem:

Neem spesiale sorg met **EZOTAK**:

- Indien u onverklaarbare spierpyn, teerheid of spierswakheid ervaar. Kontak u dokter onmiddellik.
- Indien u reeds ander medisyne gebruik om u cholesterolvlakke in die bloed te verlaag.
- Indien u warfarien-tablette gebruik om bloedklonte te voorkom, of enige ander antistollings medisyne.

U dokter moet 'n bloedtoets doen voordat u **EZOTAK** met 'n statien begin gebruik. Dit is om te kyk hoe goed u lewer werk. U dokter kan ook wil hê dat u bloedtoetse moet doen om te kyk hoe goed u lewer werk nadat u **EZOTAK** saam met statiene begin gebruik het.

Moenie **EZOTAK** aan kinders jonger as 10 jaar gee nie, aangesien veiligheid en effektiwiteit nie vasgestel is nie.

Die gebruik van ander medisyne saam met EZOTAK

Vertel altyd u gesondheidsorgverskaffer indien u enige ander medisyne neem. (Dit sluit alle komplementêre of tradisionele medisyne in.)

Vertel u dokter of apteker indien u tans enige van die volgende gebruik:

- cholestiramien (gebruik om cholesterol te verlaag), omdat dit die werking van **EZOTAK** beïnvloed;
- fibrate (medisyne wat gebruik word om cholesterol te verlaag);
- siklosporien (gebruik om orgaanverwerping na 'n oorplanting te voorkom);
- medisyne om bloedklonte te voorkom, soos warfarien (antikoagulante).

Vertel altyd u gesondheidsorgkundige indien u enige ander medisyne neem. (Dit sluit alle komplementêre of tradisionele medisyne in.)

EZOTAK met voedsel en drank:

Sien afdeling 3.

Swangerskap en borsvoeding:

Indien u swanger is of borsvoed, dink u is dalk swanger of beplan om 'n baba te hê, raadpleeg asseblief u dokter, apteker of ander gesondheidsorgverskaffer vir advies voordat u **EZOTAK** begin neem. Moenie **EZOTAK** neem indien u swanger is of borsvoed nie.

Bestuur en die gebruik van masjinerie:

EZOTAK kan newe-effekte veroorsaak, soos duiseligheid. Moenie 'n voertuig bestuur, masjinerie gebruik, of iets anders doen wat u aandag verreis, totdat u weet hoe **EZOTAK** u beïnvloed nie.

EZOTAK bevat laktose:

Indien u dokter u meegedeel het dat u 'n intoleransie vir sekere suikers het, raadpleeg u dokter voordat u **EZOTAK** neem.

3. HOE OM EZOTAK TE NEEM

Moenie medisyne wat vir u voorgeskryf met enige ander persoon deel nie.

Neem altyd presies soos u dokter voorgeskryf het. U moet u dokter of apteker raadpleeg indien u onseker is.

Voor u **EZOTAK** begin gebruik, moet u 'n dieet volg om u cholesterol te verlaag.

U moet op hierdie dieet bly terwyl u **EZOTAK** neem.

Volwassenes en kinders (10 jaar en ouer):

Die gewone dosis is een **EZOTAK** tablet eenkeer per dag.

Neem **EZOTAK** enige tyd van die dag. U kan **EZOTAK** met of sonder voedsel neem.

Indien u dokter **EZOTAK** saam met enige ander medisyne wat galsuur sekwestrante bevat, voorgeskryf het, moet u **EZOTAK** ten minste 2 uur voor of 4 uur na u die galsuur sekwetrant geneem het, neem.

U dokter sal u vertel hoe lank u behandeling met **EZOTAK** sal duur. Moenie die behandeling vroeg staak nie, aangesien u toestand weer kan voorkom.

Indien u die indruk het dat die effek van **EZOTAK** te sterk of te swak is, vertel u dokter of apteker.

Indien u meer EZOTAK neem as wat u moet:

Neem hierdie pamflet en die res van die oorblywende **EZOTAK** met u, sodat u dokter kan weet wat u geneem het.

In die geval van oordosering, raadpleeg u dokter of apteker. Indien geeneen beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

Indien u vergeet om EZOTAK te neem:

Moenie 'n dubbeldosis neem om op te maak vir vergete individuele dosisse nie.

4. MOONTLIKE NEWE-EFFEKTE

EZOTAK kan newe-effekte hê.

Nie alle newe-effekte aangemeld vir **EZOTAK**, word in hierdie pamflet ingesluit nie. Indien u algemene gesondheid agteruitgaan of indien u enige ongewensde effekte ervaar terwyl u **EZOTAK** neem, raadpleeg asseblief u gesondheidsorgverskaffer vir advies.

Indien enige van die volgende gebeur, staak die gebruik van **EZOTAK** en vertel u dokter onmiddellik of gaan na die ongevalle-afdeling van u naaste hospital:

- swelling van u hande, voete, enkels, gesig, lippe, mond of keel, wat moeilike sluk of asemhaling kan veroorsaak;
- uitslag, velbulte of jeuk;
- floute.

Hierdie is almal baie ernstige newe-effekte. Indien u dit ervaar, het u moontlik 'n ernstige allergiese reaksie vir **EZOTAK**. U benodig moontlik dringende mediese behandeling of hospitalisasie.

Vertel u dokter onmiddellik of gaan na die ongevalle-afdeling van u naaste hospital, indien u enige van die volgende opmerk:

- borspyn;
- bloeding of kneus makliker as normaalweg;
- miopatie (onverklaarbare spierpyn, teerheid of swakheid, styfheid of krampe);
- inflammasie van die pankreas (naarheid, braking, koors, pyn in die maagarea wat na die rug uitstraal, verhoogde hartklop);
- rabdomiolise (tydelike verlamming of spierswakheid);
- vergeling van u vel en oë, donker urine en moegheid wat simptome van lewerprobleme kan wees;
- inflammasie van u galblaas of galstene (aanhoudende pyn in die abdominale area, koors, naarheid en braking, sweet, verlies aan eetlus).

Hierdie is almal ernstige newe-effekte. U benodig moontlik dringende mediese behandeling.

Vertel u dokter indien u enige van die volgende opmerk

Gereelde newe-effekte

- virale infeksies, infeksies van die sinuses (loopneus, neusverstopping);
- boonste lugweginfeksie (nies, loopneus, krapperige of seer keel, koors);
- hoes;
- buikpyn, diarree, winderigheid, hardlywigheid, naarheid (siek voel);
- gewrigspyn, rugpyn, spierpyn;
- hoofpyn, duiseligheid;
- moegheid;
- verhoogde lewertunksie wanneer bloedtoetse gedoen word [verhoogde alanientransaminases (ALT) en/of aspartaattransaminase (ASAT)].