V1.1 (22.06.2021)

Professional Information

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

EZETIMIBE 10 UNICORN (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg ezetimibe.

Excipient(s) with known effect: Lactose monohydrate.

Each tablet contains 67,5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

EZETIMIBE 10 UNICORN tablets are white to almost white, oval tablets with debossing "10" on one side and "EZT" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary hypercholesterolaemia:

EZETIMIBE 10 UNICORN, 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):

EZETIMIBE 10 UNICORN, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH.

4.2 Posology and method of administration

Posology:

The patient should be on an appropriate lipid-lowering diet and weight loss program where

indicated and should continue on this diet during treatment with **EZETIMIBE 10 UNICORN**. The recommended dose of **EZETIMIBE 10 UNICORN** is 10 mg once daily, used alone, with a statin or with fenofibrate.

EZETIMIBE 10 UNICORN 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: No dosage adjustment is required (see section 5.2).

Children < 10 years: No clinical data on safety and efficacy are available; therefore, treatment with **EZETIMIBE 10 UNICORN** 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 **EZETIMIBE 10 UNICORN** is contraindicated in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) hepatic impairment due to unknown effects. (See section 4.3.)

Concomitant use with bile acid sequestrants:

Dosing of **EZETIMIBE 10 UNICORN** should occur at least 2 hours before or 4 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 **EZETIMIBE 10 UNICORN** (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Moderate to severe hepatic impairment (Child Pugh score ≥ 7).
- Children under the age of 10 years.

- **EZETIMIBE 10 UNICORN** 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 **EZETIMIBE 10 UNICORN** 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 10 UNICORN** with a statin, consecutive transaminase elevations (≥ 3 times the upper limit of normal (ULN)) have been observed. When **EZETIMIBE 10 UNICORN** 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 10 UNICORN**, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with **EZETIMIBE 10 UNICORN**. However, rhabdomyolysis has been reported with **EZETIMIBE 10 UNICORN** monotherapy and with the addition of **EZETIMIBE 10 UNICORN** to other medicines 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, **EZETIMIBE 10 UNICORN**, any statin, and any of these other medicines that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with **EZETIMIBE 10 UNICORN** 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 ezetimibe in patients with moderate or severe hepatic impairment, **EZETIMIBE 10 UNICORN** is contraindicated (see section 4.3 and 5.2).

Paediatric population:

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

The long-term efficacy of therapy with **EZETIMIBE 10 UNICORN** in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates:

The safety and efficacy of **EZETIMIBE 10 UNICORN** administered with fibrates have not been established. The co-administration of **EZETIMIBE 10 UNICORN** with fibrates other than fenofibrate has not been studied.

Fenofibrate:

If cholelithiasis is suspected in a patient receiving **EZETIMIBE 10 UNICORN** 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 **EZETIMIBE 10 UNICORN** in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving **EZETIMIBE 10 UNICORN** and ciclosporin (see section 4.5).

Anticoagulants:

If **EZETIMIBE 10 UNICORN** is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Lactose monohydrate:

EZETIMIBE 10 UNICORN contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take **EZETIMIBE 10 UNICORN**.

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 medicine metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

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) by approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding **EZETIMIBE 10 UNICORN** to cholestyramine may be lessened by this interaction (see section 4.2).

Fibrates:

In patients receiving fenofibrate and **EZETIMIBE 10 UNICORN**, the medical practitioner 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 10 UNICORN** and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued (see section 4.8).

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

Co-administration of **EZETIMIBE 10 UNICORN** with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe 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 10 UNICORN** 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 10 UNICORN** 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. In a different study, a renal transplant patient with severe renal impairment (creatinine clearance of 13,2 mL/min/1,73 m^2) who was receiving ciclosporin and multiple other medicines 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 10 UNICORN** in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving **EZETIMIBE 10 UNICORN** 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 INR in patients who had **EZETIMIBE 10 UNICORN** added to warfarin or fluindione. If **EZETIMIBE 10 UNICORN** 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

EZETIMIBE 10 UNICORN is contraindicated during pregnancy and lactation (see section 4.3).

Pregnancy

No clinical data are available on the use of **EZETIMIBE 10 UNICORN** during pregnancy.

Breastfeeding

EZETIMIBE 10 UNICORN 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. Ezetimibe had no effect on the fertility of males or females.

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

EZETIMIBE 10 UNICORN when administered alone:

Infections and infestations:

Frequent: viral infections, pharyngitis, sinusitis

Metabolism and nutrition disorders:

Less frequent: decreased appetite

Vascular disorders:

Less frequent: hot flush, hypertension

Respiratory, thoracic and mediastinal disorders:

Frequent: cough

Gastrointestinal disorders:

Frequent: abdominal pain, diarrhoea, flatulence

Less frequent: dyspepsia, gastroesophageal reflux disease, nausea

Musculoskeletal, connective tissue and bone disorders:

Frequent: arthralgia, back pain

Less frequent: muscle spasms, neck pain

General disorders and administration site conditions:

Frequent: headache, fatigue

Less frequent: chest pain, pain

Investigations:

Less frequent: increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), increased blood creatine phosphokinase, increased gamma-glutamyl transferase, abnormal liver function test

EZETIMIBE 10 UNICORN when administered with a statin:

Infections and infestations:

Frequent: pharyngitis, sinusitis, upper respiratory tract infection

Nervous system disorders:

Frequent: headache, dizziness

Less frequent: paraesthesia

Gastrointestinal disorders:

Frequent: abdominal pain, constipation, diarrhoea, flatulence, nausea

Less frequent: dry mouth, gastritis

Skin and subcutaneous tissue disorders:

Less frequent: pruritus, rash, urticaria

Musculoskeletal, connective tissue and bone disorders:

Frequent: myalgia, arthralgia, back pain

Less frequent: muscular weakness, pain in extremity

General disorders and administration site conditions:

Frequent: chest pain, fatigue

Less frequent: asthenia, peripheral oedema

Investigations:

Frequent: increased ALT and/or AST

EZETIMIBE 10 UNICORN when administered with fenofibrate:

Gastrointestinal disorders:

Frequent: abdominal pain

Post-marketing data:

Blood and the lymphatic system disorders:

Frequency unknown: thrombocytopenia

Immune system disorders:

Frequency unknown: hypersensitivity reactions (anaphylaxis, rash, urticaria, angioedema)

Psychiatric disorders:

Frequency unknown: depression

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: dyspnoea

Gastrointestinal disorders:

Frequency unknown: pancreatitis

Hepatobiliary disorders:

Frequency unknown: hepatitis, cholelithiasis, cholecystitis

Skin and subcutaneous tissue disorders:

Frequency unknown: erythema multiforme

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: myopathy/rhabdomyolysis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **EZETIMIBE 10 UNICORN** is important. It allows continued monitoring of the benefit/risk balance of **EZETIMIBE 10 UNICORN**. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/.
Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

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 inhibits 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 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 Pharmacokinetic properties

Absorption:

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

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe. Ezetimibe 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 medicine-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination:

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 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 population:

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) 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 impairment:

After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1,7-fold in patients with mild hepatic impairment (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 impairment (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 impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, **EZETIMIBE 10 UNICORN** is contraindicated in these patients (see section 4.4).

Renal impairment:

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 medicines, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Gender:

Plasma concentrations for total ezetimibe are slightly higher (approximately 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with **EZETIMIBE 10 UNICORN**. 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

Lactose monohydrate

Sodium lauryl sulfate

Croscarmellose sodium

Hypromellose

Cellulose, microcrystalline

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

EZETIMIBE 10 UNICORN Tablets are packed into Al/Al blisters or Aqua Ba blisters in packs of 30.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]
Waterfall 5-Ir
Magwa Crescent West
Waterfall City
Jukskei View

2090

Marketed by **UNICORN PHARMACEUTICALS (PTY) LTD**

8. REGISTRATION NUMBER

47/7.5/0174

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 March 2021

10. DATE OF REVISION OF THE TEXT

Not applicable

[1]Company Reg. No.: 1990/001979/07