Ezetralex®

Ezetimibe

FORMS AND PRESENTATION

Ezetralex®: Tablets: Box of 30.

COMPOSITION:

Ezetralex®: Each tablet contains Ezetimibe 10mg.

Excipients: lactose, starch, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, crospovidone.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Therapeutic class: Lipid modifying agents.

ATC code: C10AX09.

Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. 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 sterol). 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 localises 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.

Pharmacokinetic Properties

Absorption: After oral administration, Ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (Ezetimibe-glucuronide). Mean C_{max} occur within 1-2 hrs for Ezetimibe-glucuronide and 4-12 hrs for 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 drug-derived compounds detected in plasma, constituting approximately 10-20% and 80-90% 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 hrs.

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

INDICATIONS`

Primary hypercholesterolaemia: Ezetralex® monotherapy or co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH): Ezetralex® co-administered with a statin, is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozygous sitosterolaemia (phytosterolaemia): Ezetralex® is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

CONTRAINDICATIONS

Hypersensitivity to Ezetimibe or to any of the excipients.

Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation.

Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

PRECAUTIONS

Liver enzymes: In controlled co-administration trials in patients receiving Ezetimibe with a statin, consecutive transaminase elevations (≥3 X the ULN) have been observed. When Ezetimibe is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin.

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 creatinine phosphokinase (CPK) level >10 times the ULN, Ezetimibe, any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with Ezetimibe should be advised of the risk of myopathy and told to report any unexplained muscle pain, tenderness or weakness.

Excipient: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ability to drive and use machines: No studies of the effects on the ability to drive and use machines have been performed. Dizziness has been reported in some cases.

PREGNANCY AND LACTATION

Ezetimibe should be given to pregnant women only if clearly necessary. No clinical data are available on the use of Ezetimibe during pregnancy. Animal studies on the use of Ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development. Ezetimibe 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.

DRUG INTERACTIONS

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.

Cytochrome P450: 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 drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

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.

Colestyramine: Concomitant colestyramine administration decreased the mean AUC of total Ezetimibe (Ezetimibe + Ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding Ezetimibe to colestyramine may be lessened by this interaction.

Fibrates: The safety and efficacy of Ezetimibe administered with fibrates have not been established. If cholelithiasis is suspected in a patient receiving Ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued. Concomitant fenofibrate or gemfibrozil administration modestly increased total Ezetimibe concentrations by 1.5 and 1.7 fold respectively. Co-administration with other fibrates has not been studied.

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

Ciclosporin: Caution should be exercised when initiating Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe and ciclosporin.

Anticoagulants: If Ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored.

ADVERSE EFFECTS

The following common drug-related adverse experiences were reported in patients taking Ezetimibe alone:

Nervous system disorders: headache.

Gastro-intestinal disorders: abdominal pain and diarrhoea.

Laboratory values: In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between Ezetimibe (0.5%) and placebo (0.3%). In clinical trials, CPK>10 X ULN was reported for 4 of 1,674 (0.2%) patients administered Ezetimibe alone vs 1 of 786 (0.1%) patients administered placebo.

The following additional adverse reactions have been reported in post-marketing experience regardless of causality assessment. Their true frequencies are not known.

Blood disorders: thrombocytopenia.

Immune system disorders: hypersensitivity, including rash, urticaria, anaphylaxis and angioedema.

Gastro-intestinal disorders: nausea; pancreatitis.

Hepatobiliary disorders: hepatitis, cholelithiasis, cholecystitis.

Musculoskeletal disorders: arthralgia; myalgia; myopathy/rhabdomyolysis (very rare).

Laboratory values: increased transaminases; increased CPK.

DOSAGE AND ADMINISTRATION

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Ezetralex®.

The recommended dose is one Ezetralex® 10 mg tablet daily. Ezetralex® can be administered at any time of the day, with or without food.

Co-administration with bile acid sequestrants:

Dosing of Ezetralex® should occur either ≥ 2 hrs before or ≥ 4 hrs after administration of a bile acid sequestrant.

Elderly:

No dosage adjustment is required for elderly patients.

Children:

Children and adolescents ≥ 10 years: No dosage adjustment is required.

Children < 10 years: Ezetralex® is not recommended for use in children below age 10 due to insufficient data on safety and efficacy.

Hepatic impairment:

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5-6). Treatment with Ezetralex® is not recommended in patients with moderate (Child Pugh score 7-9) or severe (Child Pugh score > 9) liver dysfunction.

Renal impairment:

No dosage adjustment is required for renally impaired patients.

OVERDOSAGE

A few cases of overdosage with Ezetimibe have been reported: 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 below 30°C.

Keep in original pack in intact conditions.

Date of revision: February 2014.

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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