

**EZETROL®**  
(ezetimibe)

**PRESCRIBING INFORMATION**

Refer to Summary of Product Characteristics (SmPC) before Prescribing

**Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD (Tel: 01992-467272), UK. By clicking the above link you will leave the MSD website and be taken to the MHRA website.**

**PRESENTATION**

Tablet containing 10 mg of ezetimibe.

**USES**

As adjunctive therapy to diet in:

*Primary (heterozygous familial and non-familial) hypercholesterolaemia:* For co-administration with an HMG-CoA reductase inhibitor (statin) for patients not appropriately controlled with a statin alone or as monotherapy in patients in whom a statin is considered inappropriate or is not tolerated.

*Homozygous Familial Hypercholesterolaemia (HoFH):* For co-administration with a statin, for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis). *Homozygous sitosterolaemia (phytosterolaemia):* For use in patients with homozygous familial sitosterolaemia.

*Prevention of Cardiovascular Events:* Reduces the risk of cardiovascular events 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.

**DOSAGE AND ADMINISTRATION**

For oral administration

Put patients on an appropriate lipid-lowering diet and continue during treatment.

Recommended dose is one Ezetrol 10 mg tablet daily. When added to a statin, consult the statin dosage instructions.

*Use in Patients with Coronary Heart Disease and ACS Event History:* For incremental cardiovascular event reduction in patients with CHD and ACS event history, Ezetrol 10 mg may be administered with a statin with proven cardiovascular benefit.

*Co-administration with bile acid sequestrants:* Dosing should occur either  $\geq 2$  hours before or  $\geq 4$  hours after administration of a bile acid sequestrant.

*Use in paediatric population:* Initiation of treatment must be performed under review of a specialist. Children and adolescents  $\geq 6$

years: Safety and efficacy of ezetimibe in children aged 6 to 17 years has not been established. Clinical data are available but no recommendation on a posology can be made. Children  $<6$  years: No data available.

*Use in older people:* No dosage adjustment required.

*Use in hepatic impairment:* No dosage adjustment is required with mild hepatic impairment (Child Pugh score 5 to 6). Not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score  $>9$ ) liver dysfunction.

*Use in renal impairment:* No dosage adjustment required.

**CONTRA-INDICATIONS**

Hypersensitivity to any component. When co-administered with a statin, refer to the statin SmPC. Ezetrol co-administered with a statin during pregnancy and lactation. Ezetrol co-administered with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases.

**PRECAUTIONS**

*Liver enzymes:* When co-administered with a statin, perform liver function tests at initiation of therapy and according to the statin SmPC. In a clinical trial (Study of Heart and Renal Protection (SHARP))  $\geq 9000$  patients with chronic kidney disease were randomised to Ezetrol 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up 4.9 years), the incidence of elevations of transaminases ( $>3 \times$  ULN) was 0.7% for Ezetrol combined with simvastatin vs 0.6% for placebo. In the IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive

elevations of transaminases ( $\geq 3$  X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin.

**Skeletal muscle:** In post-marketing experience, patients who developed rhabdomyolysis were mostly on a statin and Ezetrol, very rarely on Ezetrol monotherapy and very rarely on Ezetrol added to other agents associated with increased risk of rhabdomyolysis. If myopathy is suspected, immediately discontinue Ezetrol, statin, and any of these other agents. Advise all patients starting therapy with Ezetrol of the risk of myopathy and to report promptly any unexplained muscle symptom.

**Hepatic impairment:** Not recommended in patients with moderate or severe hepatic impairment. **Fibrates:** Safety and efficacy of co-administration have not been established. There is a possible risk of cholelithiasis and gall-bladder disease in patients receiving fenofibrate and Ezetrol. If suspected, conduct gall-bladder investigations and discontinue co-administration. **Ciclosporin:** Exercise caution when initiating Ezetrol in patients taking ciclosporin and monitor ciclosporin concentrations. **Warfarin, another coumarin anticoagulant or fluindione:** Monitor the International Normalised Ratio (INR). **Excipient:** Ezetrol tablets contain lactose: do not use in patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

**Paediatric population:** Efficacy and safety of Ezetrol in patients 6 to 10 years of age with heterozygous familial or non-familial hypercholesterolaemia have been evaluated in a 12-week placebo-controlled trial. Efficacy and safety of Ezetrol co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in boys (Tanner stage II or above) and in girls who were at least one year post-menarche. Generally, there was no detectable effect on growth or sexual maturation in adolescent boys or girls, or any effect on menstrual cycle length in girls. Effects of treatment >33 weeks on growth and sexual maturation have not been studied. Long-term efficacy of Ezetrol in patients < 17 years of age on morbidity and mortality in adulthood has not been studied.

**Interactions (studies have only been performed in adults):** **Cholestyramine:** Concomitant cholestyramine administration decreased the mean AUC of total Ezetrol approximately 55%. **Statins:** No clinically significant pharmacokinetic interactions were seen upon co-administration with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

**Fertility, pregnancy and lactation:** Ezetrol co-administered with a statin is contra-indicated during pregnancy and lactation. **Pregnancy:** Ezetrol should only be given to pregnant women if clearly necessary. No clinical data are available on the use of Ezetrol during pregnancy. **Lactation:** Ezetrol is contra-indicated. **Fertility:** No clinical data are available on effects of ezetimibe on human fertility.

**Driving and using machines:** Dizziness has been reported.

## **SIDE EFFECTS**

**Refer to Summary of Product Characteristics for complete information on side effects**

### **Clinical studies and post-marketing experience**

In clinical studies where Ezetrol was administered alone (n=2,396) or with a statin, (n=11,308), or with fenofibrate (n=185), adverse reactions were usually mild and transient. The overall incidence of side effects and the discontinuation rate due to adverse experiences was comparable between Ezetrol and placebo.

Clinically important elevations in serum transaminases (ALT/AST  $\geq 3$  X ULN, consecutive) was 0.5% with Ezetrol and 0.3% with placebo; 1.3% with Ezetrol co-administered with a statin and 0.4% with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation or with continued treatment.

CPK >10 X ULN was 0.2% in patients on Ezetrol alone vs 0.1% on placebo, and 0.1% in patients co-administered Ezetrol and a statin vs 0.4% on a statin alone. There was no excess myopathy/rhabdomyolysis associated with Ezetrol compared with placebo or statin alone.

The following adverse experiences were reported. Frequencies are defined as

common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) and not known (cannot be estimated from the available data)

*Ezetrol administered (with or without a statin):*

*Investigations:* common - ALT and/or AST increased, blood CPK increased, gamma-glutamyltransferase increased, liver function test abnormal. *Respiratory, thoracic and mediastinal disorders:* uncommon – cough. *Gastro-intestinal disorders:* common - abdominal pain, diarrhoea, flatulence; uncommon – dyspepsia, gastro-oesophageal reflux disease, nausea, dry mouth, gastritis. *Musculoskeletal and connective tissue disorders:* common - myalgia; uncommon – arthralgia, muscle spasms, neck pain, back pain, muscular weakness, pain in extremity. *Nervous system disorders:* common – headache; uncommon – paraesthesia. *Skin and subcutaneous tissue disorders:* uncommon - pruritus, rash, urticaria. *Metabolism and nutrition disorders:* uncommon - decreased appetite. *Vascular disorders:* uncommon – hot flush, hypertension. *General disorders and administration site conditions:* common - fatigue; uncommon - chest pain, pain, asthenia, oedema peripheral.

Patients with Coronary Heart Disease and ACS Event History: *In the IMPROVE-IT study discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe/simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin. The incidence of consecutive elevations of transaminases ( $\geq 3 \times \text{ULN}$ ) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalisations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.*

*Patients with Chronic Kidney Disease:* In the SHARP study, only serious adverse events

and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4 % in patients treated with Ezetrol combined with simvastatin, 9.8 % in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2 % on Ezetrol combined with simvastatin and 0.1% on placebo. Consecutive elevations of transaminases ( $> 3 \times \text{ULN}$ ) occurred in 0.7% of patients on Ezetrol combined with simvastatin, vs 0.6 % of patients on placebo. No statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4 % for Ezetrol combined with simvastatin, 9.5 % for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

*Post-marketing experience (with or without a statin);* Frequency not known: *Blood and lymphatic system disorders:* thrombocytopenia. *Nervous system disorders:* dizziness; paraesthesia. *Respiratory, thoracic and mediastinal disorders:* dyspnoea. *Gastro-intestinal disorders:* pancreatitis, constipation. *Skin and subcutaneous tissue disorders:* erythema multiforme. *Musculoskeletal and connective tissue disorders:* myalgia, myopathy/rhabdomyolysis. *General disorders and administration site conditions:* asthenia. *Immune system disorders:* hypersensitivity, including rash, urticaria, anaphylaxis and angioedema. *Hepatobiliary disorders:* hepatitis, cholelithiasis, cholecystitis. *Psychiatric disorders:* depression

*Ezetrol co-administered with fenofibrate:* *Gastro-intestinal disorders:* common - abdominal pain

#### **PACKAGE QUANTITIES AND BASIC NHS COST**

28 Tablets: £26.31

#### **Marketing Authorisation number**

PL 00025/0609

#### **Marketing Authorisation holder**

Merck Sharp & Dohme Ltd  
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#### **POM**

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