Selected Safety Information for EZETROL® (ezetimibe)

Based on Product Information approved by the TGA on 24 November 2014

Indications
Adults (≥ 18 Years):

Primary Hypercholesterolaemia
EZETROL administered alone, or with an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)
EZETROL, administered with a statin, is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Homozygous Sitosterolaemia (Phytosterolaemia)
EZETROL is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia.

Children and Adolescents 10-17 Years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche):

Heterozygous Familial Hypercholesterolaemia (HeFH)
EZETROL co-administered with simvastatin (doses up to 40 mg) is indicated as an adjunctive therapy to diet in adolescent patients (10-17 years old) with heterozygous familial hypercholesterolaemia where use of a combination product is appropriate:
- Patients not appropriately controlled with a statin or ezetimibe alone
- Patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)
EZETROL co-administered with simvastatin (doses up to 40 mg) is indicated in adolescent patients (10-17 years old) with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis)

Dosage and Administration
The recommended dose of EZETROL is 10 mg once daily, used alone or with a statin.

Use in Renal Impairment/Chronic Kidney Disease

Monotherapy - In patients with renal impairment, no dosage adjustment of EZETROL is necessary.

Combination Therapy with Simvastatin - In patients with mild renal impairment (estimated GFR ≥60 mL/min/1.73 m²), no dosage adjustment of EZETROL or simvastatin is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 m², the dose of EZETROL is 10 mg and the dose of simvastatin is 20 mg once a day in the evening. In such patients, the use of higher doses of simvastatin should be closely monitored.
**Paediatric Use (10-17 years)**

Initiation of treatment must be performed under review of a specialist. No dosage adjustment is required for adolescents 10 to 17 years old (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche). EZETROL is not recommended in children < 10 years of age.

The safety and efficacy of EZETROL co-administered with simvastatin doses above 40 mg daily have not been studied in children and adolescents (10-17 years old) and are not recommended.

**Contraindications**

- EZETROL is contraindicated in patients with hypersensitivity to any component of this medication.
- When EZETROL is to be administered with a statin, please refer to the Product Information for that particular statin.
- EZETROL in combination with fenofibrate is contraindicated in patients with gall bladder disease.
- Therapy with EZETROL in combination with a statin is contraindicated during pregnancy and lactation.
- The combination of EZETROL with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

**Precautions**

When EZETROL is to be administered with a statin or with fenofibrate, please refer to the Product Information for that particular medication.

A beneficial effect of ezetimibe on cardiovascular morbidity or mortality has not been demonstrated.

**Paediatric Patients:** There are limited data on safety and efficacy in children 6-10 years of age. EZETROL is not recommended in children < 10 years of age. The use of EZETROL in combination with statins has not been studied in children < 10 years of age and EZETROL has not been studied in patients younger than 6 years of age. There are also no long-term (>1 year) safety data in the paediatric population.

The clinical safety and efficacy of EZETROL co-administered with simvastatin in children and adolescents (10-17 years old) with hypercholesterolaemia other than Heterozygous Familial Hypercholesterolaemia have not been studied.

**Liver Enzymes:** When EZETROL was co-administered with a statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed. When EZETROL 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:** Myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. Patients starting therapy with EZETROL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness.
EZETROL and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected.

**Hepatic Insufficiency:** Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, EZETROL is not recommended in these patients.

**Fibrates:** The co-administration of ezetimibe with fibrates other than fenofibrate, has not been studied and is therefore not recommended. The co-administration of ezetimibe and fenofibrate is not recommended in patients with pre-existing gallbladder disease.

**Cyclosporine:** Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving EZETROL and cyclosporine.

**Pregnancy:** No clinical data on exposed pregnancies are available. EZETROL should be used in pregnancy only if the potential benefit exceeds the potential risk however EZETROL in combination with a statin is contraindicated during pregnancy.

**Lactation:** EZETROL should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

**Interactions with Other Medicines**

**Cyclosporine:** Concomitant therapy with cyclosporine increases exposure of ezetimibe and cyclosporine.

**Fibrates:** Co-administration of EZETROL with fibrates (other than fenofibrate) is not recommended.

**Adverse Effects**

In clinical trials, the following common (≥1/100, <1/10) drug-related adverse experiences were reported in patients taking EZETROL administered alone: abdominal pain, diarrhoea, flatulence, fatigue; or co-administered with a statin: ALT and/or AST increased, headache, myalgia; or co-administered with fenofibrate: abdominal pain.

There were no drug-related adverse experiences reported occurring in ≥ 2% of patients taking EZETROL alone (n = 1691).
The following drug-related adverse experiences were reported occurring in ≥ 2% in patients taking EZETROL co-administered with a statin:

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Statins (%)</th>
<th>EZETROL 10 mg Co-administered with a statin (%)</th>
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<tbody>
<tr>
<td></td>
<td>N=1676</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<tr>
<td>Myalgia</td>
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**Paediatric Patients 10-17 Years of Age**

In a study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n=248), elevations of ALT and/or AST (≥ 3X ULN, consecutive) were observed in 3% of the ezetimibe/simvastatin patients compared to 2% in the simvastatin monotherapy group; these figures were respectively 2% and 0% for elevation of creatine kinase (≥ 10X ULN). No cases of myopathy were reported.

In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of EZETROL co-administered with simvastatin for a treatment period > 33 weeks on growth, sexual maturation intellectual and psychosocial development have not been studied.

**Use in Special Populations**

**Use in the Elderly**

No dosage adjustment is required for elderly patients.

**Use in Paediatrics**

See INDICATIONS, DOSAGE AND ADMINISTRATION, PRECAUTIONS and ADVERSE EFFECTS

**Pregnancy and Lactation**

See CONTRAINDICATIONS and PRECAUTIONS

For more information on Indications, Contraindications, Precautions, Interactions with other Medicines, and Adverse Effects, please consult the full Product Information.