

NEW DRUG EVALUATION

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EZETIMIBE

Ezetimibe is the first selective cholesterol absorption inhibitor to be launched in the UK. It is licensed for the treatment of primary hypercholesterolaemia either for co-administration with a statin or as monotherapy. In clinical trials, ezetimibe produced significant reductions in LDL-cholesterol both alone and when added to statin therapy. Ezetimibe appears to be well tolerated but there are currently no published long-term safety data or clinical outcome data for the drug. The co-administration of ezetimibe with a statin should be reserved for patients who are poorly controlled on, or unable to tolerate high doses of the statins available.

What is it?

Ezetimibe (Ezetrol[®], Merck, Sharp & Dohme and Schering-Plough) is the first selective cholesterol absorption inhibitor to be launched in the UK. Ezetimibe co-administered with a HMG-CoA reductase inhibitor (statin) is licensed for the treatment of primary hypercholesterolaemia in patients poorly controlled with a statin alone, and for homozygous familial hypercholesterolaemia. As monotherapy, it is licensed for primary hypercholesterolaemia where a statin is considered inappropriate or is not tolerated, and for homozygous sitosterolaemia. Ezetimibe selectively inhibits the absorption of dietary and biliary cholesterol and related plant sterols. It does not affect the absorption of fat soluble vitamins or triglycerides in the intestine.¹ The licensed dose is 10 mg daily.

How effective is it?

Two double-blind trials have investigated the efficacy of ezetimibe compared with placebo.^{2,3} In both trials, patients were randomised to ezetimibe 10 mg daily or placebo for 12 weeks. In the first trial (n=892), ezetimibe reduced LDL-cholesterol (LDL-C) by 16.9% compared with an increase of 0.4% with placebo (p<0.01).² In the second trial (n=827), ezetimibe produced a reduction in LDL-C of 17.7% compared with an increase of 0.8% with placebo (p<0.01).³ In both trials, ezetimibe compared with placebo was associated with small, but significant increases in HDL-cholesterol (HDL-C) (p<0.01), and small decreases in triglycerides (statistically significant only in the first trial).^{2,3}

Four double-blind, placebo-controlled trials have investigated the efficacy of ezetimibe co-administered with a statin compared with statin therapy alone in patients with primary hypercholesterolaemia.⁴⁻⁷ In an 8 week trial, 769 patients taking stable doses of atorvastatin (10 to 80 mg daily), simvastatin (10 to 80 mg daily), lovastatin (10 to 40 mg daily) fluvastatin (20 to 80 mg daily), pravastatin (10 to 40 mg daily) or cerivastatin (0.2 to 0.8 mg daily) were randomised to concurrent treatment with ezetimibe 10 mg daily or

placebo.⁴ Treatment with a statin plus ezetimibe (pooled doses) was significantly more effective than the statin alone (pooled doses) in reducing LDL-C (25.1% vs 3.7%, p<0.001). In three 12 week trials, patients were randomised to different doses of a statin either alone or in combination with ezetimibe 10 mg daily. In the first trial (n=668), ezetimibe plus simvastatin 10 to 80 mg daily produced a significantly greater reduction in LDL-C than simvastatin alone (49.9% vs 36.1%, p<0.01).⁵ In the second trial (n=628), ezetimibe plus atorvastatin 10 to 80 mg daily reduced LDL-C by 54.5% compared with 42.4% for atorvastatin alone (p<0.01).⁶ In the third trial (n=538), ezetimibe plus pravastatin 10 to 40 mg daily was associated with a significantly higher reduction in LDL-C than pravastatin alone (37.7% vs 24.3%, p<0.01).⁷

In a study published as an abstract only, 621 patients taking atorvastatin 10 mg daily were randomised to ezetimibe 10 mg daily or an additional 10 mg daily of atorvastatin for 4 weeks. Ezetimibe and atorvastatin 10 mg in combination significantly reduced LDL-C compared with atorvastatin 20 mg (22.8% vs 8.6%, p<0.01).⁸

In a small trial in patients with homozygous familial hypercholesterolaemia, ezetimibe enhanced the LDL-C lowering effect of both atorvastatin and simvastatin.⁹

How safe is it?

No published studies have investigated the long-term safety of ezetimibe. In clinical trials, the most common drug-related adverse events (incidence of ≥ 1% and <10%) in patients taking ezetimibe alone were headache, abdominal pain, and diarrhoea. When ezetimibe was co-administered with a statin, the most common drug-related adverse effects (incidence of ≥ 1% and <10%) were headache, fatigue, gastrointestinal disturbances, and myalgia. The incidence of reversible, clinically significant elevations in serum transaminases was similar for ezetimibe and placebo (0.5% vs 0.3%), but was higher for co-administration with a statin than with a statin alone

(1.3% vs 0.4%) (no statistical significance was reported). The incidence of clinically significant elevations in creatine kinase (CK) with ezetimibe alone or ezetimibe co-administered with a statin, was similar to that seen with placebo or statin alone respectively.¹

Following post-marketing reports of hypersensitivity reactions including rash and angioedema with ezetimibe, these reactions have been added to the list of adverse events included in the labelling of the drug in the US.¹⁰

What other options are there?

The statins are well established as the drugs of first choice for the treatment of hypercholesterolaemia. There are currently 5 statins licensed in the UK; atorvastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin. Simvastatin and pravastatin have considerable long-term morbidity and mortality data

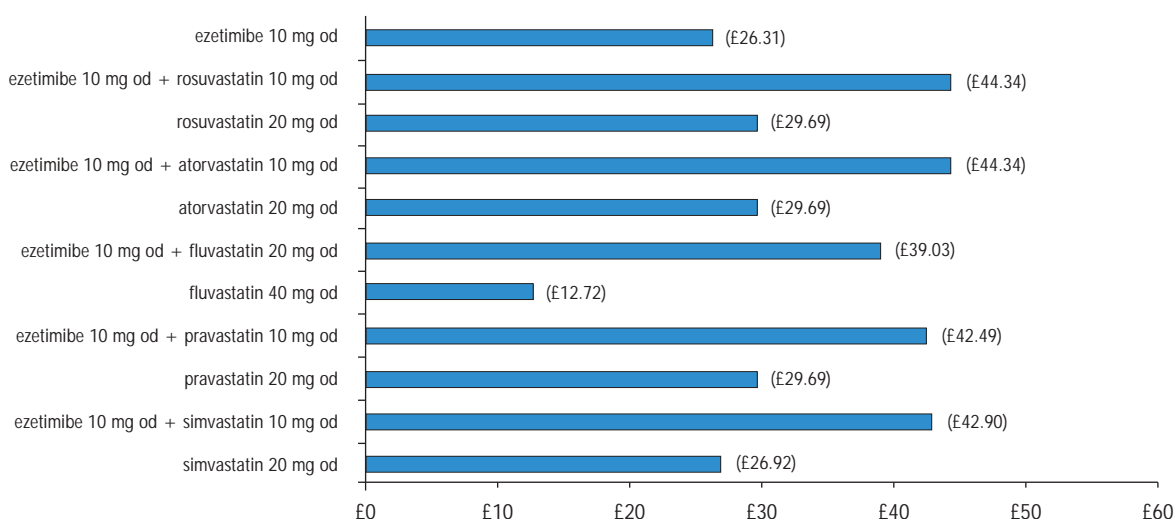
and are currently the only statins licensed for the primary and secondary prevention of cardiovascular events.¹¹ Generic simvastatin is now available and is less expensive than the branded product.

When should it be used?

When co-administered with a statin, ezetimibe does produce significant, additional reductions in LDL-C. However, there is currently no long-term safety data or clinical outcome data for ezetimibe and it is not licensed for either the primary or secondary prevention of cardiovascular events. Ezetimibe monotherapy may be an option in patients for whom a statin is contraindicated or not tolerated. On the basis of current evidence, co-administration of ezetimibe with a statin should be reserved for patients poorly controlled on or intolerant of high doses of the statins.

How much does it cost?

Cost for 28 days treatment (prices from MIMS/Drug Tariff August 2003)



NB. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, A- abstract, E-editorial

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