

Ezetimibe

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

Ezetimibe (*Ezetrol*) is a novel orally active selective inhibitor of intestinal absorption of cholesterol. Its mechanism of action differs from that of statins and other classes of cholesterol-reducing compounds.

Ezetimibe was launched in April 2003 as an adjunct to diet and statin therapy for primary hypercholesterolaemia or homozygous familial hypercholesterolaemia. It is also licensed as monotherapy in primary hypercholesterolaemia if a statin is inappropriate or not tolerated.

The efficacy of ezetimibe has been assessed in short-term clinical trials of up to 12 weeks. In primary hypercholesterolaemia ezetimibe as monotherapy reduces plasma LDL-cholesterol (LDL-C) by approximately 18%. In statin-naïve patients the combination of ezetimibe and statin reduces LDL-C by a further 12-14% compared to statin alone. The addition of ezetimibe to low-dose statin (10mg) achieves the same effect on LDL-C, HDL-cholesterol (HDL-C) and triglyceride levels, as high-dose (40-80mg) statin alone. The combination of ezetimibe plus a statin appears to be well tolerated in the short-term with an adverse effects profile similar to that of statin plus placebo.

Long-term clinical outcome and safety data are needed for ezetimibe. Until these are available, ezetimibe should be reserved for patients not reaching target lipid levels on maximum tolerated doses of statins.

The combination costs approximately one and a half times as much as high dose statin.

Introduction

Ezetimibe is a novel, orally active selective inhibitor of intestinal absorption of cholesterol and related plant sterols. Its mechanism of action differs from that of other classes of cholesterol lowering drugs.

Evidence

The phase III trial programme for ezetimibe included two randomised controlled trials (RCTs) of ezetimibe therapy and four of ezetimibe in combination with a statin. All these trials, which have been published in full, employed a 10mg daily dose of ezetimibe. Study duration was limited to 12 weeks and results as a consequence, are reported as effects on lipids rather than as clinical outcomes.

The two monotherapy trials included patients with primary hypercholesterolaemia (LDL-C ≥ 3.36 mmol/l to ≤ 6.47 mmol/l). In the first study (n=892), ezetimibe reduced LDL-C by a mean of 16.9% compared with an increase of 0.4% with placebo (p<0.01).¹ In the second study (n=827), changes in LDL-C were -17.7% and +0.8% for ezetimibe and placebo respectively (p<0.01). In both studies there was an increase in HDL-C (+1%) and a reduction in total cholesterol (-12.5%) and triglyceride (TG) levels, although in the latter study the effect on TG was non-significant (p=0.09).²

In the four studies of combination therapy, patients with primary hypercholesterolaemia were randomised to receive placebo, ezetimibe, a statin alone or ezetimibe in combination with a statin.³⁻⁶ The statins were given in a range of doses as follows: atorvastatin³ and simvastatin⁶ as 10, 20, 40 and 80mg doses, lovastatin⁴ and pravastatin⁵ as 10, 20, and 40mg doses. In the atorvastatin study (n=628), the additional reduction in LDL-C for the pooled ezetimibe + atorvastatin vs. pooled atorvastatin groups was

Brand Name, (Manufacturer): Ezetrol® (MSD, Schering-Plough)

BNF Therapeutic Class: Lipid regulating drugs (2.12)

Licensed Indications: Treatment of primary hypercholesterolaemia, homozygous familial hypercholesterolaemia and homozygous sitosterolaemia.

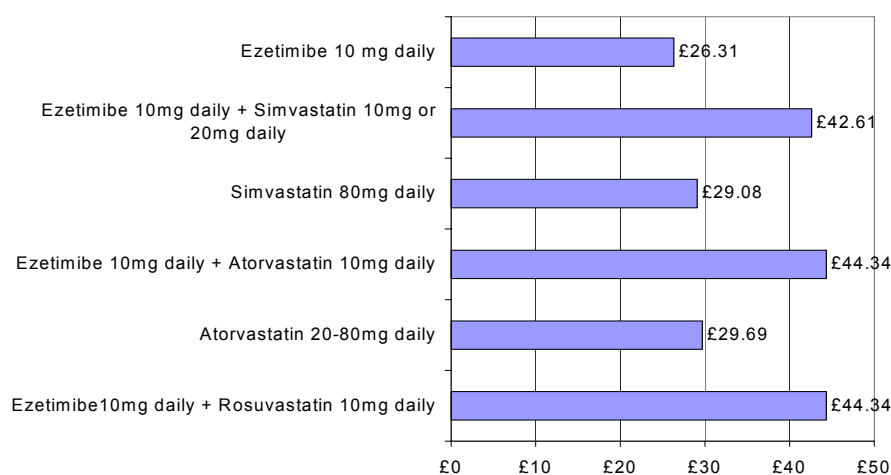
Dosage and Administration: 10mg daily in conjunction with an appropriate lipid-lowering diet and a statin if appropriate (see SPC).

Marketed: April 2003

Cost Comparisons:

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

N.B. Doses shown for general comparison and do not imply therapeutic equivalence



12%. There was a corresponding 3% increase in HDL-C and 8% decrease in TG levels. Similarly, the additional reduction in LDL-C (pooled results of the combination vs. statin alone) noted in the other studies was 13.8% for simvastatin, 14% for pravastatin and 13.4% for lovastatin. Data from these studies show that addition of ezetimibe to low dose statin (10mg) achieves similar changes in LDL-C, HDL-C and TG as high-dose statin monotherapy (simvastatin and atorvastatin 80mg, pravastatin and lovastatin 40mg).^{3-6,9}

In a further RCT of combination therapy, 769 patients with primary hypercholesterolaemia who had not achieved National Cholesterol Education Program (NCEP) target cholesterol levels on diet and statin monotherapy were randomised to statin plus placebo or ezetimibe for 8 weeks.⁷ Ongoing statin therapy plus ezetimibe led to a 25% reduction in LDL-C compared with a 3.7% reduction in the statin + placebo group. 71.5% of the statin + ezetimibe group achieved target LDL-C levels at endpoint compared with 19% in the statin + placebo group. This 'add-on' study is probably more representative of the manner in which ezetimibe is likely to be used clinically.

In a study in 50 patients with homozygous familial hypercholesterolaemia, the combination of a statin with ezetimibe resulted in an additional 20% reduction in LDL-C compared with high-dose statin alone.⁸

Safety

Data from published RCTs show that ezetimibe administered alone or with a statin is generally well-tolerated. The most common adverse effects (occurring in 1% to 10% of patients) with ezetimibe monotherapy are headache, abdominal pain and diarrhoea. In combination with a statin the most common additional adverse effects are fatigue, constipation, and myalgia. Clinically important elevations of creatine phosphokinase (CPK) in patients treated with ezetimibe alone or in combination with a statin were similar to elevations

seen with placebo or statin administered alone, respectively.¹⁰ The combination of ezetimibe and statin is contra-indicated in patients with active liver disease or unexplained persistent elevations in serum transaminases. An increase in liver transaminases (3 times the upper limit of normal) has been reported in 1.3% of patients on the combination and in 0.4% of patients on a statin alone. The changes were generally asymptomatic, not associated with cholestasis and levels returned to baseline after discontinuation of therapy or with continued treatment.¹⁰⁻¹² No changes in the absorption of lipid soluble vitamins have been shown in short-term studies.¹³ Ezetimibe is not metabolised by cytochrome p450, therefore the potential for drug interactions is minimal.¹⁰⁻¹²

Place in Therapy

Statins are the drugs of choice for the management of hyperlipidaemia. Evidence from large-scale long-term primary and secondary prevention studies shows that they reduce the risk of CHD mortality by approximately 25% when used in appropriate doses. However approximately 50% of patients treated with lipid-lowering drugs fail to achieve the National Service Framework (NSF) target of an LDL-C level <3.0mmol/l.^{14,16,17} This failure may be partly due to prescribers not titrating patients up to doses of statins used in clinical trials. However some patients cannot tolerate high-dose statins.^{16,17} The availability of a drug that can be safely combined with a low-dose statin whilst achieving the same degree of lipid-lowering as high-dose statin, may benefit these patients.

Ezetimibe may also be useful in patients unable to tolerate even low doses of a statin, but be especially valuable in patients with homozygous familial hypercholesterolaemia, in whom current agents have limited efficacy.

In the absence of long-term clinical outcome and safety data, ezetimibe, should be reserved for patients not reaching target lipid levels on maximum tolerated doses of statins.

Key Papers

1. Dujovne CA et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolaemia. *Am J Cardiol* 2002;**90**:1091-97
2. Knopp RH et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolaemia. *Eur Heart J* 2003;**24**:729-41
3. Ballantyne CM et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolaemia. *Circulation* 2003;**107**:2409-15
4. Kerzner B et al. Efficacy and safety of ezetimibe coadministered with lovastatin in patients with primary hypercholesterolaemia. *Am J Cardiol* 2003;**91**:418-24
5. Melani L et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolaemia. *Eur Heart J* 2003;**24**:717-28
6. Davidson MH et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolaemia. *J Am Coll Cardiol* 2002;**40**:2125-34
7. Gagne C et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolaemia. *Am J Cardiol* 2002;**90**:1084-91

Appendix I: Table of Clinical Trials

Appendix II: Bibliography

Risk Management Issues:

None noted



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Appendix I

Table 1. Selection of phase III studies of ezetimibe

Ref. No.	Study population	Study design	Drug treatment	Main outcome measures Mean % change from baseline		
				% LDL-C	% Tri-glyceride	%HDL-C
1	892 patients (458 F) aged 18-85 with primary hypercholesterolaemia on dietary control, with LDL-C ≥ 3.36 mmol/l to ≤ 6.47 mmol/l and TG ≤ 4 mmol/l	Randomised, multicentre double-blind 4 to 8 week placebo lead-in and 12 week study period	Placebo (n= 226) [*]	+0.4	+5.7	-1.6
			Ezetimibe 10mg (n=666) [*]	-19.9 P<0.01	-5.6 P<0.01	+1.3 P<0.01
2	827 patients with primary hypercholesterolaemia (430 F) on dietary control, with LDL-C ≥ 3.36 mmol/l to ≤ 6.47 mmol/l and TG ≤ 4 mmol/l	Randomised, multicentre double-blind 4 week placebo lead-in and 12 week study period	Placebo (n=205) [*]	+0.8	+2.4	-1.3
			Ezetimibe 10mg (n=622) [*]	-17.7 P<0.01	-1.7 P=0.09	+1.0 P<0.01
3	628 patients with primary hypercholesterolaemia (368F) on dietary control, with LDL-C ≥ 3.75 mmol/l to ≤ 6.47 mmol/l and TG ≤ 4 mmol/l	Randomised, multicentre, double-blind 4 week placebo lead-in and 12 week study period	Placebo (n=60) [*]	+5.9	-6.4 ^{**}	+3.7
			Ezetimibe 10mg(n=65) [*]	-18.4	-5.1 ^{**}	+4.2
			Atorvastatin 10mg/20mg/40mg/80mg (pooled n=248)	-42.4	-24.5 ^{**}	+4.3
			Ezetimibe 10mg + atorvastatin 10mg/20mg/40mg/80mg (pooled n=253)	-54.5 P<0.01 vs atorvastatin	-32.8 ^{**} P<0.01 vs atorvastatin	+7.3 P<0.01 vs atorvastatin
4	548 patients with primary hypercholesterolaemia (319F) on dietary control, with LDL-C ≥ 3.75 mmol/l to ≤ 6.47 mmol/l and TG ≤ 4 mmol/l	Randomised, double-blind, multicentre 4 week placebo lead-in and 12 week study period	Placebo (n=64) [*]	0	+4	0
			Ezetimibe 10mg (n=72) [*]	-19	-3	+3
			Lovastatin 10/20/40mg (pooled n=220) [*]	-25	-11	+4
			Ezetimibe 10mg + lovastatin 10/20/40mg (pooled n=192) [*]	-39 P<0.01 vs lovastatin	-22 P<0.01 vs lovastatin	+9 P<0.01 vs lovastatin
5	538 patients aged 20-86 (300F) with primary hypercholesterolaemia on dietary control with LDL-C ≥ 3.8 mmol/l and ≤ 6.5 mmol/l and TG ≤ 4 mmol/l	Randomised, double-blind, multicentre 4 week placebo lead-in and 12 week study period	Placebo (n=65) [*]	+1.3	+2.0	+2.0
			Ezetimibe 10mg (n=64) [*]	-18.7	-2.1	+4.1
			Pravastatin 10/20/40mg (pooled n=205) [*]	-24.3	-7.6	+6.7
			Ezetimibe 10mg + pravastatin 10/20/40mg (pooled n=204) [*]	-37.7 P<0.01 vs pravastatin	-17.6 P<0.01 vs pravastatin	+8.1 P<0.01 vs pravastatin

Ezetimibe

Ref. No.	Study population	Study design	Drug treatment	Main outcome measures Mean % change from baseline			
				%LDL-C	%Tri-glyceride	%HDL-C	
6	668 patients (aged 25-87) (377F) with primary hypercholesterolaemia on dietary control with LDL-C ≥ 3.75 to ≤ 6.47 mmol/l and TG ≤ 4 mmol/l	Randomised, double-blind, multicentre 4 week placebo lead-in and 12 week study period	Placebo (n=69) [*]	-1.3	+2.4	0.9	
			Ezetimibe 10mg (n=60) [*]	-18.1	-8.3	+5.1	
			Simvastatin 10/20/40/80mg (pooled n=261) [*]	-36.1	-16.6	+6.9	
			Ezetimibe 10mg + simvastatin 10/20/40/80mg (pooled n=269) [*]	-49.9 P<0.01 vs simvastatin	-24.1 P<0.01 vs simvastatin	+9.3 P=0.03 vs simvastatin	
7	769 patients with primary hypercholesterolaemia LDL-C ≥ 2.6 mmol/l to ≥ 4.1 mmol/l and TG ≤ 4 mmol/l on diet and statin monotherapy for ≥ 6 weeks, stratified according to target LDL-C levels and other CHD risk factors	Randomised, double-blind, multicentre 8 week study.	Statin + placebo (n=390) (atorvastatin 10-80mg n=162, simvastatin 10-80mg n=117, others n=111)	-3.7	-2.9 ^{**}	+1.0	
			Statin + ezetimibe 10mg (n=379) (atorvastatin 10-80mg n=146, simvastatin 10-80mg n=123, others = 110)	-25 P<0.001	-14 ^{**} P<0.001	+2.7 P<0.05	
8	50 patients with homozygous familial hypercholesterolaemia on dietary control and open label atorvastatin or simvastatin 40mg daily and LDL-C ≥ 2.6 mmol/l and TG ≤ 4 mmol/l. 50% of patients were undergoing concomitant LDL apheresis	Randomised, double-blind, multicentre 6 to 14 week lead-in phase with open-label statin and 12 week study period	Atorvastatin or simvastatin 80mg (n=17) [*]	%LDL-C		% total-C	
			Ezetimibe 10mg + statin 40/80mg (n=33) [*]	-6.7	-5.3		
			Ezetimibe 10mg + statin 80mg (n=17)	-20.7 P=0.007 vs statin	-18.7 P=0.01 vs statin		
				-27.5 P=0.0001 vs statin			

TG = triglycerides

^{*} Measurements for each parameter were not necessarily available for all subjects

^{**} These values represent median percent change from baseline

Appendix II

Bibliography

References

1. Dujovne CA et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, inpatients with primary hypercholesterolaemia. *Am J Cardiol* 2002; **90**:1091-97
2. Knopp RH et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolaemia. *Eur Heart J* 2003; **24**: 729-41
3. Ballantyne CM et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolaemia. *Circulation* 2003; **107**:2409-15
4. Kerzner B et al. Efficacy and safety of ezetimibe coadministered with lovastatin in patients with primary hypercholesterolaemia. *Am J Cardiol* 2003; **91**:418-24
5. Melani L et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolaemia. *Eur Heart J* 2003; **24**:717-28
6. Davidson MH et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolaemia. *J Am Coll Cardiol* 2002; **40**:2125-34
7. Gagne C et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolaemia. *Am J Cardiol* 2002; **90**:1084-91
8. Gagne C et al. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolaemia. *Circulation* 2002; **105**: 2469-75
8. Sager P et al. Ezetimibe coadministered with low dose statins in primary hypercholesterolaemia: lipid profiles comparable to high-dose statin monotherapy. *J Am Coll Cardiol* 2003; **41**(6) Suppl. A Abstr.No.1083-142
9. MSD Ezetrol Summary of Product Characteristics 24.4.03
10. Darkes MJM et al. Ezetimibe. *Am J Cardiovasc Drugs* 2003; **3**: 67-76
11. Sudhop T and von Bergmann K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. *Drugs* 2002; **62**: 2333-47
12. Knopp RH et al. Effect of ezetimibe on serum concentrations of lipid-soluble vitamins. *Atherosclerosis*; 2001; **2** Suppl., Jan., P.90, Abstr.No.P175
13. Williams H and Stevens M. Cholesterol control. *Pharm J* 2003; **270**:688-90
14. Therapeutic Class Summaries. Statins. UKMIPG July 2003
15. Leitersdorf E. Selective cholesterol absorption inhibition: a novel strategy in lipid-lowering management. *Int J Clin Pract* 2002; **56**:116-19
16. Kastelein JJP and Van Dam MJ. A new role for combination therapy in lipid management. *Brit J Cardiol* 2001; **8**:639-53
17. Ezetimibe. New Drugs in Clinical Development. UKMi/NPC October 2002

Further Reading

Farnier M. Ezetimibe in hypercholesterolaemia. *Int J Clin Pract* 2002; **56**:611-14

Shepherd J. Combined lipid lowering drug therapy for the effective treatment of hypercholesterolaemia. *Eur Heart J* 2003; **24**:685-89

Cada DJ et al. Ezetimibe. *Hospital Pharmacy* 2003; **38**: 357-64

Stein E. Results of phase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. *Eur Heart J* 2001; **3** (Suppl. E) E11-E16

Sager P et al. C-Reactive protein is reduced during ezetimibe coadministration with simvastatin in patients with primary hypercholesterolaemia. *J Am Coll Cardiol* **41**(6) Suppl. A 2003 Abstr. 876-6

Reyderman L et al. Pharmacokinetics of ezetimibe in subjects with normal renal function or severe chronic renal insufficiency. *Clin Pharmacol Ther* 2002; **71**:P27

Vermaak W et al. Heterozygous familial hypercholesterolaemia: coadministration of ezetimibe plus atorvastatin. *Atherosclerosis* 2002; **3**:230-31

von Bergmann K et al. Ezetimibe effectively reduces serum plant sterols in patients with sitosterolaemia. *Atherosclerosis* 2002; **3**:232