NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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Key Points

- **Ezetimibe (Ezetrol) is a cholesterol lowering agent that works in the small intestine as a cholesterol absorption inhibitor.**
- **Prescribers should ensure that the use of ezetimibe is confined within licensed indications (i.e. in primary (heterozygous-familial or non-familial) hypercholesterolaemia, homozygous familial hypercholesterolaemia and homozygous sitosterolaemia).**
- **Despite its modest and undisputed total cholesterol and LDL-C lowering abilities (12-13% and 17-22% respectively), ezetimibe has not been proven to reduce cardiovascular morbidity or mortality. It is not licensed for the primary or secondary prevention of cardiovascular disease (CVD).**
- **Practices are urged to review all patients currently taking ezetimibe as a matter of priority. All ezetimibe use for primary prevention of CVD should be stopped. Only simvastatin 40mg or pravastatin 40mg (or lower doses if not tolerated) are cost-effective for this indication.**
- **Ezetimibe should only be used for secondary prevention of CVD where all other options have been exhausted including higher intensity statins and fibrates. The cost-effectiveness of ezetimibe, even within this context, remains questionable.**
- **Where ezetimibe is discontinued, it is recommended that consideration is given to leaving other therapies unchanged (at least initially). Where a change to other therapies is considered necessary this should be in-line with PACEF Lipid Management Guidelines (*PACE Bulletin*, Vol.4, No 13 (August 2010)).**

CLARIFICATION OF THE ROLE OF EZETIMIBE (EZETROL) AS A BASIS FOR EZETIMIBE REVIEW IN PRACTICE

Ezetimibe (Ezetrol) is a cholesterol lowering agent that works in the small intestine as a cholesterol absorption inhibitor. It is licensed solely for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia, homozygous familial hypercholesterolaemia and homozygous sitosterolaemia. Despite this, it has become widely established as a component of lipid lowering therapy in primary and secondary prevention of CVD, both as monotherapy and in combination with statins. ULHT cardiologists have expressed their concern over the increasing use of ezetimibe in Lincolnshire primary care; particular concerns have been raised about ezetimibe monotherapy in primary and secondary prevention of CVD on the basis of the lack of evidence of effectiveness on CV morbidity and mortality and serious concerns over cost-effectiveness linked to the high cost of ezetimibe in comparison to statins. Lincolnshire prescribing figures reveal significant growth and a current annual expenditure of £1.1M pa. The vast majority of this prescribing is off license, unnecessary and likely to be contributing little or nothing to the improvement of

patient outcomes. It is the purpose of this feature to review the current evidence base for ezetimibe and to clearly define the role of the product for practices and Clinical Commissioning Groups. It will also identify significant opportunities to improve productivity through the audit, review and discontinuation of unnecessary ezetimibe therapy in practice.

What have the most recent ezetimibe trials revealed?

ENHANCE (2008)[1]

The ENHANCE study found no significant difference between the combination of ezetimibe and simvastatin compared to simvastatin alone in patients with heterozygous familial hypercholesterolemia (FH). 720 people were randomized to ezetimibe 10mg and simvastatin 80mg or simvastatin 80mg alone for 2 years. No statistically significant difference was found between the two groups in the primary outcome of mean change in the intima media thickness measured at three sites in the carotid arteries despite a greater reduction in Low Density Lipoprotein–Cholesterol (LDL-C) in the ezetimibe / simvastatin group. Although the trial was not powered to assess it, there was also no significant difference in CV events.

PACEF Comment:
This study shows that, even within licensed indications, ezetimibe is of little value in terms of improving CV outcomes when prescribed in addition to high intensity statin therapy. The greater reduction in LDL-C in the ezetimibe / simvastatin group appears to make no appreciable difference to patient outcomes.

SEAS (2008)[2]

The SEAS study randomised 1873 people with aortic valve stenosis to simvastatin 40mg plus ezetimibe 10mg or placebo for at least 4 years. No difference was found in the primary outcome measure of a composite of major CV events despite a greater fall in mean LDL-C with active treatment (fall of 53.8% vs. 3.8%, $p<0.001$). Notably this study found an increased risk of cancer with simvastatin and ezetimibe treatment (10.7% vs. 7% with placebo, $p=0.01$). This apparent excess risk is based on only a small number of patients and the excess cancers were not clustered at any one particular anatomical site suggesting that this might just be a chance finding. The risk has been further analyzed using data from larger studies (none of these were designed to address cancer risk, but cancer incidence and mortality would be expected to be a reliable endpoint) and no significant excess incidence of cancer was found (RR 0.96; 95% CI 0.82 – 1.12, $p=0.61$). The MHRA advised that current data were insufficient to draw conclusions.

PACEF Comment:
Again significant reduction in LDL-C (this time in patients with aortic valve stenosis) with simvastatin/ezetimibe combination therapy appears to have made no difference to the primary outcome of major CV events. Data derived from this study reflecting an apparent increased risk of cancer with simvastatin/ezetimibe combination therapy is insufficient to be conclusive.

Stop Atherosclerosis in Native Diabetics Study (SANDS) (2008)[3]

This pre-specified secondary analysis of the SANDS study compared the effects of statins (n=154) versus statins plus ezetimibe (n=69) in one arm of the original trial. The study was in native American Indians with type 2 diabetes but no history of CVD. A similar regression of carotid artery intima media thickness was found in patients who attained equivalent LDL-C reductions with either statin monotherapy or statin

plus ezetimibe. Whilst this is an encouraging conclusion for the use of ezetimibe it is very low grade evidence using a surrogate marker (LDL-C).

PACEF Comment:
This study links reduction in carotid artery intima media thickness to LDL-C reduction in a population of type 2 diabetics with no history of CVD treated with simvastatin/ezetimibe. However, the study was small and of poor quality and the results remain inconclusive.

The ARBITER 6-HALTS trial (Arterial Biology for the Investigation of the treatment effects of reducing cholesterol 6-HDL and LDL treatment strategies in atherosclerosis) (2009)[4]

In this small, open-label trial, people with CV disease or at high risk of CV disease and on statin therapy were randomised to ezetimibe10mg daily or niacin modified release (MR) up to 2g daily. It was stopped early on the basis of a pre-specified interim analysis of the primary outcome (carotid intima media thickness (CIMT)) which showed superiority of niacin over ezetimibe. Furthermore ezetimibe was found to reduce both LDL-C and High Density Lipoprotein-Cholesterol (HDL –C). Niacin reduced LDL-C but increased HDL-C. This small study was not powered to detect a difference, but more people who received ezetimibe had CV events compared to those on niacin (ezetimibe 5/165 events, 5% vs. niacin 2/160, 2% p=0.04). The authors report a statistically significant inverse relationship between reduction in LDL-C by ezetimibe and an increase in artery wall thickness (R=-0.31, p<0.01). The authors propose that this paradoxical relationship is biologically plausible if, as they speculate, ezetimibe disrupts reverse cholesterol transport.

PACEF Comment:
This is relatively low grade evidence that suggests that niacin MR may be superior to ezetimibe in terms of both LDL-C reduction and reduction in carotid intima media thickness in patients with CVD or at high risk of CVD. Of particular concern is the finding that ezetimibe appears to decrease HDL-C in this patient group.

Study of Heart and Renal Protection (SHARP) (2010)[5]

The SHARP study was an RCT of more than 9,000 patients with chronic kidney disease (CKD), who received either a combination of ezetimibe 10mg and simvastatin 20mg, placebo, or (for the first year only) simvastatin 20mg only (patients in this group were reallocated to one of the other groups after the first year). Ezetimibe/simvastatin was significantly more effective than placebo in reducing major CV events (15.2% vs. 17.9%, P=0.001; NNT 37 over 4.9 years).

PACEF Comment:
In the absence of a simvastatin only arm, this study is unable to provide evidence that ezetimibe reduces CV events.

IMPROVE-IT (ongoing)[6]

In the future, the results of the IMPROVE-IT study will hopefully provide definitive evidence to support or discredit the use of ezetimibe. This large RCT compares simvastatin 40mg with combined treatment with ezetimibe 10mg and simvastatin 40mg in people with stabilized acute coronary syndrome (ACS). The primary outcome is a composite of CV death, major coronary events and stroke. In order to be able to show a statistical difference between the two arms (should one exist) the trial will continue until a minimum of 5250 people have an event. Recruitment has

ceased and from statistical modelling the estimated completion date is June 2013 with the results following sometime after this.

PACEF Comment:
This study promises to provide definitive evidence on the benefit or disbenefit of adding ezetimibe into a simvastatin 40mg regime for patients with stabilized ACS. Unfortunately, publication of results is likely to be at least two years from now.

What is the cost and potential LDL-C/ TC lowering potential of ezetimibe in comparison to available statins?

Cost Comparison and Percentage Reductions in LDL Cholesterol and Total Cholesterol

Statin	Daily Dose	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol
Atorvastatin	10mg	£13.00	37%	32%
Atorvastatin	20mg	£24.64	43%	36%
Atorvastatin	40mg	£24.64	49%	42%
Atorvastatin	80mg	£28.21	55%	47%
Pravastatin	40mg	£2.36	29%	29%
Rosuvastatin	5mg	£18.03	38%	33%
Rosuvastatin	10mg	£18.03	43%	37%
Rosuvastatin	20mg	£26.02	48%	40%
Simvastatin	**40mg**	**£1.26**	**37%**	**31%**
Ezetimibe	10mg	£26.31	17- 22%	12-13%
Ezetimibe/simvastatin	10mg/20mg	£33.42		
Ezetimibe/simvastatin	10mg/40mg	£38.98		
Ezetimibe/simvastatin	10mg/80mg	£41.21		

(Prices quoted are from the *Drug Tariff*, September 2011 and *MIMS* September2011)

PACEF Comment:
Ezetimibe is priced comparably with the higher doses of the higher potency statins atorvastatin (Lipitor) and rosuvastatin (Crestor). High-cost high-potency statins are effective, but have emerged from NICE cost-effectiveness evaluations as not cost-effective in most patients. £1M spent on simvastatin delivers 854 avoided events; £1M spent on atorvastatin delivers 55 avoided events. Across a population, this level of return from atorvastatin is unaffordable. Ezetimibe costs more than high-potency statins, delivers significantly less in terms of LDL-C and TC reduction and may deliver nothing in terms of changing patient outcomes. This raises serious concerns about the cost-effectiveness of prescribing ezetimibe in any context.

PACEF Recommendations: Updated Advice on Ezetimibe

Ezetimibe in the primary prevention of Cardiovascular Disease (CVD)
Ezetimibe is not licensed for the primary prevention of CVD. Recently published studies have failed to demonstrate any improvement in CV outcomes linked to the use of ezetimibe in primary prevention. All patients currently taking ezetimibe for primary prevention of CVD should be identified and their treatment reviewed with the intention of stopping therapy. Only simvastatin 40mg or pravastatin 40mg (or lower doses if not tolerated) are cost-effective for this indication.

Ezetimibe in the secondary prevention of Cardiovascular Disease (CVD)

Ezetimibe is not licensed for the secondary prevention of CVD. Recently published studies have failed to demonstrate any improvement in CV outcomes linked to the use of ezetimibe in secondary prevention.

All patients currently taking ezetimibe for secondary prevention of CVD should be identified and their treatment reviewed with the intention of stopping therapy. If ezetimibe therapy is continued, it should be as a last resort after all other options including high-potency statins and fibrates have been tried but have been found to be insufficiently effective or poorly tolerated. Even within this context, ezetimibe does not represent a cost-effective use of resources.

Ezetimibe and statin combination therapy and ezetimibe monotherapy in primary (heterozygous familial or non-familial) hypercholesterolaemia, homozygous familial hypercholesterolaemia and homozygous sitosterolaemia

NICE has endorsed the use of ezetimibe within licensed indications (see above) where statins are contraindicated or not tolerated. Statin and ezetimibe combination therapy (prescribed as separate components) is also advocated as an option for adults with heterozygous FH if TC or LDL-C concentrations are not appropriately controlled with statins alone.

Use simvastatin first line and aim to achieve at least 50% reduction of LDL-C concentration from baseline. High-intensity statins are recommended, increased to the maximum licensed or tolerated dose. Alternative statins should be tried and found to be poorly tolerated before ezetimibe monotherapy can be considered.

If high intensity statins at maximum licensed or tolerated doses do not achieve sufficient LDL-C reduction from baseline, consider ezetimibe and simvastatin combination therapy prescribed as separate components. Co-prescribing of high-cost, high-potency statins (i.e. rosuvastatin or atorvastatin) with ezetimibe is prohibitively expensive and should be reserved for exceptional circumstances. A fixed dose combination formulation of ezetimibe and simvastatin (Inegy) is available in a variety of strengths, but is significantly more expensive than separate components and should not be prescribed.

Designation: RED-RED. Statin and ezetimibe combination therapy is only indicated in adults with heterozygous FH where second line statins (even high-cost high-potency statins) have failed to adequately control TC or LDL-C.

References

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4. Villines TC et al. The ARBITER 6-HALTS trial (Arterial Biology for the Investigation of the treatment effects of reducing cholesterol 6-HDL and LDL treatment strategies in atherosclerosis). *J Am Coll Cardiol* 2010; 55: 2721 - 2726

5. SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): Randomised trial to assess the effects of lowering low-density lipoprotein cholesterol among 9438 patients with chronic kidney disease. *Am Heart J* 2010; 160(5): 785 - 794

6. IMPROVE-IT: Examining outcomes in subjects with acute coronary syndrome: Vytorin (ezetimibe / simvastatin) vs. simvastatin (Study P04103AM3). Clinical Trials.gov identifier NCT00202878 (www.clinicaltrials.gov, last accessed 25th July 2011)

Further Reading

Peto R et al Analyses of cancer data from three ezetimibe trials. *N Engl J Med* 2008; 359: 1357 – 1466

MHRA Drug Safety Update November 2008; 2(4) 7 (available at www.mhra.gov.uk/safetyinformation/drugsafetyupdate/CON087926, last accessed 25th July 2011)

Drug and Therapeutics Bulletin 2010; 48:73 *(article questioning the value of ezetimibe)*

Stephen Gibson
Head of Prescribing and Medicines Management
NHS Lincolnshire
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ALGORITHM: REVIEW OF EZETIMIBE THERAPY