

## Inegy<sup>®</sup> (Ezetimibe/Simvastatin)

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

### Summary

- Inegy<sup>®</sup> is a fixed dose combination containing two cholesterol lowering agents, ezetimibe and simvastatin, for the treatment of primary hypercholesterolaemia, mixed hyperlipidaemia and homozygous hypercholesterolaemia.
- Nine trials of up to 24 weeks duration and a 48-week extension study have been published. Two consider the combined tablet, others concern ezetimibe plus simvastatin co-administration.
- The mean reduction in LDL-C was the primary end-point evaluated. None of the trials considered clinical outcomes such as total mortality or cardiovascular end-points.
- The dual mechanism of action produced greater reductions in LDL-C than simvastatin and atorvastatin monotherapy at mg equivalent doses and the addition of ezetimibe to simvastatin produced greater reductions than increasing the simvastatin or atorvastatin dose.
- Common drug-related adverse events associated with ezetimibe/simvastatin co-administration are headache, dizziness, fatigue, gastro-intestinal disturbances and myalgia.
- The ezetimibe/simvastatin combination should be reserved for patients not reaching target lipid levels on maximum tolerated doses of statin alone.
- The decision to either use the combination tablet (Inegy<sup>®</sup>) or to co-administer ezetimibe plus simvastatin is likely to be based on cost. The combination tablet costs approximately one and a quarter times as much as ezetimibe plus simvastatin co-administration.

### Introduction

Inegy<sup>®</sup> (MSD/Schering-Plough) is a fixed dose combination tablet containing two cholesterol lowering agents with complementary mechanisms of action: ezetimibe 10 mg and simvastatin 20, 40 or 80 mg.<sup>1</sup> Ezetimibe inhibits the intestinal absorption of cholesterol whereas simvastatin inhibits the synthesis of cholesterol.

### Evidence

There are currently no published long-term trials evaluating clinical outcomes with ezetimibe or ezetimibe plus statin combination. The IMPROVE IT trial aims to assess the risk reduction in death and major coronary events with ezetimibe/simvastatin combination tablet compared to simvastatin 40 mg in approximately 10,000 patients with acute coronary syndromes.<sup>2</sup> Three other long-term studies, to demonstrate the efficacy of the combination in the prevention of atherosclerosis, are in progress.<sup>3-5</sup> Available clinical trials have focused on the percentage change in LDL-C as the primary end-point. Two published studies evaluated the combination tablet; other studies involve co-administration of ezetimibe 10 mg daily and simvastatin. However, Inegy<sup>®</sup> is considered bioequivalent to co-administered ezetimibe and simvastatin.<sup>1</sup>

### Primary hypercholesterolaemia

In the first double-blind study (n=1,528) assessing the combined tablet, adults with primary hypercholesterolaemia were randomised to daily ezetimibe/simvastatin 10/10, 10/20, 10/40 or 10/80 mg; simvastatin 10, 20, 40 or 80 mg; ezetimibe 10 mg or placebo.<sup>6</sup> Pooled analysis demonstrated that ezetimibe/simvastatin was associated with greater absolute reductions from baseline in LDL-C than simvastatin and ezetimibe monotherapy over 12 weeks ((2.41 mmol/L versus 1.79 mmol/L (p<0.001) and 0.88 mmol/L (p<0.001)). Similarly, significant reductions in LDL-C were achieved with ezetimibe/simvastatin compared with the corresponding dose of simvastatin

**Brand Name, (Manufacturer):** Inegy<sup>®</sup> (MSD/Schering-Plough)

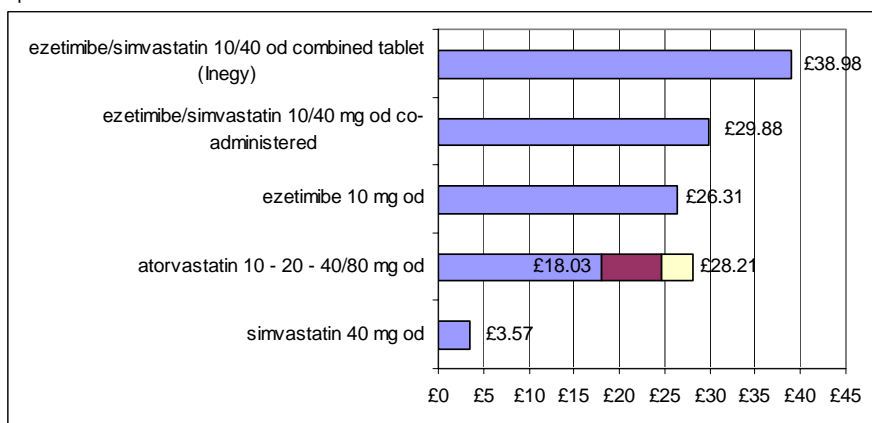
**BNF Therapeutic Class:** 2.12 Lipid-regulating drugs

**Licensed Indications:** Inegy<sup>®</sup> is licensed as adjunctive therapy to diet for the treatment of primary hypercholesterolaemia, mixed hyperlipidaemia (in patients not appropriately controlled on a statin alone or patients already treated with a statin and ezetimibe) and homozygous familial hypercholesterolaemia (HoFH).

**Dosage and Administration:** Typically 10/20 mg/day or 10/40 mg/day for hypercholesterolaemia. 10/40 mg/day or 10/80 mg/day for HoFH. It should be given as a single dose in the evening.

**Marketed:** June 2005.

**Cost Comparisons:** Cost for 28 days treatment [Prices from MIMS/Drug Tariff – July 2005]. N.B. Doses shown for general comparison and do not imply therapeutic equivalence



alone. Ezetimibe/simvastatin was associated with a significantly greater mean percent reduction in LDL-C compared with the next highest dose of simvastatin ( $p < 0.001$ ).

In the second study assessing the combined tablet ( $n = 1,902$ ) adults with primary hypercholesterolaemia were randomised to daily ezetimibe/simvastatin 10/10, 10/20, 10/40 or 10/80 mg; or atorvastatin 10, 20, 40 or 80 mg for 6 weeks.<sup>7</sup> Pooled analysis demonstrated that ezetimibe/simvastatin was associated with greater absolute reductions from baseline in LDL-C than atorvastatin (2.46 mmol/L versus 2.10 mmol/L ( $p < 0.001$ )). Similarly, significant reductions in LDL-C were achieved with ezetimibe/simvastatin compared with the mg equivalent dose of atorvastatin alone. Ezetimibe/simvastatin was associated with a greater mean percent reduction in LDL-C compared with the next highest dose of atorvastatin ( $p = \text{not stated}$ ).

Two randomised, double-blind trials of similar design have assessed the effect of adding ezetimibe to various doses of simvastatin for 12 weeks.<sup>8,9</sup> Ezetimibe plus simvastatin 10, 20, 40 or 80 mg daily reduced LDL-C concentration by 44-46%, 45-51%, 53-55% or 57-61%, respectively, compared with 27-31%, 35-36%, 36-42% or 44-46% on simvastatin alone ( $p < 0.01$  for each comparison).<sup>8-10</sup>

Two further randomised controlled studies ( $n = 1,498$ )<sup>11,12</sup> and an extension study ( $n = 433$ )<sup>13</sup> demonstrated that the mean percentage reductions in LDL-C with ezetimibe plus simvastatin relative to simvastatin or atorvastatin monotherapy were maintained in the longer-term, up to 48 weeks.

### Type 2 diabetes

214 patients with type 2 diabetes on a stable dose of thiazolidinedione were assigned open-label simvastatin 20 mg/day for 6 weeks.<sup>14</sup> Patients were then randomised to ezetimibe 10 mg or simvastatin 20 mg in addition for 24 weeks. Reductions in LDL-C from baseline (approximately 2.4 mmol/L) were 0.3% and 20.8% in the simvastatin only and ezetimibe/simvastatin groups respectively,  $p < 0.001$ . The LDL-C

response with doubling the dose of simvastatin was less than expected, possibly explained by a relatively low LDL-C baseline value.

### Homozygous familial hypercholesterolaemia (HoFH)

Pharmacological therapies, including statins, often fail to reduce LDL-C sufficiently in patients with HoFH. In a small trial ( $n = 50$ ) in patients with HoFH, ezetimibe enhanced the LDL-C lowering effect of both atorvastatin and simvastatin.<sup>15</sup> Sub-group analysis showed that increasing the dose of simvastatin from 40 mg to 80mg ( $n = 5$ ) produced a reduction in LDL-C of 13% from baseline vs. 23% for pooled ezetimibe plus simvastatin 40/80mg ( $n = 9$ ).<sup>1</sup>

### Safety

Adverse effects reported in clinical trials were generally similar to those seen with simvastatin monotherapy. Common (incidence  $\geq 1\%$   $\leq 10\%$ ) adverse effects associated with ezetimibe/simvastatin combination were headache, dizziness, fatigue, gastro-intestinal disturbances, asthenia and myalgia.<sup>1</sup> Rarely, hypersensitivity reactions, rash and angioedema, have been associated with ezetimibe monotherapy. In co-administration trials, incidence of elevations in serum alanine and/or aspartate aminotransferase  $\geq 3$  times upper limit of normal (ULN) was 1.9%.<sup>1</sup> Clinically important elevations of creatine kinase ( $\geq 10$  times ULN) were seen in 0.3% of patients.<sup>1</sup> The 48-week extension study demonstrated no clinically meaningful differences between ezetimibe/simvastatin and simvastatin groups in the incidence of adverse effects.<sup>13</sup>

### Place in Therapy

The NSF on coronary heart disease (CHD) states that patients with clinical evidence of CHD or those with a 10-year risk greater than 30% should be prescribed lipid lowering therapy with the aim of reducing total cholesterol to  $< 5$  mmol/L (LDL-C to  $< 3$  mmol/L) or by 30%, whichever is the greater.<sup>16</sup> However, subsequent guidance and clinical trials have advocated lower treatment thresholds.<sup>17,18</sup>

Generic simvastatin at a dose of 40 mg daily can achieve these goals and its use is supported by robust outcome data.<sup>19,20</sup> It should be considered the agent of choice for the primary and secondary prevention of CHD. However, some patients may fail to reach 'targets' with simvastatin 40 mg. For these patients titrating the dose to the maximum recommended/tolerated dose is logical. Non-responders could be switched to an alternative statin, with clinical outcome data, and the dose titrated again if required.

The ezetimibe/simvastatin combination should be reserved for patients not reaching target lipid levels on maximum tolerated doses of statin alone.<sup>21,22</sup> The dual mechanism of action produces greater reductions in LDL-C than simvastatin and atorvastatin monotherapy at mg equivalent doses and the addition of ezetimibe to simvastatin produces greater reductions than increasing the simvastatin or atorvastatin dose. However, further investigation is required to determine whether ezetimibe added to low-dose simvastatin is associated with fewer adverse events than high-dose simvastatin in the longer-term. Ezetimibe/simvastatin combination tablet is not licensed for the primary or secondary prevention of CHD; the results of on-going clinical outcome studies are awaited. The decision to either use the combined tablet (Inegy®) or to co-administer ezetimibe plus statin is likely to be based on cost. The combination tablet costs approximately one and a quarter times as much as ezetimibe plus simvastatin co-administration.

### Risk Management Issues:

Prescribers are reminded that Inegy® contains ezetimibe and simvastatin, therefore, it should not be prescribed concurrently with other statin therapy.

Produced for the UK Medicines Information Service

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## Appendix I

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Inegy® (Ezetimibe/Simvastatin combination)

Appendix II: Table of key clinical trials evaluating ezetimibe/simvastatin combination

Study	Trial Design	Trial Population	Primary Endpoint	Treatment	Efficacy Outcomes (% change from baseline)		
					LDL-C	HDL-C	TG
Bays HE et al (Ref. 6)	12-week randomised placebo controlled double blind factorial design multi-centre multi-national 4-week diet/placebo run-in	<b>1,528 patients with hypercholesterolaemia</b> Mean baseline LDL-C 4.60 mmol/L and TG ≤3.96 mmol/L	Mean % change in LDL-C from baseline to study end (pooled groups)	Placebo (n=148) Ezetimibe 10 mg (n=149) Pooled simvastatin 10-80 mg (n=622) Pooled ezetimibe 10 mg plus simvastatin 10-80 mg (n=609)	-2.2% -18.9% -39.0% -53.0%	-0.3% +5.0% +6.8% +7.2%	-1.9% -10.7% -20.8% -24.3%
					p<0.001 for ezetimibe/simvastatin vs. simvastatin	p=NS	p<0.001 for ezetimibe/simvastatin vs. simvastatin
Ballantyne C et al. 2005 (Ref. 7)	6-week randomised active controlled double blind parallel group multi-centreUS only 4-week diet/placebo run-in	<b>1,902 patients with hypercholesterolaemia</b> Mean baseline LDL-C 4.61 mmol/L and TG ≤3.96 mmol/L	Mean % change in LDL-C from baseline to study end (pooled groups)	Atorvastatin 10-80 mg (n=951) Ezetimibe 10 mg plus simvastatin 10-80 mg (n=951)	-45.3% -53.4%	+4.3% +7.9%	-25.5% -27.4%
					p<0.001	p<0.001	p=NS
Davidson MH et al (Ref. 8)	12-week randomised placebo controlled double blind factorial design multi-centre US only 4-week diet/placebo run-in	<b>668 patients with primary hypercholesterolaemia</b> Mean baseline LDL-C 4.61 mmol/L and TG ≤3.96 mmol/L	Mean % change in LDL-C from baseline to study end (pooled groups)	Placebo (n=70) Ezetimibe 10 mg (n=61) Pooled simvastatin 10-80 mg (n=263) Pooled ezetimibe 10 mg plus simvastatin 10-80 mg (n=274)	-1.3% -18.1% -36.1% -49.9%	+0.9% +5.1% +6.9% +9.3%	+2.4% -8.3% -16.6% -24.1%
					p<0.01 for ezetimibe/simvastatin vs. simvastatin	p=0.03 for ezetimibe/simvastatin vs. simvastatin	p<0.01 for ezetimibe/simvastatin vs. simvastatin
Goldberg AC et al. (Ref. 9)	12-week randomised placebo controlled double blind factorial design multi-centre multi-national 4-week diet/placebo run-in	<b>887 patients with primary hypercholesterolaemia</b> Mean baseline LDL-C 4.53 mmol/L	Mean % change in LDL-C from baseline to study end (pooled groups)	Placebo (n=93) Ezetimibe 10 mg (n=92) Pooled simvastatin 10-80 mg (n=349) Pooled ezetimibe 10 mg plus simvastatin 10-80 mg (n=353)	+2.7% -19.8% -38.5% -53.2%	+2.3% +7.0% +7.6% +8.2%	-2.2% -13.2% -15.2% -28.0%
					p<0.001 for ezetimibe/simvastatin vs. simvastatin	p=NS	p<0.001 for ezetimibe/simvastatin vs. simvastatin

**Inegy® (Ezetimibe/Simvastatin combination)**

Study	Trial Design	Trial Population	Primary Endpoint	Treatment	Efficacy Outcomes (% change from baseline)		
					LDL-C	HDL-C	TG
Feldman T et al. (Ref. 11)	23-week randomised placebo controlled partial blind parallel group multi-centre US only 4-week diet/placebo run-in	<b>710 patients with CHD or CHD risk equivalent</b> Mean baseline LDL-C 4.37 mmol/L and TG ≤3.96 mmol/L	Target LDL-C goal of <2.58 mmol/L after 5 weeks	Placebo plus simvastatin 20 mg (n=253) Ezetimibe 10 mg plus simvastatin 10 mg (n=251) Ezetimibe 10 mg plus simvastatin 20 mg (n=109) Ezetimibe 10 mg plus simvastatin 40 mg (n=97) (results presented are at week 5)	-38% -47%* -53%* -59%* *p<0.001 vs. simvastatin 20 mg	+5.1% +6.2% +8.0%* +7.4% *p<0.05 vs. simvastatin 20 mg	-19% -19% -25%* -30%* *p<0.001 vs. simvastatin 20 mg
Ballantyne C et al. 2004 (Ref. 12)	24-week randomised active controlled double blind forced titration multi-centre US only 4-week diet/placebo run-in then 4 x 6-week study periods	<b>788 patients with hypercholesterolaemia, CHD or CHD risk equivalent</b> Mean baseline LDL-C 4.64 mmol/L and TG ≤3.96 mmol/L	Mean % change in LDL-C from baseline to the end of initial 6-week treatment period	Atorvastatin 10 mg (n=262) Ezetimibe 10 mg plus simvastatin 10 mg (n=262) Ezetimibe 10 mg plus simvastatin 20 mg (n=263)	-37.2% -46.1% -50.3% p≤0.001 for both comparisons vs. atorvastatin	+5.1% +8.0% +9.5% p≤0.05 for both comparisons vs. atorvastatin	-22.5% -26.3% -24.6% p=NS for both comparisons vs. atorvastatin
	Forced titration of statin dose occurred over last three 6-week periods to: ezetimibe plus simvastatin 80 mg and atorvastatin 80 mg			Atorvastatin 80mg (n=227) Ezetimibe 10mg plus simvastatin 80mg (n=460)	-52.5% -59.4% p<0.001 vs. atorvastatin	+6.5% +12.3% p<0.001 vs. atorvastatin	-34.8% -35.3% p=NS
Gaudiani LM et al. (Ref. 14)	24-week randomised comparative double blind parallel group multi-centre US only 6-week open label simvastatin 20 mg	<b>214 type 2 diabetics on stable dose of thiazolidinedione with LDL-C &gt; 2.6 mmol/l</b> Mean baseline LDL-C after open-label simvastatin 2.4 mmol/l	Mean % change in LDL-C from baseline to study end	Open-label simvastatin 20 mg plus simvastatin 20 mg (total 40 mg) (n=110) Open-label simvastatin 20 mg plus ezetimibe 10 mg (n=104)	-0.3% -20.8% p<0.001	+0.3% +0.2% p=NS	+0.9% -3.6% p=NS
Gagne C et al. (Ref. 15)	12-week randomised comparative double blind parallel group multi-centre 6-12 week open label statin 40 mg)	<b>50 adults and children (≥12 years and ≥40 kg) with HoFH</b> Mean baseline LDL-C 8.41 mmol/l while receiving open label statin	Mean % change in LDL-C from baseline while receiving open label statin to study end	Simvastatin or atorvastatin 80 mg (n=17) Ezetimibe 10 mg plus statin 40/80 mg (n=33) (pooled analysis)	-6.7% -20.7% p=0.007	+4.4% -2.8% p=NS	-5.8% -10.8% p=NS

NS = not significant