Scottish Medicines Consortium

Re-Submission

nicotinic acid modified release tablets (Niaspan®) No. 93/04

Merck Pharmaceuticals

10 December 2004

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and ADTCs on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full resubmission

Nicotinic acid modified release tablets (Niaspan®) is not recommended for use in NHS Scotland for the treatment of dyslipidaemia and primary hypercholesterolaemia as monotherapy in patients who do not tolerate HMG-CoA reductase inhibitors and is not recommended for use when prescribed in combination with HMG-CoA reductase inhibitors (statins).

There is evidence that nicotinic acid modified release tablets lowers LDL cholesterol levels to a small extent and raises HDL-cholesterol levels to a greater extent. However the evidence for use in combination with HMG-CoA reductase inhibitors is less convincing. The economic case for use as monotherapy or co-therapy in the licensed indication was not demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Nicotinic acid modified release tablets (Niaspan^{Ò})

Licensed indication under review: Treatment of dyslipidaemia (particularly in combined mixed dyslipidaemia, characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol), and primary hypercholesterolaemia. Niaspan should be used in combination with HMG-CoA reductase inhibitors (statins), when the cholesterol lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate. Niaspan is used as monotherapy only in patients who do not tolerate HMG-CoA reductase inhibitors. Diet and other non-pharmacological treatments should be continued during therapy with Niaspan.

Dosing information under review:

Starting dose: 375mg daily (dose is gradually escalated -see cost per treatment section)
Maintenance dose: 1000-2000mg daily
Maximum dose: 2000mg daily
The dose is taken at bedtime after a low-fat snack

UK launch date 4 November 2003

Comparator Medications Fibrates, Acipimox

Cost per treatment period and relevant comparators

Drug	Comments	Dose	Cost per day (£)
Niaspan	**Titration dose**	**375mg daily for 1 week 500mg daily for 1 week 750mg daily for 1 week**	**0.66**
Niaspan	**Maintenance dose**	**1-2g per day**	**0.53-1.05**
Acipimox	Capsules	500 -750mg daily	1.03-1.54
Gemfibrozil	Capsules (non-proprietary)	600mg twice daily	0.82
Ciprofibrate	Tablets	100mg daily	0.53
Bezafibrate	Tablets (non-proprietary)	200mg thrice daily	0.29
Bezafibrate	Modified release	400mg daily	0.29
Fenofibrate	Capsules (non-proprietary)	200mg daily	0.17

Summary of evidence on comparative efficacy

Primary endpoints

Statin or Niaspan vs Niaspan/lovastatin

Two randomised controlled trials compared lovastatin and Niaspan with fixed doses of Niaspan/lovastatin; 40mg v 2000mg v 1000/20 v 2000/40 and 40mg v 2500mg v 2500/10 v 2500/20 v 2500/40 in the first and second trials respectively. The first trial recruited 236 patients with either a low density lipoprotein (LDL) = 4.91 mmol/l or LDL = 4.14mmol/l plus two risk factors for coronary artery disease. Patients were treated for 28 weeks but due to titration period of Niaspan the number of weeks at the maximum dose was five weeks. The primary endpoint of % change in LDL for the lovastatin, Niaspan, Niaspan/lovastatin 1000/20 and 2000/40 groups were -32.2%, -13.5%, -27.6% and -41.9% respectively and was statistically superior for the Niaspan/lovastatin 2000/40 group over all other groups ($p<0.05$). The second trial recruited 164 patients with a LDL = 4.91 mmol/l or LDL = 4.14mmol/l plus two risk factors for coronary artery disease or LDL = 3.36mmol/l plus coronary heart disease or type 2 diabetes mellitus. Patients took study drugs for 20 weeks with the Niaspan dose titrated up to 2500 mg and the lovastatin monotherapy dose up to 40 mg. All groups took the full dose for 5 of the 20 weeks. The primary endpoint of % change in LDL for the lovastatin, Niaspan, Niaspan/lovastatin 2500/10, 2500/20 and 2500/40 groups were -24.4%, -19.7%, -36.3%, -36.4%, and -46.6%, respectively.

An open label study recruited 315 patients whose LDL was = 4.14mmol/l or = 3.36mmol/l plus coronary artery disease and HDL < 1.16mmol/l (males) or < 1.29mmol/l (females). Patients were randomised to receive atorvastatin 40mg, simvastatin 40mg, Niaspan/lovastatin 1000/40 or 2000/40 for at least 4 weeks and up to 16 weeks. The primary efficacy endpoint of % change in LDL was statistically significant for atorvastatin (-49%) versus simvastatin (-39%), Niaspan 1000/40 (-39%) and 2000/40 (-42%). The second primary efficacy endpoint of % change in high density lipoprotein (HDL) was statistically significant for both Niaspan/lovastatin 2000/40 (+32%) and 1000/40 (+17%) versus atorvastatin (+6%) and simvastatin (+7%).

Rosuvastatin v Niaspan v Niaspan/rosuvastatin

An open label study comparing rosuvastatin 40mg, Niaspan 2000mg, Niaspan/rosuvastatin 1000/40 and Niaspan/rosuvastatin 2000/10 recruited 270 patients with a total cholesterol = 5.17mmol/l and (HDL) <1.16 mmol/l. Maximum doses of drugs for all arms were taken for 6 weeks following titration over 18 weeks. The primary endpoint of % change in LDL for rosuvastatin, Niaspan, Niaspan/rosuvastatin 1000/40 and 2000/10 groups was -48%, -0.1%, -42% and -36%, respectively. The rosuvastatin group was statistically superior versus the Niaspan and Niaspan/rosuvastatin 2000/10 groups.

Niaspan/lovastatin v fenofibrate

A 20 week double blind randomised controlled trial compared Niaspan/lovastatin 1000/40 and 1500/40 with fenofibrate 200mg. The trial recruited 197 patients with type 2 diabetes mellitus (on a stable dose of metformin and/or a thiazolidenedione) and who had HDL = 1.03 mmol/l (males) or =1.29 mmol/l (females) and triglycerides =1.69 mmol/l. The primary endpoint of % change in HDL for Niaspan/lovastatin 1000/40, 1500/40 and fenofibrate 200mg was +14%, +26% and +12% respectively and was statistically superior for the Niaspan/lovastatin 1500/40 group versus fenofibrate.

Niaspan v gemfibrozil

Niaspan 2000mg (for 8 weeks) was compared with gemfibrozil 1200mg (for 16 weeks) in 173 patients with LDL = 4.14mmol/l,or LDL < 3.36mmol/l with coronary heart disease, and HDL ≤ 1.03mmol/l. The primary efficacy endpoint of % change in HDL was statistically significant for Niaspan 2000mg (+26.0%) versus gemfibrozil 1200mg (+13.3%).

Summary of evidence on comparative safety

Flushing was the most common adverse effect reported, and reason for patient withdrawal in the trials of Niaspan in combination with a statin, versus placebo and versus gemfibrozil. Flushing was reported in 88% of patients recruited to the placebo controlled trials and patient withdrawal from the trials was observed in 6% of patients. In an open label extension study of Niaspan the incidence of flushing appeared to be reduced with continued treatment with Niaspan.

Elevation of hepatic enzymes with alternative sustained release nicotinic acid preparations under study, compared with immediate release nicotinic acid, has been observed. The new extended release formulation, Niaspan, has not shown similar elevations. In the placebo controlled trials elevation of transaminases resulting in withdrawal occurred in six patients, although no patient had elevations greater than three times the upper limit of normal. In an open label extension study six and five patients, respectively had elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2 times the upper limit although no patients had elevations of AST and ALT >3 times the upper limit. Patients prescribed Niaspan should have liver tests checked periodically and Niaspan should be discontinued if transaminases increase to greater than three times the upper limit of normal. No confirmed cases of Niaspan induced myopathy were reported in any of the trials.

A study recruited 148 patients with stable type 2 diabetes and investigated changes in HbA1c as a primary safety measure. At 16 weeks, the change in HbA1c for placebo, Niaspan 1000mg and 1500mg were marginally statistically significant for Niaspan 1500mg only. There were rises in fasting blood glucose levels in weeks 4-8 in both Niaspan groups but these returned to baseline by week 16, possibly as a result of adjustments in anti-diabetic drug therapy. Assessments of diabetes control and medication changes indicate that Niaspan 1000mg produced little or no alteration in diabetes control, whereas a larger proportion of patients receiving 1500mg required adjustments to their anti-diabetic drug therapy. A second trial in patients with diabetes compared Niaspan/lovastatin 1000/40 and 1500/40 with fenofibrate 200mg and concluded that the effect of Niaspan containing drug combination on glycaemic control was minimal. Close monitoring of patients with diabetes or potentially diabetic patients is advised.

Rhabdomyolysis was not observed in any of the clinical trials with Niaspan but there have been spontaneous reports of the condition in the US. The risk of rhabdomyolysis in patients on combined therapy with Niaspan and HMG-CoA reductase inhibitors is noted in the Niaspan Summary of Product Characteristics and the potential benefits and risks should be considered by the prescriber.

Summary of clinical effectiveness issues

In all trials comparing Niaspan in combination with statins, alone versus placebo and gemfibrozil, patients were following dietary modification guidelines in addition to drug therapy.

The benefits of reducing LDL levels for the prevention of atherosclerosis are well established. However, despite a strong inverse relationship between HDL levels and coronary artery disease, the benefits of increasing HDL levels on cardiovascular outcomes have not been established. Accordingly, no specific goal value for raising HDL levels has been set in cholesterol treatment guidelines, including the recently updated National Cholesterol Education Programme Adult Treatment Panel III Guidelines.

Many of the trials combining Niaspan with a statin used lovastatin, which is not available in the UK. In addition, the controlled trials did not extend beyond 28 weeks. One open label study did investigate the long-term safety and effectiveness of Niaspan/lovastatin over 52 weeks. There is, however, limited data on the long- term use of Niaspan with HMG-CoA reductase inhibitors available in the UK.

Summary of comparative health economic evidence

Two Markov models were presented for secondary prevention of cardiovascular disease. The first model calculated mean lipid values after drug therapy. This model had a 5-year time horizon. The second model used the results of the first model to assess the long-term development of Coronary Heart Disease (CHD) complications. This model had a 40-year time horizon. Outputs of the overall analysis were total costs, quality adjusted life years and life years gained.

Clinical experts advise the comparator in the co-therapy arm is inappropriate. The licensed indication is to treat dyslipidaemia, particularly in patients with combined mixed dyslipidaemia, characterised by elevated levels of LDL-C and triglycerides and low HDL-cholesterol, The clinical experts advise that in such patients with elevated LDL levels, where the effect the initial statin dose is inadequate, the statin dose is titrated upwards, possible to the maximum dose before Niaspan would be introduced.

The comparator in the mono-therapy arm is a potential option to use where patients are intolerant of statins. However, the clinical effectiveness data used in the model came from a trial that showed gemfibrozil increased LDL by 9%. This was not an expected effect and is inconsistent with other studies with Gemfibrozil and guidance including fibrates that report no change on a 5% – 20% reduction in LDL.

Limitations with the economic models for co-therapy include:

- the baseline patient population characteristics represent a high-risk patient group who are likely to receive higher doses of statins and are more likely to have adverse events than those covered by the licensed indication of Niaspan.
- it is likely that drug therapies will be prescribed for lifetime duration and not for 5 years.
- In the absence of long-term data it is not possible to ascertain whether the clinical effectiveness observed in short term trials can be extrapolated onto a long-term time horizon.
- The Niaspan dosage assumed in the co-therapy model is not related to the dosage or efficacy observed in the clinical trials.

- The clinical trial effectiveness data excluded data from the rosuvastatin v Niaspan trial.
- Finally there is no transparency of the absolute number of subsequent CHD events in each arm to enable the outcome results to be validated clinically.

The monotherapy model used clinical trial data that showed gemfibrozil raised LDL and therefore appeared not to be clinically effective and hence not cost-effective in reducing LDL.

Budget Impact

The estimated annual budget impact presented for Niaspan is £0.13m in year 1, £0.5m in year 2, £1 million in year 3, £1.8 million in year 4 and £2.3 million in year 5. This is based on an initial patient population of 1,750 patients in year 1, 4,800 in year 2, 10,000 in year 3, 15,700 in year 4 and 20,400 in year 5. Assumptions include a drop out rate of 22%, and 80% of patients take 1g, 10% take 1.5g and 10% take 2g of Niaspan.

Existing or proposed guidelines and protocols

The US recently updated National Cholesterol Education Programme Adult Treatment Panel III Guidelines (2004) recommend the use of a fibrate or nicotinic acid in combination with a statin in high risk patients with high triglycerides or low HDL.

The American Heart Association guideline, Evidence-based Guidelines for Cardiovascular Disease Prevention in Women (2004) recommends the use of nicotinic acid or a fibrate when the HDL cholesterol level is low (<50mg/dl), for all levels of risk, but for low- or intermediate-risk patients, only after the LDL-C goal has been reached.

The management of hyperlipidaemia is discussed in the Scottish Intercollegiate Guidelines Network (SIGN) guidelines; Lipids and the primary prevention of coronary heart disease- guideline number 40 (1999) and Secondary prevention of coronary heart disease following myocardial infarction- guideline number 41 (2000). Both these guidelines predate the availability of Niaspan. The SIGN guideline Management of Diabetes - guideline number 55 (2001) recommends the use of gemfibrozil in patients with established CVD who are not receiving statin and whose cholesterol is <5mmol/l and HDL cholesterol <1.0mmol/l. The expected publication date of the SIGN guidelines, Coronary Heart Disease: primary prevention and Coronary Heart Disease; secondary prevention after myocardial infarction is 2006.

The guideline on Management of Blood Pressure and Lipids in type 2 Diabetes (2002) developed by the Royal College of General Practitioners Effective Clinical Practice Programme was part of the Inherited Clinical Guidelines work programme and was commissioned by the Department of Health in 1999, before NICE was formed. NICE have a provisional schedule for a guideline on Hyperlipidaemia and Cardiovascular Risk which includes a first guideline development group meeting in January 2005.

Other Considerations

This is a re-submission. The previous guidance issued on 13 April 2004, was as follows;

Niaspan is not recommended for use within NHS Scotland for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia.

Limited information comparing Niaspan with standard release nicotinic acid tablets showed similar efficacy in improving lipid parameters and a similar adverse-effect profile. However, there is a lack of information from prospective, double-blind trials comparing Niaspan with statins, fibrates and in combination with other lipid-lowering agents.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 1 December 2004.

Drug prices are those available at the time of SMC assessment.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

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