PUBLIC SUMMARY DOCUMENT

Product: Nicotinic Acid, tablets (prolonged release), 500 mg, 750 mg and 1 g, Niaspan®

Sponsor: Alphapharm Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

This re-submission sought listing of a prolonged release formulation of nicotinic acid as a restricted benefit for use in combination with an HMG CoA reductase inhibitor (statin) in patients with dyslipidaemia with adequately controlled Low Density Lipoprotein (LDL-C) and whose High Density Lipoprotein Cholesterol (HDL-C) levels are inadequately controlled despite monotherapy with a statin.

2. Background

A submission seeking listing of this product was considered at the July 2006 PBAC meeting, as a restricted benefit for use in combination with an HMG CoA reductase inhibitor (statin) in Type II diabetic patients with dyslipidaemia whose HDL-C levels are inadequately controlled despite monotherapy with a statin.

The PBAC rejected the submission on the basis that the comparator was not appropriate and there was a lack of clinical evidence to support the implicit claim that an increase in HDL levels reduces cardiovascular risk.

3. Registration Status

The TGA registered Niaspan on the 27 February 2006 for "the treatment of mixed dyslipidaemia, and primary hypercholesterolaemia, as adjunctive therapy to diet. Prior to initiating therapy with nicotinic acid, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated."

4. Listing Requested and PBAC's View

Restricted benefit
Niaspan is indicated for use in combination with a HMG CoA reductase inhibitor (statin) in patients with dyslipidaemia with adequately controlled LDL-C and whose HDL-C levels are inadequately controlled despite monotherapy with a statin.

Inadequate control is defined as HDL-C<1 mmol/L after at least 3 month's treatment with a statin.

See Recommendation and Reasons for PBAC's view

5. Clinical Place for the Proposed Therapy

Niaspan will provide add-on treatment for patients with dyslipidaemia whose HDL-C levels are inadequately controlled with a statin alone.

6. Comparator

The submission nominated placebo as an add-on to statin therapy as the comparator. This was considered appropriate by the PBAC.

7. Clinical Trials

The submission provided one randomised, placebo-controlled trial comparing prolonged release nicotinic acid added to ongoing statin therapy with placebo plus ongoing statin therapy.

First Author	Publication Title	Publication Citation
Taylor AJ et al	Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) 2. A double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins.	*Circulation* 2004; 110:3512-3517.

A meta-analysis of evidence from randomised, placebo-controlled, lipid-altering therapy trials in high-risk patients was also included. A total of 23 individual trials whose primary outcome was either predefined clinical event composites or change in coronary artery stenosis were included in this analysis, aimed at linking LDL-C and HDL-C changes to stenosis change or event reduction.

First Author	Publication Title	Publication Citation
Brown B G	Stimultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomised lipid trials.	*Current Opinion in Lipidology* 2006; 17: 631-636.

8. Results of Trials

The primary outcome of the trial was mean change from baseline in common carotid intima-media thickness (CIMT). Changes in serum lipid concentrations and a composite of clinical cardiovascular outcomes were included as secondary outcomes.

There was no statistically significant difference in mean change from baseline to endpoint CIMT for patients treated with prolonged release nicotinic acid plus a statin, however, there was a significant increase in CIMT in patients treated with placebo plus a statin. The difference between the two treatment groups did not reach statistical significance.

There was a statistically significant increase in HDL-C during the 12-month trial duration for patients treated with prolonged release nicotinic acid plus a statin. There was no evidence of a change in HDL-C for patients treated with placebo plus a statin. The results of the key trial are summarised below:

Changes from baseline in carotid intima-media thickness (CIMT) and lipid concentrations

Outcome	PRNA+statin N=78	PBO+statin N=71	Between-group p-value
CIMT [mean (SD) mm] - baseline - endpoint - mean change	 0.893 (0.259) 0.907 (0.234) 0.014 (0.104) [p=0.23]	 0.868 (0.207) 0.912 (0.202) 0.044 (0.100) [p<0.001]	 0.52 0.89 0.08
TC [mean (SD) mmol/L)] - baseline - endpoint - mean change	 3.99 (0.70) 4.01 (0.98) p=0.92	 4.17 (0.75) 4.04 (0.62) p=0.06	 0.13 0.73 NR
LDL-C [mean (SD) mmol/L)] - baseline - endpoint - mean change	 2.25 (0.44) 2.20 (0.65) p=0.42	 2.36 (0.57) 2.23 (0.52) p=0.37	 0.19 0.61 NR
HDL-C [mean (SD) mmol/L)] - baseline - endpoint - mean change	 1.01 (0.18) 1.22 (0.41) p<0.001	 1.04 (0.18) 1.04 (0.23) p=0.61	 0.52 0.003 NR
TG [mean (SD) mmol/L)] - baseline - endpoint - mean change	 1.74 (0.93) 1.51 (0.98) p=0.009	 1.94 (1.18) 1.85 (0.94) p=0.07	 0.25 0.03 NR

CIMT: carotid intima-media thickness; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; PRNA: prolonged release nicotinic acid; PBO: placebo

Three patients (3.8%) treated with prolonged release nicotinic acid plus a statin had four cardiovascular events over the 12-month trial duration, compared with seven (9.6%) placebo plus statin patients, who experienced a total of 11 events. There was no evidence of a difference between treatment groups in the proportion of patients with cardiovascular events.

9. Clinical Claim

The submission claimed that prolonged release nicotinic acid in combination with a statin has significant advantages in effectiveness over placebo plus ongoing statin therapy and has similar or less toxicity.

See Recommendation and Reasons for PBAC's view.

10. Economic Analysis

The submission presented a preliminary economic evaluation. The choice of the cost-effectiveness approach was considered by the PBAC to be valid if the superior efficacy and similar toxicity of prolonged release nicotinic acid were considered to have been adequately demonstrated.

The resources included were drug costs, the percentage reduction in HDL-C and the relationship between increase in HDL-C and reduction in cardiovascular risk. The submission

assumed that a 1% increase in HDL-C is associated with a 1% reduction in cardiovascular risk, based on a recently published meta-analysis (Brown et al, 2006).

The PBAC noted that the meta-analysis combined 23 trials and plotted the HDL-C response in the intervention arm of the trial against the reduction in one year cardiovascular event rates. The submission argued that this constituted sufficient trial evidence to support the claim that a HDL-C increase translated into a reduction in cardiovascular events. However, there was only one data point for nicotinic acid and the confidence intervals crossed zero. In addition, the publication did not explain the rationale for the zero placebo event rate shown by the graph, nor did it discuss the individual variation across the trials. Overall, the meta-regression as presented in this submission was subject to possible ecological confounding and therefore the results could not be relied upon to provide evidence of the relationship between reduction in HDL and clinical events.

The submission estimated the trial-based incremental cost/additional patient avoiding a cardiovascular event (based on clinical data from the trial) to be less than $15,000.

A modelled economic evaluation was not presented. A modelled economic evaluation using long term mortality and morbidity data would have provided more information to the PBAC on which to base its decision.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients/year would be more than 200,000 in Year 4. The submission estimated the financial cost/year to the PBS would be less than $10 million in Year 4.

12. Recommendation and Reasons

With respect to the trial data submitted, the PBAC noted there was no statistically significant difference in mean change from baseline to endpoint CIMT (carotid intima-media thickness) for patients treated with prolonged release nicotinic acid plus a statin, however, there was a significant difference for patients treated with placebo plus a statin. The difference between the two treatment groups did not reach statistical significance.

There was a statistically significant increase in HDL-C during the 12-month trial duration for patients treated with prolonged release nicotinic acid plus a statin, and there was no evidence of a change in HDL-C for patients treated with placebo plus a statin. However, no comparative statistics were provided for the outcome which was of primary interest in the economic evaluation, mean change from baseline in HDL-C.

The PBAC also noted that although only limited toxicity data were presented, prolonged release nicotinic acid appeared to be associated with more toxicity, compared with placebo, with more than two-thirds of patients treated with prolonged release nicotinic acid experiencing flushing. The product information contains a precaution that diabetic patients should be observed closely since there may be a dose-related increase in glucose intolerance and adjustment of diet and/or antidiabetics and/or insulin therapy may become necessary.

The use of changes in CIMT as a surrogate outcome for change in HDL-C was not considered by the PBAC to be adequately validated at this time. The PBAC noted this matter would be discussed at the March 2007 meeting of American College of Cardiology. Further, the PBAC noted the epidemiological data suggest that raising HDL-C may provide independent and additive cardiovascular benefit and that the clinical trial evidence is weakly supportive. However the PBAC did not consider a conclusion on this issue could be reached, in general, nor for Niaspan, in particular, by the evidence provided in the submission.

The PBAC therefore rejected the application on clinical grounds because in the key trial submitted there was no statistically significant benefit demonstrated for prolonged release nicotinic acid over placebo plus statin, uncertainty that the key trial outcome (change in CIMT) was a validate surrogate for improved cardiovascular outcomes, and uncertainty associated with the impact of raising HDL-C on cardiovascular outcomes.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor is currently reviewing it's position regarding this decision.