Public Summary Document

Product:	Blood beta-ketone, electrode strips, MediSense Optium® Ketone Blood β-Ketone Electrodes®
Sponsor:	Abbott Diagnostics Division (MediSense Products)
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The submission requested a restricted benefit listing on the Pharmaceutical Benefits Scheme (PBS) for quantitatively measuring blood ketones in diabetic patients who are on insulin therapy.

2. Background

This diagnostic agent has not previously been considered by the Pharmaceutical Benefits Advisory Committee (PBAC).

3. Registration Status

Blood beta (β)-ketone indicator electrode strips were listed as a device on the Australian Register of Therapeutic Goods on 1 June 2000.

4. Listing Requested and PBAC's View

Restricted Benefit.

For quantitatively measuring ketones in diabetic patients who are on insulin therapy for their diabetes, and who are at risk of diabetic ketosis or ketoacidosis, or for use during the management of diabetic ketosis or ketoacidosis, and who thus require an estimation of ketones in the blood.

The PBAC's view was that there were doubts about the predicted usage of the product, both in terms of patient numbers and frequency of use, based on the requested restriction.

5. Clinical Place for the Proposed Therapy

Blood β-ketone electrodes provide an alternative to urine ketone indicators.

6. Comparator

The submission nominated Keto-Diastix and Keto Diabur Test 5000 urine test strips as comparators. The PBAC accepted this as appropriate.

7. Clinical Trials

The submission presented two key randomised clinical outcomes trials and five supportive diagnostic accuracy studies. These studies had been published at the time of submission, as follows:

Trial/First author	Protocol/Publication title	Publication citation
Key randomised trials		
Laffel LMB et al,	Sick day management (SDM) using blood (beta-hydroxybuyrate (beta OHB) vs urine ketones significantly reduces hospital visits in youth with T1DM: A Randomized clinical trial.	Diabetic Medicine 2006; 23(3) 278 – 84. Diabetes. 2002; 51(Suppl. 2):A105-A105.

Trial/First author	Protocol/Publication title	Publication citation
Key randomised trials		
Vanelli M et al	The direct measurement of 3-beta-hydroxybutyrate enhances the management of diabetic ketoacidosis in children and reduces time and costs of treatment.	Diabetes Nutrition and Metabolism. 2003; 16(5-6):312-316.
Supportive diagnostic accuracy studies presented		
Taboulet P et al	Urinary acetoacetate or capillary beta-hydroxybutyrate for the diagnosis of ketoacidosis in the Emergency Department setting.	European Journal of Emergency Medicine. 2004; 11(5):251-8.
Fineberg SE et al	Comparison of blood beta-hydroxybutyrate and urine ketones in 4 weeks of home monitoring by insulin-requiring children and adults.	Diabetes. 2000; 49(Suppl. 1):A105-A106.
Harris S et al	Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosis.	Diabetic Medicine. 2005; 22(2):221-224.
Guerci B et al.	Accuracy of an electrochemical sensor for measuring capillary blood ketones by fingerstick samples during metabolic deterioration after continuous subcutaneous insulin infusion interruption in type 1 diabetic patients.	Diabetes Care. 2003; 26(4):1137-1141.
Bektas F et al	Point of care blood ketone testing of diabetic patients in the emergency department.	Endocrine Research. 2004; 30: 395-402.

8. Results of Trials

In the more directly relevant randomised, but unblinded trial (Laffel et al) there were more emergency room visits and hospitalisations in the urine ketone testing group compared with the blood β-ketone testing arm. The reasons for the hospitalisations and emergency room visits were not given, although it is stated that they included both hyperglycaemia and hypoglycaemia.

Emergency visits and hospitalisations during 6 months' follow-up testing of blood ketones compared to urine ketones in Type 1 diabetic patients in the key randomised trial

Laffel et al (in press)	Blood ketone (n=29.9 patient-years) N=62	Urine ketone (n=29.1 patient-years) N=61
All cause emergency visits and hospitalisations		
Emergency visits	8	14
Per 100 patient-years	26.8	48.1
Hospitalisations	3	8
Per 100 patient-years	10.0	27.5
Total episodes	11 (in 10 patients) 10/62 (16%)	22 (in 15 patients) 15/61 (25%)
Per 100 patient-years	36.8	75.6

Likelihood ratios were calculated during the evaluation to facilitate comparison between the arms of the supportive diagnostic accuracy studies. In general, the blood β-ketone electrodes had higher positive likelihood ratios than urine ketone testing, but with similar negative likelihood ratios. This suggested that patients who test positive with the blood β-ketone electrodes were more likely to have diabetic keto acidosis (DKA) than those who test positive with the urine ketone test. However, the criteria for diagnosing DKA were not uniform in the studies and the study quality was relatively low with the potential for significant bias affecting the results.

No toxicity results were presented. Since the blood β-ketone electrodes were used externally it was appropriate not to consider toxicity. However, if a diagnostic test produced false

negative or false positive results, this may have a clinically relevant impact on the patient. This possibility was not considered in the submission.

For PBAC's comments on these results, *see Recommendation and Reasons*.

9. Clinical Claim

The submission claimed that the MediSense Optium Ketone Blood β-Ketone electrodes had significant advantages over the main comparator, the urine ketone test strips. Toxicity was not a relevant issue for diagnostic agents.

For PBAC's view of this claim, *see Recommendation and Reasons*.

10. Economic Analysis

A preliminary economic evaluation was presented based on the results of the Laffel et al study. The incremental cost per emergency room visit or hospitalisation avoided over 100 patient years was calculated in the submission to be less than zero (i.e. to represent an overall saving to Government)

A modelled economic evaluation was not presented. The PBAC considered that this was not appropriate since diabetes is a chronic condition and a 6-month study period as used in Laffel et al may be inadequate to capture the full clinical and economic consequences of the tests.

The PBAC considered that the cost effectiveness of the blood β-ketone electrodes based on a price at about twenty times the cost of the comparator was unacceptable, given the doubts about the clinical claims, and that the corresponding claimed cost off-sets would be unlikely to be realised in an Australian population.

11. Estimated PBS Usage and Financial Implications

The estimated financial cost per year to the PBS (excluding co-payments) is < $10 million per year. The PBAC considered these to be likely underestimates and had doubts about the predicted usage of the product, both in terms of patient numbers and frequency of use.

12. Recommendation and Reasons

The PBAC noted that the premise of the submission is the higher sensitivity of the proposed test, which would translate into a better detection rate of early diabetic keto-acidosis (DKA). The patient relevant outcomes of interest would be fewer or less severe cases of DKA occurring, fewer hospital admissions with DKA, or lower mortality rates with DKA. Other examples of clinical benefits would be the avoidance of unnecessary treatments for DKA or better diabetes control.

The PBAC considered that it was likely that the blood β-ketone electrodes provided better diagnostic accuracy than the urine ketone tests with the caveat that the evidence presented in the submission was relatively weak. It was noted that in the more directly relevant randomised, but unblinded trial (Laffel et al) there were more emergency room visits and hospitalisations in the urine ketone testing group compared with the blood β-ketone testing arm. The reasons for the hospitalisations and emergency room visits were not given, although it was stated that they involved both hyperglycaemia and hypoglycaemia. As ketone testing is used for the earlier detection or prevention of DKA (ie hyperglycaemia and not hypoglycaemia), the PBAC considered that there was uncertainty regarding the

magnitude and the relevance of the emergency room visit and hospitalisation data, including whether a less frequent use of these facilities necessarily indicates better management of the clinical condition. Further, the confidence intervals of the incidence density ratios (calculated during the evaluation) for the all-cause emergency visits and hospitalisations include unity, suggesting there was no statistically significant difference between the groups for these outcomes.

Based on the evidence provided, the submission's claim that blood β-ketone electrodes have significant advantages in clinical effectiveness compared with urine ketone tests was uncertain as the evidence of effectiveness was limited to a single trial on Type 1 diabetic patients aged 3 to 22 years and uncertainty existed as to whether the results would be reproducible in the Australian setting. The PBAC considered that the patients in the trial would be a highly trained group and the results may not be reproducible in a general population in Australia, where any training effect would be less and likely to diminish further over time beyond the 6-month time horizon of the trial. No evidence was presented to suggest that patients would be more compliant with use of the blood β-ketone electrodes over the comparator or that Australian patients would necessarily follow either the trial-recommended practices involving the conditions for or frequency of the use of ketone testing or the trial-recommended practices following the detection of abnormal ketone readings. Also, the potential for clinically important outcomes arising from false negative or false positive test results (with a potential for increased toxicity) was not considered in the submission.

Thus, the overall benefits of the proposed product were uncertain because they were based on only one relevant trial, which was small and of poor quality and of uncertain applicability to Australian patients in the longer-term, and where the results, presented as event rates were difficult to interpret and likely to be overestimated for the reasons outlined above.

The PBAC considered that the cost effectiveness of the blood β-ketone electrodes based on a price at about twenty times the cost of the comparator was unacceptable, given the doubts about the clinical claims, and that the corresponding claimed cost off-sets would be unlikely to be realised in an Australian population. There were also doubts about the predicted usage of the product, both in terms of patient numbers and frequency of use.

The PBAC thus rejected the submission because of uncertain clinical benefit and uncertain and unacceptable cost-effectiveness.

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 disagrees with the position of the PBAC regarding clinical benefit and cost effectiveness, and is exploring options for a way forward.