Public Summary Document

Product:	Insulin glargine, injection, 100 units per mL, 10 mL vials and 3 mL x 5 cartridges, Lantus®
Sponsor:	Sanofi-aventis Group
Date of PBAC Consideration:	March 2006

1. Purpose of Application

This application sought listing of insulin glargine on the Pharmaceutical Benefits Scheme (PBS) as a restricted benefit for use in diabetic patients who meet certain criteria.

2. Background

This was the fifth submission to the Pharmaceutical Benefits Advisory Committee (PBAC) for insulin glargine.

At the July 2005 meeting, the PBAC rejected the fourth submission for listing as an unrestricted benefit.

A stakeholder meeting was held in October 2005 to discuss ways forward towards possible listings of the basal insulins (detemir and glargine) on the PBS. The attendees included representatives of PBAC, clinicians, diabetes organisations, the sponsors and Government. A stakeholder meeting is non-binding on any party and is conducted without prejudice.

3. Registration Status

Insulin glargine has been registered by the Therapeutic Goods Administration (TGA) for "once daily subcutaneous administration in the treatment of Type 1 diabetes mellitus in adults and children and Type 2 diabetes mellitus in adults who require insulin for the control of hyperglycaemia".

4. Listing Requested and PBAC's View

The sponsor proposed the following listing:

<u>Restricted benefit</u>
For the treatment of Type 1 diabetes;
For the treatment of Type 2 diabetes when used in combination with three or more prandial doses of insulin per day;
For the treatment of patients with diabetes who have documented systemic protamine hypersensitivity.

This proposal was based on the recommendations of the participants at the stakeholder meeting. The PBAC's view was that concern remained about the high potential for use outside the requested restriction in the population with Type 2 diabetes. Although acknowledging that this issue could be addressed by a risk-sharing arrangement between the Government and the sponsor, the success of such an arrangement would depend on accurate estimates of the eligible Type 2 population, about which there remains considerable uncertainty.

5. Clinical Place for the Proposed Therapy

The management of insulin dependent diabetes in some patients may be complicated by the trade-off between achieving better glycaemic control, as measured by a reduction in HbA1c levels, and a greater risk of hypoglycaemia resulting from a temporary relative oversupply of insulin seen with existing intermediate acting insulins. Insulin glargine provides a smooth, peakless predictable time concentration profile and a prolonged duration of action, allowing once daily dosing to meet a patients basal insulin needs.

6. Comparator

The submission nominated insulin NPH as the comparator. This had previously been accepted by PBAC.

7. Clinical Trials

The submission did not provide any new trial data, but focused on Type 1 diabetes. The submission was based on a meta-analysis of patient level data from 5 previously-presented head-to-head trials comparing insulin glargine to NPH insulin in Type 1 diabetes. The submission presented results from regression analyses and "lumping" of data presented in the previous submission for Type 1 patients only, and also provided a meta-analysis using trial level data (and using the outcome of 'overall' hypoglycaemia) including the 11 Type 1 and 2 trials presented in the previous submissions meta-analysis and three published trials previously excluded.

The studies that were published or had been presented at conferences at the time of submission are detailed in the table below:

Trial/First author	Protocol/Publication title	Publication citation
3004/ Ratner RE	28-week multicentre controlled randomised open clinical trial comparing HOE901 with NPH human insulin in subjects with Type 1 diabetes.	Diabetes Care May 2000; 23(5): 639-43.
3005/ Raskin P	16-week multicentre controlled randomised open-label clinical trial comparing HOE901 insulin and NPH human insulin in subjects with Type 1 diabetes treated with insulin Lispro.	Diabetes Care 2000; 23(11): 1666-71.
4006/ Ashwell S	32-week, five centre, two-way cross-over study in Type 1 diabetes comparing insulin glargine and insulin Lispro with NPH and unmodified human insulin.	ADA 2003: conference poster 784
4010/ Fulcher G	30-week multicentre controlled randomised single blind clinical trial comparing insulin glargine and insulin Lispro with NPH human insulin and Insulin Lispro in subjects with Type 1 diabetes.	Diabetologia (2002): 43 (suppl) Eur. Association for the Study of Diabetes (EASD) September 2002 Abstract 801.
3002/ 1. Yki-Jarvinen 2. Benedetti M	52-week multicentre controlled randomised open clinical trial comparing HOE 901 with NPH human insulin subjects with Type 2 diabetes.	1. Diabetes Care 2000; 23(8) 1130-36 2. Hormone Metabolism Res. (2003); 35: 189-196
3006/ Rosenstock J	28-wk multicentre controlled randomised open clinical trial comparing HOE 901 with NPH human insulin in subjects with Type 2 diabetes.	Diabetes Care 2001; 24(4) 631-36.
4001/ Fritsche A	28-week open controlled randomised multinational multicentre clinical study to investigate the efficacy and safety of different combination therapies, HOE901 insulin analogue (once daily, at bedtime or in the morning) plus glimepiride and NPH basal insulin (once daily, at bedtime) plus glimepiride, in Type 2 diabetes	Diabetologia (2002); 45 (Suppl 2); 38th annual meeting of the European Association for the Study of Diabetes (EASD) Abs: 149.

Trial/First author	Protocol/Publication title	Publication citation
	mellitus patients who fail good metabolic control with oral antidiabetic drugs.	
4002/ Riddle	Target glycaemic control and the incidence of symptomatic nocturnal hypoglycaemia in insulin naïve subjects with Type 2 diabetes on oral hypoglycaemic agent(s) and treated with insulin glargine or NPH human insulin.	62nd Sci Sess Am Diabetes Assoc (ADA), June 2002, Diabetes 2002; 51 (suppl 2): A113, abs 457-P.
Rossetti P.	Intensive replacement of basal insulin in patients with Type 1 diabetes given rapid-acting insulin analog at mealtime. A 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime.	Diabetes Care, Volume 26, Number 5, May 2003, pp 1490-1496
Porcellati F	Glargine vs NPH as Basal Insulin in Intensive Treatment of T1DM Given Lispro at Meals: One Year Comparison.	ADA Abstract, 2002.
Yki-Jarvinen, H	The LANMET Study. No: 2181 – P0.	ADA 2004 – Study 6001

The results of 36 observational studies (11 new studies) were also presented as supportive evidence.

8. Results of Trials

The hypoglycaemic event rate data presented in the current submission were presented in the previous submission. The results of the submission's "meta-analysis" of patient level data from five head-to-head randomised trials in type 1 diabetes were a 5.2% and a 16.78% reduction in symptomatic and severe hypoglycaemic events with insulin glargine, respectively. The PBAC considered the approach presented was not a meta-analysis with proper pooling. A meta-analysis using appropriate methods conducted during the previous evaluation showed that the reduction in symptomatic hypoglycaemic events was statistically significant while the reduction is severe hypoglycaemia was not.

The submission also presented meta-analyses assessing the effect of excluding published trials to address concerns raised by the PBAC at the July 2005 meeting. However, the PBAC considered these new analyses, which still excluded some trials, did not sufficiently address their concerns for a number of reasons.

The Committee agreed that, albeit with a residual unresolved concern about reporting bias, the most appropriate analysis of the trial data remained the negative binomial analysis provided in the previous submission, because it used the most appropriate method of pooling the available individual patient data. This analysis showed an event rate reduction for glargine over NPH in Type 1 diabetes of 10.1% for symptomatic hypoglycaemia and 27.1% for severe hypoglycaemia. The reduction in severe events was not statistically significant. These events are relatively rare and this finding could have arisen by chance. In the absence of convincing evidence to the contrary, the PBAC concluded that the statistically significant 10% reduction in hypoglycaemic event rates overall probably provided the most robust estimate of relative reduction in any sub-set of hypoglycaemic events and thus that the numerically higher but non-significant result for the sub-set of severe hypoglycaemic events was not accepted as being a truly different result.

The data from the 36 observational studies showed that the incidence of severe hypoglycaemia in diabetic patients could be higher than that observed in the randomised clinical trials.

For additional PBAC comments on these results, see Recommendations and Reasons

9. Clinical Claim

The submission claimed insulin glargine had similar effectiveness to insulin NPH, but less toxicity. Overall, the Committee again concluded that based on the available evidence, the size of reduction in hypoglycaemic events during therapy with insulin glargine was at best very small, and there was also a lack of evidence of long-term benefit.

10. Economic Analysis

An updated preliminary economic evaluation was presented. The evaluation in the current submission assessed the incremental cost/extra symptomatic hypoglycaemic event avoided and incremental cost/extra severe hypoglycaemic event avoided. This differed from the previous submission in that Type 1 patients were used as a proxy for the entire proposed population, the category of "major" hypoglycaemia had been excluded, drug and needle costs had been changed and sensitivity analyses were provided. The resulting incremental costs were all <$15,000. Lower incremental costs were associated with the more common "symptomatic" events, and the higher incremental costs with the less common "severe" events.

A new modelled economic evaluation was presented using a cost utility approach. The submission estimated the incremental cost per quality adjusted life year gained (QALY) to be <$15,000.

The PBAC had a number of major concerns with the economic model presented. As a result of these concerns the Committee concluded that the incremental cost per extra quality-adjusted life-year (QALY) gained is highly uncertain and, under one of the twenty-four scenarios, could be >$200,000 in the combined Type 1 and 2 populations. *(see also Recommendation and Reasons).*

11. Estimated PBS Usage and Financial Implications

The submission estimated the annual number of patients to be in the range 50,000 – 100,000 for Type 1 diabetes and < 10,000 per year for Type 2 diabetes by the fourth year after listing.

The submission estimated additional direct costs to the PBS in the range of $10 - 30M in Year 4. The PBAC considered there to be considerable uncertainty in the estimate of the Type 2 population.

12. Recommendation and Reasons

The PBAC again acknowledged the clinical need for an insulin product that reduces hypoglycaemic events without compromising long-term diabetic control as measured using HbA1c. The Committee expressed sympathy with those patients and clinicians who report benefit from treatment with long-acting basal insulins, but continued to have difficulty reconciling these individual clinical experiences with the body of randomised trial evidence provided in the sponsors' submissions.

The Committee agreed that, albeit with a residual unresolved concern about reporting bias, the most appropriate analysis of the trial data remained the negative binomial analysis provided in the previous submission, because it used the most appropriate method of pooling the available individual patient data. This analysis showed an event rate reduction for glargine over NPH in Type 1 diabetes of 10.1% for symptomatic hypoglycaemia and 27.1% for severe hypoglycaemia. The reduction in severe events was not statistically significant. These events are relatively rare and this finding could have arisen by chance. In the absence of convincing evidence to the contrary, the PBAC concluded that the statistically significant 10% reduction in hypoglycaemic event rates overall probably provided the most robust estimate of relative reduction in any sub-set of hypoglycaemic events and thus that the numerically higher but non-significant result for the sub-set of severe hypoglycaemic events was not accepted as being a truly different result.

The PBAC noted that there was uncertainty surrounding the impact of these reductions for the average patients. If the average change in rates does not have an important impact on the average patient, then this raises substantial doubt regarding the assumption for the modelled economic evaluation that, on average, there will be a utility gain associated with a reduction in the fear of subsequent hypoglycaemic events. Such a utility gain may only arise in the small sub-set of patients with a directly perceptible reduction in event rates, in which case the claimed utility gain from reduced fear should only apply to this sub-set.

Overall the Committee again concluded that based on the available evidence, the size of reduction in hypoglycaemic events during therapy with insulin glargine was at best very small, and there was also a lack of evidence of long-term benefit.

The PBAC noted that the current submission presented a new modelled economic evaluation focusing on the impact of reductions in hypoglycaemic events. The new Markov model included two health states, alive and dead; only “symptomatic” and “severe” hypoglycaemic events; the hypoglycaemic event rates and event rate reductions based on trial data; the disutility values derived from a Time Trade Off (TTO) study in the general population; and only Type 1 patients.

The Committee agreed that there are a few sources of uncertainty with the TTO utility study. Although acknowledging that it may not be possible to do the ideal utility study in this setting, there remained concern that the model did not capture the chronic nature of the disease, in which there will be considerable variability in symptoms over time, rather than a health state that can be adequately described by a “typical week” which is then treated as constant over the patient’s lifetime, thus creating an unrealistic scenario for the time trade-off. Additionally a proposition inherent in the utilities is that hypoglycaemic events disappear upon treatment with insulin glargine, whereas in reality these events only occur at a reduced rate.

The Committee also had concerns about whether the modelled economic evaluation provides an informative estimate of the cost-effectiveness of insulin glargine given: the assumptions of constancy across hypoglycaemic events, event rate reductions, utility impact/event and mortality over each and every cycle of the model, meant that the model is independent of the time horizon and the results of the model based on one cycle (3 months) are the same as those following the full 30-year duration.

Although the base case incremental cost-effectiveness ratio (ICER) for glargine over NPH appeared numerically to be acceptable, the uncertainty remained high and, under one out of 24 scenarios could be >$200,000 in the combined Type 1 and Type 2 population. The Committee did not accept the sponsor's argument that the high ICERs should be disregarded.

The Juvenile Diabetes Research Foundation (JDRF) Survey results, tabled at the meeting, were based upon 302 responses obtained from an on-line survey of 1000 randomly chosen members of JDRF with a connection with Type 1 diabetes, and for whom on-line address details were available. As such the population was likely to be biased, and the Committee felt unable to draw any conclusions from the results although it commended JDRF for attempting this work.

Overall, taking into account the possibility of usage beyond the restriction, doubts over the clinical importance of the reduction in hypoglycaemic events and uncertainties with the economic model and resulting cost effectiveness ratios, the PBAC did not consider that the price advantage over insulin NPH requested in the submission was justified.

The Committee however recalled that insulin analogues were recommended for listing as unrestricted benefits on a cost effectiveness basis over neutral insulin on the grounds of an improvement in the rate of hypoglycaemic events. Taking this into account, the PBAC indicated that a listing of insulin glargine could follow the same logic.

The Committee consequently deferred this item, indicated that, should the sponsor formally indicate an acceptable basis for a cost-effectiveness recommendation, the PBAC would be prepared to reconsider this matter out-of-session.

Further information

Following a response from the sponsor, further consideration by the PBAC occurred at an extraordinary meeting held on 29 March 2006. At this meeting the PBAC recommended the listing of insulin glargine as an unrestricted benefit.

The cost effectiveness of insulin glargine was accepted at the new price proposed.

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

Glargine is the most prescribed basal insulin in the world. Sanofi-aventis, on behalf of people with diabetes, thanks the Committee for working with us to find a way forward to provide Lantus as a general benefit to this population. We note that the PBAC has recommended a general benefit listing because of its concerns about uncertainty in identifying the appropriate size of the insulin dependent type 2 diabetic population. Sanofi-aventis looks forward to the Government's favourable consideration of the PBAC recommendation and the PBS listing of Lantus in the very near future.