PUBLIC SUMMARY DOCUMENT

Product: Insulin Glulisine, injection (human analogue), 100 units per mL, 3 mL, 5, Apidra®, Apidra SoloStar®

Sponsor: sanofi-aventis australia pty ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

The submission sought an unrestricted listing for the treatment of Type 1 and Type 2 diabetes mellitus.

2. Background

Insulin glulisine had has not previously been considered by the PBAC.

3. Registration Status

Insulin glulisine is TGA-registered for the treatment of type 1 and type 2 diabetes mellitus in adults and children older than 12 years who require insulin for the control of hyperglycaemia.

4. Listing Requested and PBAC's view

Unrestricted benefit

The PBAC had no objection to the requested listing.

5. Clinical place for the proposed therapy

Insulin glulisine will provide another treatment option for patients with Type 1 diabetes or Type 2 diabetes requiring a combination of a basal and a prandial insulin to maintain an appropriate glycaemic control.

6. Comparator

The submission nominated insulin lispro as the main comparator while noting that insulin aspart had been listed on a cost-minimisation basis compared to insulin lispro. The PBAC considered the comparator appropriate.

7. Clinical trials

The scientific basis of comparison for Type 1 diabetes in terms of efficacy involved a 26-week randomised, open-label, head-to-head trial (Study 3001) comparing insulin glulisine with insulin lispro. Comparison of safety was based on a 26-week extension phase of the same trial.

Studies that compare insulin glulisine with insulin lispro in the treatment of Type 1 diabetes

Study	Publication title & citation
Study 3001 (week 1-26)	Main publication: Dreyer M et al (2005) Efficacy and safety of insulin glulisine in patients with Type 1 diabetes. *Hormone & Metabolic Research* 37(11): 702-707 Abstract only: Prager R (2004) Efficacy and safety on insulin glulisine and insulin lispro combined with insulin glargine in patients with Type 1 diabetes. *Diabetologia* 2004; 47 (Suppl 2): Abstract 835

For Type 2 diabetes, evaluation of efficacy was based on an indirect comparison of results from 2 meta-analyses: (i) Meta-analysis 1 which compared insulin glulisine and regular human insulin (Study 3002 to 26 weeks and extension to 52 weeks reported as study 3012; and separate Study 3005 to 26 weeks) and (ii) Meta-analysis 2 which compared insulin lispro with regular human insulin (4 studies).

Studies that compare insulin glulisine with regular human insulin in the treatment of Type 2 diabetes

Study	Publication title & citation
Study 3002 (week 1-26)	Dailey G et al. *(2004)* Insulin glulisine provides improved glycaemic control in patients with Type 2 diabetes. *Diabetes Care* 27(10): 2363-2368
Study 3002 (week 27-52)*	Clinical Study Report only, not published.
Study 3005	Rayman et al (Article in press, corrected proof): Insulin glulisine imparts effective glycaemic control in patients with Type 2 diabetes. *Diabetes Research and Clinical Practice* (2006), doi:10.1016/j.diabres.2006.09.006

* Note that Study 3002 (week 27-52) is not an independent study.

Studies that compare insulin lispro with regular human insulin in the treatment of Type 2 diabetes

Study	Publication title & citation
Ross (2001)	Canadian Lispro Study Group A comparative study of insulin lispro and human regular insulin in patients with Type 2 diabetes mellitus and secondary failure of oral hypoglycaemic agents. *Clinical and investigative medicine Medicine clinique et experimentale*. 24(6):292-8
Anderson (1997)	Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. *Clinical Therapeutics* 19(1):62-72
Anderson (1997)	Improved mealtime treatment of diabetes mellitus using an insulin analogue. Multicenter Insulin Lispro Study Group. *Clinical Therapeutics* 19(1):62-72
Bastyr (2000)	Factors associated with nocturnal hypoglycaemia among patients with type 2 diabetes new to insulin therapy: experience with insulin lispro. *Diabetes, Obesity & Metabolism* 2(1):39-46

8. Results of trials

The results of the key trials are summarised in the table below:

Results of primary efficacy analysis in Study 3001 (week 1- 26)

Time point	Insulin glulisine group		Insulin lispro group	
	n	Mean HbA_{1c} (%) ± sd	n	Mean HbA_{1c} (%) ± sd

Time point	Insulin glulisine group		Insulin lispro group	
	n	Mean HbA_{1c} (%) ± sd	n	Mean HbA_{1c} (%) ± sd
Baseline	331	7.60 ± 0.96	322	7.58 ± 0.89
Week 12	301	7.51 ± 0.94	293	7.44 ± 0.87
Week 26	279	7.42 ± 0.89	270	7.42 ± 0.92
Endpoint	331	7.46 ± 0.91	322	7.45 ± 0.92
Mean change from baseline to endpoint ± sd		-0.14 ± 0.709		-0.13 ± 0.685
Adjusted mean change from baseline to endpoint (%) *		-0.14		-0.14
Difference (glulisine - lispro) in adjusted mean (%) ± sd (95% CI)	0.00 ± 0.949 (-0.09, 0.10) p=0.9329			

n=number of subjects contributing data; sd=standard deviation
* Adjusted means and differences from ANCOVA model

Based on the results from Study 3001 (week 1-26), which compared insulin glulisine with insulin lispro in Type 1 diabetes, there was no statistically significant difference between the treatment groups in mean change in HbA_{1c} from baseline to endpoint of the study.

Similar results were obtained in Meta-analysis 1, which compared the efficacy of insulin glulisine with regular human insulin (RHI) in Type 2 diabetes, and in Meta-analysis 2, which compared the efficacy of insulin lispro with RHI in Type 2 diabetes.

There was no statistically significant difference between results from Meta-analysis 1 and Meta-analysis 2 in the mean change in HbA_{1c} from baseline to endpoint, which was cited as evidence of the equivalence of insulin glulisine and insulin lispro in Type II diabetes.

The data support a lack of difference in rates of hypoglycaemia between glulisine and regular human insulin.

9. Clinical Claim

The submission claimed that insulin glulisine is no worse than the comparator (insulin lispro) in terms of effectiveness and toxicity**.** The submission claimed that insulin glulisine was non-inferior to insulin lispro in effecting a mean decrease HbA_{1c} level in Type 1 diabetes and was non-inferior to RHI in Type 2 diabetes.

The PBAC accepted that the non-inferiority of insulin glulisine compared with insulin lispro in effecting a mean decrease HbA_{1c} had been adequately demonstrated in both Type 1 and 2 diabetes.

10. Economic analysis

The PBAC agreed that the choice of a cost-minimisation approach was valid and that the equi-effective doses in this context were insulin glulisine 100 IU/mL and insulin lispro 100 IU/mL.

A preliminary economic evaluation based on the clinical trial results was not presented. However, using the average daily dose at the end-point of the trial in Type 1 diabetes, the cost of rapid-acting insulin per Type 1 diabetic patient per year is presented below:

Cost of rapid acting insulin in T1 diabetes per patient/year

	IU per presentation	ADD *	Scripts per year	DPMQ* $	Cost of rapid acting insulin per patient/year
Insulin Glulisine	7,500 IU	29.47 IU	1.43	$262.95	$376.02
Insulin Lispro	7,500 IU	30.68 IU	1.49	$262.95	$391.80

* ADD, average daily dose, calculated at the endpoint (52-week) of Study 3011

11. Estimated PBS Usage and Financial Implications:

The likely script numbers for Type 1 and Type 2 diabetics per year was estimated to be between 45,000- 75,000 in year 4. The predicted extra financial cost/saving to the PBS was claimed to be cost neutral to Government.

12. Recommendation and Reasons:

The PBAC recommended listing as an unrestricted benefit on a cost-minimisation basis against insulin lispro, with the equi-effective doses being 1 unit of insulin glulisine and 1 unit of insulin lispro.

The PBAC accepted that the non-inferiority of insulin glulisine compared with insulin lispro in effecting a mean decrease HbA_{1c} had been adequately demonstrated in both Type 1 and 2 diabetes. The Committee also agreed with the ESC that there is unlikely to be any clinically important difference in safety between the two rapid-acting insulins.

Recommendation

INSULIN GLULISINE, injection (human analogue), 100 units per mL, 3 mL, 5

Restriction: Unrestricted benefit

Maximum quantity: 5
Repeats: 1

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

Sanofi-aventis welcomes the PBAC's decision to make insulin glulisine available on the PBS as an unrestricted listing for the treatment of Type 1 and Type 2 diabetes.